CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-395/S029

Trade Name: SPIRIVA® HandiHaler®

Generic Name: tiotropium bromide monohydrate

Sponsor: Boehringer Ingelheim

Approval Date: 12/17/2009

Indication: SPIRIVA HandiHaler is an anticholinergic indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), and for reducing COPD exacerbations.

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APPLICATION NUMBER:

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CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	✓
Other Action Letters	
Labeling	✓
REMS	
Summary Review	✓
Officer/Employee List	✓
Office Director Memo	
Cross Discipline Team Leader Review	✓
Medical Review(s)	✓
Chemistry Review(s)	✓
Environmental Assessment	
Pharmacology Review(s)	✓
Statistical Review(s)	✓
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	✓
Other Reviews	✓
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	✓

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21395/S-029

SUPPLEMENT APPROVAL

Boehringer Ingelheim
900 Ridgebury Road
PO Box 368
Ridgefield, CT 06877-0368

Attention: Tacy Pack, Director
Drug Regulatory Affairs

Dear Ms. Pack:

Please refer to your supplemental new drug application dated November 17, 2008, received November 18, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for SPIRIVA® HandiHaler® (tiotropium bromide inhalation powder).

We acknowledge receipt of your submissions dated January 26 and 30, February 17, March 12, 13, and 20, April 17 and 21, June 22 and 24, July 22, September 10, November 13, and December 9, 15, and 16, 2009.

This Prior Approval supplemental new drug application provides for revisions to multiple sections of the package insert to reflect the results of Clinical Trials 205.235 (UPLIFT) and 205.266 (VA Study) in support of an exacerbation claim.

CONTENT OF LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling text for the package insert (PI) and patient instructions for use (PIU) and patient information leaflet (PIL) submitted December 16, 2009. For administrative purposes, please designate this submission, "SPL for approved NDA 21395/S-029.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of

administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

The PREA requirements do not apply to SPIRIVA® HandiHaler® since this product is used for the treatment of chronic obstructive pulmonary disease which does not occur in children.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
5600 Fishers Lane, Room 12B05
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Miranda Raggio, Senior Regulatory Project Manager, at (301) 796-2109.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure
Content of Labeling Submitted 12-16-09

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21395	SUPPL-29	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	SPIRIVA HANDIHALER

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BADRUL A CHOWDHURY
12/17/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

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21-395/S029

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SPIRIVA HandiHaler safely and effectively. See full prescribing information for SPIRIVA HandiHaler.

SPIRIVA® HandiHaler® (tiotropium bromide inhalation powder) Capsules for Respiratory Inhalation

DO NOT Swallow SPIRIVA Capsules
FOR ORAL INHALATION ONLY with the HandiHaler Device

Initial U.S. Approval: 2004

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	12/2009
Dosage and Administration (2)	12/2009
Contraindications (4)	12/2009
Warnings and Precautions,	
Immediate Hypersensitivity Reactions (5.2)	12/2009
Worsening of Narrow-Angle Glaucoma (5.4)	12/2009
Worsening of Urinary Retention (5.5)	12/2009
Renal Impairment (5.6)	12/2009

----------INDICATIONS AND USAGE----------
SPIRIVA HandiHaler is an anticholinergic indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), and for reducing COPD exacerbations (1)

----------DOSAGE AND ADMINISTRATION----------
DO NOT swallow SPIRIVA capsules (2)
For Use with the HandiHaler Device ONLY (2)
For Oral Inhalation ONLY (2)

- Two inhalations of the powder contents of a single SPIRIVA capsule (18 mcg) once daily (2)

----------DOSAGE FORMS AND STRENGTHS----------
SPIRIVA capsules for oral inhalation: 18 mcg tiotropium powder, for use with HandiHaler device (3)

----------CONTRAINDICATIONS----------

- Hypersensitivity to ipratropium or tiotropium (4)

----------WARNINGS AND PRECAUTIONS----------

- Not for acute use: Not for use as a rescue medication (5.1)
- Immediate hypersensitivity reactions: Discontinue SPIRIVA HandiHaler at once and consider alternatives if immediate hypersensitivity reactions, including angioedema, occur. Use with caution in patients with severe hypersensitivity to milk proteins. (5.2)
- Paradoxical bronchospasm: Discontinue SPIRIVA HandiHaler and consider other treatments if paradoxical bronchospasm occurs (5.3)
- Worsening of narrow-angle glaucoma may occur. Use with caution in patients with narrow-angle glaucoma and instruct patients to consult a physician immediately if this occurs (5.4)
- Worsening of urinary retention may occur. Use with caution in patients with prostatic hyperplasia or bladder-neck obstruction and instruct patients to consult a physician immediately if this occurs. (5.5)

----------ADVERSE REACTIONS----------

- The most common adverse reactions (>5% incidence in the 1-year placebo-controlled trials) were upper respiratory tract infection, dry mouth, sinusitis, pharyngitis, non-specific chest pain, urinary tract infection, dyspepsia, and rhinitis (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Boehringer Ingelheim Pharmaceuticals, Inc. at (800) 542-6257 or (800) 459-9906 TTY, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
Not recommended for use with other anticholinergics since this has not been studied (7.2)

----------USE IN SPECIFIC POPULATIONS----------
Patients with moderate to severe renal impairment should be monitored closely for potential anticholinergic side effects (2, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: [12/2009]

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Not for Acute Use
5.2 Immediate Hypersensitivity Reactions
5.3 Paradoxical Bronchospasm
5.4 Worsening of Narrow-Angle Glaucoma
5.5 Worsening of Urinary Retention
5.6 Renal Impairment
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Sympathomimetic, Methylxanthines, Steroids
7.2 Anticholinergics
7.3 Cimetidine, Ranitidine
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
8.7 Hepatic Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and Pharmacology
14 CLINICAL STUDIES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION
17.1 Instructions for Administering SPIRIVA HandiHaler
17.2 Paradoxical Bronchospasm
17.3 Urinary Retention
17.4 Visual Effects
17.5 Acute Exacerbation
17.6 FDA-approved Patient Labeling

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SPIRIVA HandiHaler (tiotropium bromide inhalation powder) is indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. SPIRIVA HandiHaler is indicated to reduce exacerbations in COPD patients.

2 DOSAGE AND ADMINISTRATION

DO NOT SWALLOW SPIRIVA CAPSULES
FOR USE WITH HANDIHALER DEVICE ONLY

FOR ORAL INHALATION ONLY

SPIRIVA capsules must not be swallowed as the intended effects on the lungs will not be obtained. The contents of the SPIRIVA capsules are only for oral inhalation and should only be used with the HandiHaler device [*see Overdosage (10)*]**.**

The recommended dose of SPIRIVA HandiHaler is two inhalations of the powder contents of one SPIRIVA capsule, once-daily, with the HandiHaler device [*see Patient Counseling Information (17.6)*].

For administration of SPIRIVA HandiHaler, a SPIRIVA capsule is placed into the center chamber of the HandiHaler device. The SPIRIVA capsule is pierced by pressing and releasing the green piercing button on the side of the HandiHaler device. The tiotropium formulation is dispersed into the air stream when the patient inhales through the mouthpiece [*see Patient Counseling Information (17.6)*].

No dosage adjustment is required for geriatric, hepatically-impaired, or renally-impaired patients. However, patients with moderate to severe renal impairment given SPIRIVA HandiHaler should be monitored closely for anticholinergic effects [*see Warnings and Precautions (5.6), Use in Specific Populations (8.5, 8.6, 8.7), and Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

SPIRIVA HandiHaler consists of SPIRIVA capsules and a HandiHaler device. SPIRIVA capsules contain 18 mcg dry powder formulation of tiotropium in a light green, hard gelatin capsule with TI 01 printed on one side and Boehringer Ingelheim company logo on the other side. Supplied with a HandiHaler device.

4 CONTRAINDICATIONS

SPIRIVA HandiHaler is contraindicated in patients with a hypersensitivity to ipratropium or tiotropium. In clinical trials and post-marketing experience with SPIRIVA HandiHaler, immediate hypersensitivity reactions, including angioedema (including swelling of the lips, tongue, or throat), itching, or rash have been reported.

5 WARNINGS AND PRECAUTIONS

5.1 Not for Acute Use

SPIRIVA HandiHaler is intended as a once-daily maintenance treatment for COPD and is not indicated for the initial treatment of acute episodes of bronchospasm (i.e., rescue therapy).

5.2 Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions, including angioedema (including swelling of the lips, tongue, or throat), itching, or rash may occur after administration of SPIRIVA HandiHaler. If such a reaction occurs, therapy with SPIRIVA HandiHaler should be stopped at once and alternative treatments should be considered. Given the similar structural formula of atropine to tiotropium, patients with a history of hypersensitivity reactions to atropine should be closely monitored for similar hypersensitivity reactions to SPIRIVA HandiHaler. In addition, SPIRIVA HandiHaler should be used with caution in patients with severe hypersensitivity to milk proteins.

5.3 Paradoxical Bronchospasm

Inhaled medicines, including SPIRIVA HandiHaler, may cause paradoxical bronchospasm. If this occurs, treatment with SPIRIVA HandiHaler should be stopped and other treatments considered.

5.4 Worsening of Narrow-Angle Glaucoma

SPIRIVA HandiHaler should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

5.5 Worsening of Urinary Retention

SPIRIVA HandiHaler should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of prostatic hyperplasia or bladder-neck obstruction (e.g., difficulty passing urine, painful urination). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

5.6 Renal Impairment

As a predominantly renally excreted drug, patients with moderate to severe renal impairment (creatinine clearance of ≤50 mL/min) treated with SPIRIVA HandiHaler should be monitored closely for anticholinergic side effects [*see Clinical Pharmacology (12.3)*].

6 ADVERSE REACTIONS

The following adverse reactions are described, or described in greater detail, in other sections:

- Immediate hypersensitivity reactions [*see Warnings and Precautions (5.2)*]
- Paradoxical bronchospasm [*see Warnings and Precautions (5.3)*]
- Worsening of narrow-angle glaucoma [*see Warnings and Precautions (5.4)*]
- Worsening of urinary retention [see *Warnings and Precautions* (5.5)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6-Month to 1-Year- Trials

The data described below reflect exposure to SPIRIVA HandiHaler in 2663 patients. SPIRIVA HandiHaler was studied in two 1-year placebo-controlled trials, two 1-

year active-controlled trials, and two 6-month placebo-controlled trials in patients with COPD. In these trials, 1,308 patients were treated with SPIRIVA HandiHaler at the recommended dose of 18 mcg once a day. The population had an age ranging from 39 to 87 years with 65% to 85% males, 95% Caucasian, and had COPD with a mean pre-bronchodilator forced expiratory volume in one second (FEV_1) percent predicted of 39% to 43%. Patients with narrow-angle glaucoma, or symptomatic prostatic hypertrophy or bladder outlet obstruction were excluded from these trials. An additional 6-month trial conducted in a Veteran's Affairs setting is not included in this safety database because only serious adverse events were collected.

The most commonly reported adverse drug reaction was dry mouth. Dry mouth was usually mild and often resolved during continued treatment. Other reactions reported in individual patients and consistent with possible anticholinergic effects included constipation, tachycardia, blurred vision, glaucoma (new onset or worsening), dysuria, and urinary retention.

Four multicenter, 1-year, placebo-controlled and active-controlled trials evaluated SPIRIVA HandiHaler in patients with COPD. Table 1 shows all adverse reactions that occurred with a frequency of ≥3% in the SPIRIVA HandiHaler group in the 1-year placebo-controlled trials where the rates in the SPIRIVA HandiHaler group exceeded placebo by ≥1%. The frequency of corresponding reactions in the ipratropium-controlled trials is included for comparison.

Table 1 Adverse Reactions (% Patients) in One-Year-COPD Clinical Trials

Body System (Event)	Placebo-Controlled Trials		Ipratropium-Controlled Trials	
	SPIRIVA (n = 550)	Placebo (n = 371)	SPIRIVA (n = 356)	Ipratropium (n = 179)
Body as a Whole				
Chest Pain (non-specific)	7	5	5	2
Edema, Dependent	5	4	3	5
Gastrointestinal System Disorders				
Dry Mouth	16	3	12	6
Dyspepsia	6	5	1	1
Abdominal Pain	5	3	6	6
Constipation	4	2	1	1
Vomiting	4	2	1	2
Musculoskeletal System				
Myalgia	4	3	4	3
Resistance Mechanism Disorders				
Infection	4	3	1	3
Moniliasis	4	2	3	2
Respiratory System (Upper)				
Upper Respiratory Tract Infection	41	37	43	35
Sinusitis	11	9	3	2
Pharyngitis	9	7	7	3
Rhinitis	6	5	3	2
Epistaxis	4	2	1	1
Skin and Appendage Disorders				
Rash	4	2	2	2
Urinary System				
Urinary Tract Infection	7	5	4	2

Arthritis, coughing, and influenza-like symptoms occurred at a rate of ≥3% in the SPIRIVA HandiHaler treatment group, but were <1% in excess of the placebo group.

Other reactions that occurred in the SPIRIVA HandiHaler group at a frequency of 1 to 3% in the placebo-controlled trials where the rates exceeded that in the placebo group include: *Body as a Whole* allergic reaction, leg pain; *Central and Peripheral Nervous System* dysphonia, paresthesia; *Gastrointestinal System Disorders* gastrointestinal disorder not otherwise specified (NOS), gastroesophageal reflux, stomatitis (including ulcerative stomatitis); *Metabolic and Nutritional Disorders* hypercholesterolemia, hyperglycemia; *Musculoskeletal System Disorders* skeletal pain; *Cardiac Events* angina pectoris (including aggravated angina pectoris); *Psychiatric Disorder* depression; *Infections* herpes zoster; *Respiratory System Disorder (Upper)* laryngitis; *Vision Disorder* cataract. In addition, among the adverse reactions observed in the clinical trials with an incidence of <1% were atrial fibrillation, supraventricular tachycardia, angioedema, and urinary retention.
In the 1-year trials, the incidence of dry mouth, constipation, and urinary tract infection increased with age [*see Use in Specific Populations (8.5)*].

Two multicenter, 6-month, controlled studies evaluated SPIRIVA HandiHaler in patients with COPD. The adverse reactions and the incidence rates were similar to those seen in the 1-year controlled trials.

4-Year Trial

The data described below reflect exposure to SPIRIVA HandiHaler in 5,992 COPD patients in a 4-year placebo-controlled trial. In this trial, 2,986 patients were treated with SPIRIVA HandiHaler at the recommended dose of 18 mcg once a day. The population had an age range from 40 to 88 years, was 75% male, 90% Caucasian, and had COPD with a mean pre-bronchodilator FEV_1 percent predicted of 40%. Patients with narrow-angle glaucoma, or symptomatic prostatic hypertrophy or bladder outlet obstruction were excluded from these trials. When the adverse reactions were analyzed with a frequency of ≥3% in the SPIRIVA HandiHaler group where the rates in the SPIRIVA HandiHaler group exceeded placebo by ≥1%, adverse reactions included (SPIRIVA HandiHaler, placebo): pharyngitis (12.5%, 10.8%), sinusitis (6.5%, 5.3%), headache (5.7%, 4.5%), constipation (5.1%, 3.7%), dry mouth (5.1%, 2.7%), depression (4.4%, 3.3%), insomnia (4.4%, 3.0%), and arthralgia (4.2%, 3.1%).

Additional Adverse Reactions

Other adverse reactions not previously listed that were reported more frequently in COPD patients treated with SPIRIVA HandiHaler than placebo include: dehydration, skin ulcer, stomatitis, gingivitis, oropharyngeal candidiasis, dry skin, skin infection, and joint swelling.

6.2 Postmarketing Experience

Adverse reactions have been identified during worldwide post-approval use of SPIRIVA HandiHaler. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These adverse reactions are: application site irritation (glossitis, mouth ulceration, and pharyngolaryngeal pain), dizziness, dysphagia, hoarseness, intestinal obstruction including ileus paralytic, intraocular pressure increased, oral candidiasis, palpitations, pruritus, tachycardia, throat irritation, and urticaria.

7 DRUG INTERACTIONS

7.1 Sympathomimetics, Methylxanthines, Steroids

SPIRIVA HandiHaler has been used concomitantly with short-acting and long-acting sympathomimetic (beta-agonists) bronchodilators, methylxanthines, and oral and inhaled steroids without increases in adverse drug reactions.

7.2 Anticholinergics

The co-administration of SPIRIVA HandiHaler with other anticholinergic-containing drugs (e.g., ipratropium) has not been studied and is therefore not recommended.

7.3 Cimetidine, Ranitidine

No clinically significant interaction occurred between tiotropium and cimetidine or ranitidine [*see Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects, Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women. SPIRIVA HandiHaler should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

No evidence of structural alterations was observed in rats and rabbits at inhalation tiotropium doses of up to approximately 660 and 6 times the recommended human daily inhalation dose (RHDID) on a mg/m^2 basis, respectively. However, in rats, tiotropium caused fetal resorption, litter loss, decreases in the number of live pups at birth and the mean pup weights, and a delay in pup sexual maturation at inhalation tiotropium doses of approximately 35 times the RHDID on a mg/m^2 basis. In rabbits, tiotropium caused an increase in post-implantation loss at an inhalation dose of approximately 360 times the RHDID on a mg/m^2 basis~~)~~. Such effects were not observed at inhalation doses of approximately 4 and 80 times the RHDID on a mg/m^2 basis, respectively. These dose multiples may be over-estimated due to difficulties in measuring deposited doses in animal inhalation studies.

8.2 Labor and Delivery

The safety and effectiveness of SPIRIVA HandiHaler has not been studied during labor and delivery.

8.3 Nursing Mothers

Clinical data from nursing women exposed to tiotropium are not available. Based on lactating rodent studies, tiotropium is excreted into breast milk. It is not known whether tiotropium is excreted in human milk, but because many drugs are excreted in human milk and given these findings in rats, caution should be exercised if SPIRIVA HandiHaler is administered to a nursing woman.

8.4 Pediatric Use

SPIRIVA HandiHaler is approved for use in the maintenance treatment of bronchospasm associated with COPD and for the reduction of COPD exacerbations. COPD does not normally occur in children. The safety and effectiveness of SPIRIVA HandiHaler in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of patients who received SPIRIVA HandiHaler in the 1-year clinical trials, 426 were <65 years, 375 were 65 to 74 years and 105 were ≥75 years of age. Within each age subgroup, there were no differences between the proportion of patients with adverse events in the SPIRIVA HandiHaler and the comparator groups for most events. Dry mouth increased with age in the SPIRIVA HandiHaler group (differences from placebo were 9.0%, 17.1%, and 16.2% in the aforementioned age subgroups). A higher frequency of constipation and urinary tract infections with increasing age was observed in the SPIRIVA HandiHaler group in the placebo-controlled studies. The differences from placebo for constipation were 0%, 1.8%, and 7.8% for each of the age groups. The differences from placebo for urinary tract infections were –0.6%, 4.6%, and 4.5%. No overall differences in effectiveness were observed among these groups. Based on available data, no adjustment of SPIRIVA HandiHaler dosage in geriatric patients is warranted [*see Clinical Pharmacology (12.3)*].

8.6 Renal Impairment

Patients with moderate to severe renal impairment (creatinine clearance of ≤50 mL/min) treated with SPIRIVA HandiHaler should be monitored closely for anticholinergic side effects [*see Dosage and Administration (2), Warnings and Precautions (5.4), and Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment

The effects of hepatic impairment on the pharmacokinetics of tiotropium were not studied.

10 OVERDOSAGE

High doses of tiotropium may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a single inhaled dose of up to 282 mcg tiotropium in 6 healthy volunteers. In a study of 12 healthy volunteers, bilateral conjunctivitis and dry mouth were seen following repeated once-daily inhalation of 141 mcg of tiotropium.

Accidental Ingestion

Acute intoxication by inadvertent oral ingestion of SPIRIVA capsules is unlikely since it is not well-absorbed systemically.

A case of overdose has been reported from post-marketing experience. A female patient was reported to have inhaled 30 capsules over a 2.5 day period, and developed altered mental status, tremors, abdominal pain, and severe constipation. The patient was hospitalized, SPIRIVA HandiHaler was discontinued, and the constipation was treated with an enema. The patient recovered and was discharged on the same day.

No mortality was observed at inhalation tiotropium doses up to 32.4 mg/kg in mice, 267.7 mg/kg in rats, and 0.6 mg/kg in dogs. These doses correspond to 7-300, 120,000, and 850 times the recommended human daily inhalation dose on a mg/m^2 basis, respectively. These dose multiples may be over-estimated due to difficulties in measuring deposited doses in animal inhalation studies.

11 DESCRIPTION

SPIRIVA HandiHaler consists of a capsule dosage form containing a dry powder formulation of tiotropium intended for oral inhalation only with the HandiHaler device.

Each light green, hard gelatin SPIRIVA capsule contains 18 mcg tiotropium (equivalent to 22.5 mcg tiotropium bromide monohydrate) blended with lactose monohydrate (which may contain milk proteins) as the carrier.

The dry powder formulation within the SPIRIVA capsule is intended for oral inhalation only.

The active component of SPIRIVA HandiHaler is tiotropium. The drug substance, tiotropium bromide monohydrate, is an anticholinergic with specificity for muscarinic receptors. It is chemically described as (1α, 2ß, 4ß, 5α, 7ß)-7-[(Hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.0^{2,4}]nonane bromide monohydrate. It is a synthetic, non-chiral, quaternary ammonium compound. Tiotropium bromide is a white or yellowish white powder. It is sparingly soluble in water and soluble in methanol.

The structural formula is:

Tiotropium bromide (monohydrate) has a molecular mass of 490.4 and a molecular formula of $C_{19}H_{22}NO_4S_2Br \bullet H_2O$.

The HandiHaler device is an inhalation device used to inhale the dry powder contained in the SPIRIVA capsule. The dry powder is delivered from the HandiHaler device at flow rates as low as 20 L/min. Under standardized *in vitro* testing, the HandiHaler device delivers a mean of 10.4 mcg tiotropium when tested at a flow rate of 39 L/min for 3.1 seconds (2 L total). In a study of 26 adult patients with COPD and severely compromised lung function [mean FEV_1 1.02 L (range 0.45 to 2.24 L); 37.6% of predicted (range 16% to 65%)], the median peak inspiratory flow (PIF) through the HandiHaler device was 30.0 L/min (range 20.4 to 45.6 L/min). The amount of drug delivered to the lungs will vary depending on patient factors such as inspiratory flow and peak inspiratory flow through the HandiHaler device, which may vary from patient to patient, and may vary with the exposure time of the SPIRIVA capsule outside the blister pack.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tiotropium is a long-acting, antimuscarinic agent, which is often referred to as an anticholinergic. It has similar affinity to the subtypes of muscarinic receptors, M_1 to M_5. In the airways, it exhibits pharmacological effects through inhibition of M_3-receptors at the smooth muscle leading to bronchodilation. The competitive and reversible nature of antagonism was shown with human and animal origin receptors and isolated organ preparations. In preclinical *in vitro* as well as *in vivo* studies, prevention of methacholine-induced bronchoconstriction effects was dose-dependent and lasted longer than 24 hours. The bronchodilation following inhalation of tiotropium is predominantly a site-specific effect.

12.2 Pharmacodynamics

Cardiovascular Effects

In a multicenter, randomized, double-blind trial that enrolled 198 patients with COPD, the number of subjects with changes from baseline-corrected QT interval of 30 to 60 msec was higher in the SPIRIVA HandiHaler group as compared with placebo. This difference was apparent using both the Bazett (QTcB) [20 (20%) patients vs 12 (12%) patients] and Fredericia (QTcF) [16 (16%) patients vs 1 (1%) patient] corrections of QT for heart rate. No patients in either group had either QTcB or QTcF of >500 msec. Other clinical studies with SPIRIVA HandiHaler did not detect an effect of the drug on QTc intervals.

The effect of SPIRIVA HandiHaler on QT interval was also evaluated in a randomized, placebo- and positive-controlled crossover study in 53 healthy volunteers. Subjects received SPIRIVA HandiHaler 18 mcg, 54 mcg (3 times the recommended dose), or placebo for 12 days. ECG assessments were performed at baseline and throughout the dosing interval following the first and last dose of study medication. Relative to placebo, the maximum mean change from baseline in study-specific QTc interval was 3.2 msec and 0.8 msec for SPIRIVA HandiHaler 18 mcg and 54 mcg, respectively. No subject showed a new onset of QTc >500 msec or QTc changes from baseline of ≥60 msec.

12.3 Pharmacokinetics

Tiotropium is administered by dry powder inhalation. In common with other inhaled drugs, the majority of the delivered dose is deposited in the gastrointestinal tract and, to a lesser extent, in the lung, the intended organ. Many of the pharmacokinetic data described below were obtained with higher doses than recommended for therapy.

Absorption

Following dry powder inhalation by young healthy volunteers, the absolute bioavailability of 19.5% suggests that the fraction reaching the lung is highly bioavailable. It is expected from the chemical structure of the compound (quaternary ammonium compound) that tiotropium is poorly absorbed from the gastrointestinal tract. The effect of food on tiotropium's bioavailability has not been studied. Oral solutions of tiotropium have an absolute bioavailability of 2% to 3%. Maximum tiotropium plasma concentrations were observed 5 minutes after inhalation.

Distribution

Tiotropium shows a volume of distribution of 32 L/kg, indicating that the drug binds extensively to tissues. The human plasma protein binding for tiotropium is 72%. At steady state, peak tiotropium plasma levels in COPD patients were 17 to 19 pg/mL when measured 5 minutes after dry powder inhalation of an 18 mcg dose and decreased in a multi-compartmental manner. Steady-state trough plasma concentrations were 3 to 4 pg/mL. Local concentrations in the lung are not known, but the mode of administration suggests substantially higher concentrations in the lung. Studies in rats have shown that tiotropium does not readily penetrate the blood-brain barrier.

Metabolism

The extent of metabolism appears to be small. This is evident from a urinary excretion of 74% of unchanged substance after an intravenous dose to young healthy volunteers. Tiotropium, an ester, is nonenzymatically cleaved to the alcohol *N*-methylscopine and dithienylglycolic acid, neither of which bind to muscarinic receptors.

In vitro experiments with human liver microsomes and human hepatocytes suggest that a fraction of the administered dose (74% of an intravenous dose is excreted unchanged in the urine, leaving 25% for metabolism) is metabolized by cytochrome P450-dependent oxidation and subsequent glutathione conjugation to a variety of Phase II metabolites. This enzymatic pathway can be inhibited by CYP450 2D6 and 3A4 inhibitors, such as quinidine, ketoconazole, and gestodene. Thus, CYP450 2D6 and 3A4 are involved in the metabolic pathway that is responsible for the elimination of a small part of the administered dose. *In vitro* studies using human liver microsomes showed that tiotropium in supra-therapeutic concentrations did not inhibit CYP450 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4.

Elimination

The terminal elimination half-life of tiotropium was between 5 and 6 days following inhalation. Total clearance was 880 mL/min after an intravenous dose in young healthy volunteers with an inter-individual variability of 22%. Intravenously administered tiotropium was mainly excreted unchanged in urine (74%). After dry powder inhalation, urinary excretion was 14% of the dose, the remainder being mainly non-absorbed drug in the gut which was eliminated via the feces. The renal clearance of tiotropium exceeds the creatinine clearance, indicating active secretion into the urine. After chronic once-daily inhalation by COPD patients, pharmacokinetic steady state was reached after 2 to 3 weeks with no accumulation thereafter.

Drug Interactions

An interaction study with tiotropium (14.4 mcg intravenous infusion over 15 minutes) and cimetidine 400 mg three times daily or ranitidine 300 mg once daily was conducted. Concomitant administration of cimetidine with tiotropium resulted in a 20% increase in the $AUC_{0\text{-}4h}$, a 28% decrease in the renal clearance of tiotropium and no significant change in the C_{max} and amount excreted in urine over 96 hours. Co-administration of tiotropium with ranitidine did not affect the pharmacokinetics of tiotropium.

Specific Populations

Geriatric Patients

As expected for drugs predominantly excreted renally, advanced age was associated with a decrease of tiotropium renal clearance (326 mL/min in COPD patients <58 years to 163 mL/min in COPD patients >70 years), which may be explained by decreased renal function. Tiotropium excretion in urine after inhalation decreased from 14% (young healthy volunteers) to about 7% (COPD patients). Plasma concentrations were numerically increased with advancing age within COPD patients (43% increase in $AUC_{0\text{-}4}$ after dry powder inhalation), which was not significant when considered in relation to inter- and intra-individual variability [*see Dosage and Administration (2) and Use in Specific Populations (8.5)*].

Renal Impairment

Since tiotropium is predominantly renally excreted, renal impairment was associated with increased plasma drug concentrations and reduced drug clearance after both intravenous infusion and dry powder inhalation. Mild renal impairment (creatinine clearance of 50 to 80 mL/min), which is often seen in elderly patients, increased tiotropium plasma concentrations (39% increase in $AUC_{0\text{-}4}$ after intravenous infusion). In COPD patients with moderate to severe renal impairment (creatinine clearance of <50 mL/min), the intravenous administration of tiotropium resulted in doubling of the plasma concentrations (82% increase in $AUC_{0\text{-}4}$), which was confirmed by plasma concentrations after dry powder inhalation**.** Patients with moderate to severe renal impairment (creatinine clearance of ≤50 mL/min) treated with SPIRIVA HandiHaler should be monitored closely for anticholinergic side effects [*see Dosage and Administration (2), Warnings and Precautions (5.4), and Use in Specific Populations (8.6)*].

Hepatic Impairment

The effects of hepatic impairment on the pharmacokinetics of tiotropium were not studied.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of tumorigenicity was observed in a 104-week inhalation study in rats at tiotropium doses up to 0.059 mg/kg/day, in an 83-week inhalation study in female mice at doses up to 0.145 mg/kg/day, and in a 101-week inhalation study in male mice at doses up to 0.002 mg/kg/day. These doses correspond to approximately 25, 35, and 0.5 times the recommended human daily inhalation dose (RHDID) on a mg/m^2 basis, respectively. These dose multiples may be over-estimated due to difficulties in measuring deposited doses in animal inhalation studies.

Tiotropium bromide demonstrated no evidence of mutagenicity or clastogenicity in the following assays: the bacterial gene mutation assay, the V79 Chinese hamster cell mutagenesis assay, the chromosomal aberration assays in human lymphocytes *in vitro* and mouse micronucleus formation *in vivo*, and the unscheduled DNA synthesis in primary rat hepatocytes *in vitro* assay.

In rats, decreases in the number of corpora lutea and the percentage of implants were noted at inhalation tiotropium doses of 0.078 mg/kg/day or greater (approximately 35 times the RHDID on a mg/m^2 basis). No such effects were observed at 0.009 mg/kg/day (approximately 4 times than the RHDID on a mg/m^2 basis). The fertility index, however, was not affected at inhalation doses up to 1.689 mg/kg/day (approximately 760 times the RHDID on a mg/m^2 basis). These dose multiples may be over-estimated due to difficulties in measuring deposited doses in animal inhalation studies.

13.2 Animal Toxicology and Pharmacology

Reproductive Toxicology Studies

No evidence of fetal structural alteration was observed in rats and rabbits at inhalation tiotropium doses of up to 1.471 and 0.007 mg/kg/day, respectively. These doses correspond to approximately 660 and 6 times the RHDID on a mg/m^2 basis, respectively. However, in rats, fetal resorption, litter loss, decreases in the number of live pups at birth and the mean pup weights, and a delay in pup sexual maturation were observed at inhalation tiotropium doses of ≥0.078 mg/kg (approximately 35 times the RHDID on a mg/m^2 basis). In rabbits, an increase in post-implantation loss was observed at an inhalation dose of 0.4 mg/kg/day (approximately 360 times the RHDID on a mg/m^2 basis). Such effects were not observed at inhalation doses of 0.009 and up to 0.088 mg/kg/day in rats and rabbits, respectively. These doses correspond to approximately 4 and 80 times the RHDID on a mg/m^2 basis, respectively. These dose multiples may be over-estimated due to difficulties in measuring deposited doses in animal inhalation studies.

14 CLINICAL STUDIES

The SPIRIVA HandiHaler (tiotropium bromide inhalation powder) clinical development program consisted of six Phase 3 studies in 2663 patients with COPD (1308 receiving SPIRIVA HandiHaler): two 1-year, placebo-controlled studies, two 6-month, placebo-controlled studies and two 1-year, ipratropium-controlled studies. These

studies enrolled patients who had a clinical diagnosis of COPD, were 40 years of age or older, had a history of smoking greater than 10 pack-years, had a forced expiratory volume in one second (FEV_1) less than or equal to 60% or 65% of predicted, and a ratio of FEV_1/FVC of less than or equal to 0.7.

In these studies, SPIRIVA HandiHaler, administered once-daily in the morning, provided improvement in lung function (FEV_1), with peak effect occurring within 3 hours following the first dose.

Two additional trials evaluated exacerbations: a 6-month, randomized, double-blind, placebo-controlled, multicenter clinical trial of 1829 COPD patients in a US Veterans Affairs setting and a 4-year, randomized, double-blind, placebo-controlled, multicenter, clinical trial of 5992 COPD patients. Long-term effects on lung function and other outcomes were also evaluated in the 4-year multicenter trial.

6-Month to 1-Year Effects on Lung Function

In the 1-year, placebo-controlled trials, the mean improvement in FEV_1 at 30 minutes was 0.13 liters (13%) with a peak improvement of 0.24 liters (24%) relative to baseline after the first dose (Day 1). Further improvements in FEV_1 and forced vital capacity (FVC) were observed with pharmacodynamic steady state reached by Day 8 with once-daily treatment. The mean peak improvement in FEV_1, relative to baseline, was 0.28 to 0.31 liters (28% to 31%), after 1 week (Day 8) of once-daily treatment. Improvement of lung function was maintained for 24 hours after a single dose and consistently maintained over the 1-year treatment period with no evidence of tolerance.

In the two 6-month, placebo-controlled trials, serial spirometric evaluations were performed throughout daytime hours in Trial A (12 hours) and limited to 3 hours in Trial B. The serial FEV_1 values over 12 hours (Trial A) are displayed in Figure 1. These trials further support the improvement in pulmonary function (FEV_1) with SPIRIVA HandiHaler, which persisted over the spirometric observational period. Effectiveness was maintained for 24 hours after administration over the 6-month treatment period.

Figure 1 Mean FEV_1 Over Time (prior to and after administration of study drug) on Days 1 and 169 for Trial A (a Six-Month Placebo-Controlled Study)*

Day 1 Day 169

*Means adjusted for center, treatment, and baseline effect. On Day 169, a total of 183 and 149 patients in the SPIRIVA HandiHaler and placebo groups, respectively, completed the trial. The data for the remaining patients were imputed using the last observation or least favorable observation carried forward.

Results of each of the 1-year ipratropium-controlled trials were similar to the results of the 1-year placebo-controlled trials. The results of one of these trials are shown in Figure 2.

Figure 2 Mean FEV_1 Over Time (0 to 6 hours post-dose) on Days 1 and 92, Respectively for One of the Two Ipratropium-Controlled Studies*

Day 1 Day 92

*Means adjusted for center, treatment, and baseline effect. On Day 92 (primary endpoint), a total of 151 and 69 patients in the SPIRIVA HandiHaler and ipratropium groups, respectively, completed through three months of observation. The data for the remaining patients were imputed using the last observation or least favorable observation carried forward.

A randomized, placebo-controlled clinical study in 105 patients with COPD demonstrated that bronchodilation was maintained throughout the 24-hour dosing interval in comparison to placebo, regardless of whether SPIRIVA HandiHaler was administered in the morning or in the evening.

Throughout each week of the one-year treatment period in the two placebo-controlled trials, patients taking SPIRIVA HandiHaler had a reduced requirement for the use of rescue short-acting $beta_2$-agonists. Reduction in the use of rescue short-acting $beta_2$-agonists, as compared to placebo, was demonstrated in one of the two 6-month studies.

4-Year Effects on Lung Function

A 4-year, randomized, double-blind, placebo-controlled, multicenter clinical trial involving 5992 COPD patients was conducted to evaluate the long-term effects of SPIRIVA HandiHaler on disease progression (rate of decline in FEV_1). Patients were permitted to use all respiratory medications (including short-acting and long-acting beta-agonists, inhaled and systemic steroids, and theophyllines) other than inhaled anticholinergics. The patients were 40 to 88 years of age, 75% male, and 90%

Caucasian with a diagnosis of COPD and a mean pre-bronchodilator FEV_1 of 39% predicted (range = 9% to 76%) at study entry. There was no difference between the groups in either of the co-primary efficacy endpoints, yearly rate of decline in pre- and post-bronchodilator FEV_1, as demonstrated by similar slopes of FEV_1 decline over time (Figure 3).

SPIRIVA HandiHaler maintained improvements in trough (pre-dose) FEV_1 (adjusted means over time: 87 to 103 mL) throughout the 4 years of the study (Figure 3).

Figure 3 Trough (pre-dose) FEV_1 Mean Values at Each Time Point

Repeated measure ANOVA was used to estimate means. Means are adjusted for baseline measurements. Baseline trough FEV_1 (observed mean) = 1.12. Patients with ≥3 acceptable pulmonary function tests after day 30 and non-missing baseline value were included in the analysis.

Exacerbations

The effect of SPIRIVA HandiHaler on COPD exacerbations was evaluated in two clinical trials: a 4 year clinical trial described above and a 6-month clinical trial of 1829 COPD patients in a Veterans Affairs setting.-In the 6-month trial, COPD exacerbations were defined as a complex of respiratory symptoms (increase or new onset) of more than one of the following: cough, sputum, wheezing, dyspnea, or chest tightness with a duration of at least 3 days requiring treatment with antibiotics, systemic steroids, or hospitalization. The population had an age ranging from 40 to 90 years with 99% males, 91% Caucasian, and had COPD with a mean pre-bronchodilator FEV_1 percent predicted of 36% (range = 8% to 93%). Patients were permitted to use respiratory medications (including short-acting and long-acting beta-agonists, inhaled and systemic steroids, and theophyllines) other than inhaled anticholinergics. In the 6-month trial, the co-primary endpoints were the proportion of patients with COPD exacerbation and the proportion of patients with hospitalization due to COPD exacerbation. SPIRIVA HandiHaler significantly reduced the proportion of COPD patients who experienced exacerbations compared to placebo (27.9% vs 32.3%, respectively; Odds Ratio (OR) (tiotropium/placebo) = 0.81; 95% CI = 0.66, 0.99; p = 0.037). The proportion of patients with hospitalization due to COPD exacerbations in patients who used SPIRIVA HandiHaler compared to placebo was 7.0% vs 9.5%, respectively; OR = 0.72; 95% CI = 0.51, 1.01; p = 0.056.

Exacerbations were evaluated as a secondary outcome in the 4-year multicenter trial. In this trial, COPD exacerbations were defined as an increase or new onset of more than one of the following respiratory symptoms (cough, sputum, sputum purulence, wheezing, dyspnea) with a duration of three or more days requiring treatment with antibiotics and/or systemic (oral, intramuscular or intravenous) steroids. SPIRIVA HandiHaler significantly reduced the risk of an exacerbation by 14% (Hazard Ratio (HR) = 0.86; 95% CI = 0.81, 0.91; p<0.001) and reduced the risk of exacerbation-related hospitalization by 14% (HR = 0.86; 95% CI = 0.78, 0.95; p<0.002) compared to placebo. The median time to first exacerbation was delayed from 12.5 months (95% CI = 11.5, 13.8) in the placebo group to 16.7 months (95% CI = 14.9, 17.9) in the SPIRIVA HandiHaler group.

16 HOW SUPPLIED/STORAGE AND HANDLING

SPIRIVA HandiHaler consists of SPIRIVA capsules and the HandiHaler device. SPIRIVA capsules contain 18 mcg of tiotropium- and are light green, with the Boehringer Ingelheim company logo on the SPIRIVA capsule cap and TI 01 on the SPIRIVA capsule body, or vice versa.

The HandiHaler device is gray colored with a green piercing button. It is imprinted with SPIRIVA HandiHaler (tiotropium bromide inhalation powder), the Boehringer Ingelheim company logo, and the Pfizer company logo. It is also imprinted to indicate that SPIRIVA capsules should not be stored in the HandiHaler device and that the HandiHaler device is only to be used with SPIRIVA capsules.

SPIRIVA capsules are packaged in an aluminum/aluminum blister card and joined along a perforated-cut line. SPIRIVA capsules should always be stored in the blister and only removed immediately before use. The drug should be used immediately after the packaging over an individual SPIRIVA capsule is opened.

The following packages are available:

- carton containing 5 SPIRIVA capsules (1 unit-dose blister card) and 1 HandiHaler device (NDC 0597-0075-75)
- carton containing 30 SPIRIVA capsules (3 unit-dose blister cards) and 1 HandiHaler device (NDC 0597-0075-41)
- carton containing 90 SPIRIVA capsules (9 unit-dose blister cards) and 1 HandiHaler device (NDC 0597-0075-47)

Storage

Store at 25°C (77°F); excursions permitted to 15°–30°C (59°–86°F) [see USP Controlled Room Temperature].

The SPIRIVA capsules should not be exposed to extreme temperature or moisture. Do not store SPIRIVA capsules in the HandiHaler device.

17 PATIENT COUNSELING INFORMATION

See FDA-approved Patient Labeling (17.6)

17.1 Instructions for Administering SPIRIVA HandiHaler

It is important for patients to understand how to correctly administer SPIRIVA capsules using the HandiHaler device [*see Patient Counseling Information (17.6)*]. Patients should be instructed that SPIRIVA capsules should only be administered via the HandiHaler device and the HandiHaler device should not be used for administering other medications. **The contents of SPIRIVA capsules are for oral inhalation only and must not be swallowed**.

SPIRIVA capsules should always be stored in sealed blisters. Only one SPIRIVA capsule should be removed immediately before use~~,~~ or its effectiveness may be reduced. Additional SPIRIVA capsules that are exposed to air (i.e., not intended for immediate use) should be discarded.

17.2 Paradoxical Bronchospasm

Patients should be informed that SPIRIVA HandiHaler can produce paradoxical bronchospasm. If paradoxical bronchospasm occurs, patients should discontinue SPIRIVA HandiHaler.

17.3 Urinary Retention

Difficulty passing urine and dysuria may be symptoms of new or worsening prostatic hyperplasia or bladder outlet obstruction. Patients should be instructed to consult a physician immediately should any of these signs or symptoms develop.

17.4 Visual Effects

Eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema may be signs of acute narrow-angle glaucoma. Patients should be told to consult a physician immediately should any of these signs and symptoms develop. Miotic eye drops alone are not considered to be effective treatment.

Patients should be told that care must be taken not to allow the powder to enter into the eyes as this may cause blurring of vision and pupil dilation.

17.5 Acute Exacerbation

Patients should understand that SPIRIVA HandiHaler is a once-daily maintenance bronchodilator and should not be used for immediate relief of breathing problems, i.e., as a rescue medication.

17.6 FDA-approved Patient Labeling

Patient Information and Patient's Instructions for Use are supplied as tear-off leaflets following the full prescribing information and should be dispensed with each new prescription and refill.

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SPIRIVA® (tiotropium bromide inhalation powder) is covered by U.S. Patent Nos. RE38,912, RE39,820, 5,478,578, 6,777,423, 6,908,928, ~~and~~ 7,070,800 and 7,309,707 with other patents pending. The HandiHaler® inhalation device is covered by U.S. Design Patent No. D355,029 with other patents pending.

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Patient Information

SPIRIVA® (speh REE vah) HandiHaler®
(tiotropium bromide inhalation powder)

Do NOT swallow SPIRIVA capsules.

After putting the SPIRIVA capsule into the HandiHaler device, breathe in your medicine through your mouth.

<u>Important Information:</u> Do not swallow SPIRIVA capsules. SPIRIVA capsules should only be used with the HandiHaler device. SPIRIVA HandiHaler should only be inhaled by mouth (oral inhalation).

Read the information that comes with your SPIRIVA HandiHaler before you start using it and each time you refill your prescription. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or your treatment.

What is SPIRIVA HandiHaler?

SPIRIVA HandiHaler is a prescription medicine that you use one time every day (a maintenance medicine) to control symptoms of chronic obstructive pulmonary disease (COPD). SPIRIVA HandiHaler helps make your lungs work better for 24 hours. SPIRIVA HandiHaler relaxes your airways and helps keep them open. You may start to feel like it is easier to breathe on the first day, but it may take longer for you to feel the full effects of the medicine. SPIRIVA HandiHaler works best and may help make it easier to breathe when you use it every day.

SPIRIVA HandiHaler also reduces the likelihood of flare-ups and worsening of COPD symptoms (COPD exacerbations). A COPD exacerbation is defined as an increase or new onset of more than one COPD symptom such as cough, mucus, shortness of breath, and wheezing that requires medicine beyond your rescue medicine.

SPIRIVA HandiHaler is **not** a rescue medicine and should not be used for treating sudden breathing problems. Your doctor may give you other medicine to use for sudden breathing problems.

SPIRIVA HandiHaler has not been studied in children.

Who should not take SPIRIVA HandiHaler?

Do not use SPIRIVA HandiHaler if you:

- are allergic to tiotropium. See the end of this leaflet for a complete list of ingredients.
- have had an allergic reaction to ipratropium (Atrovent®).

Allergic reactions may include itching, rash, or swelling of the lips, tongue or throat (trouble swallowing).

What should I tell my doctor before using SPIRIVA HandiHaler?

Before taking SPIRIVA HandiHaler, tell your doctor about all your medical conditions, including if you:

- have kidney problems.
- have glaucoma. SPIRIVA HandiHaler may make your glaucoma worse.
- have an enlarged prostate, problems passing urine, or a blockage in your bladder. SPIRIVA HandiHaler may make

these problems worse.

- are pregnant or plan to become pregnant. It is not known if SPIRIVA HandiHaler could harm your unborn baby.
- are breast-feeding or plan to breast-feed. It is not known if SPIRIVA HandiHaler passes into breast milk. You and your doctor will decide if SPIRIVA HandiHaler is right for you while you breast-feed.
- have a severe allergy to milk proteins. Ask your doctor if you are not sure.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines and eye drops, vitamins, and herbal supplements. Some of your other medicines or supplements may affect the way SPIRIVA HandiHaler works. SPIRIVA HandiHaler is an anticholinergic medicine. You should not take other anticholinergic medicines while using SPIRIVA HandiHaler, including ipratropium. Ask your doctor or pharmacist if you are not sure if one of your medicines is an anticholinergic.

Know the medicines you take. Keep a list of your medicines with you to show your doctor and pharmacist when you get a new medicine.

How should I take SPIRIVA HandiHaler?

- Use SPIRIVA HandiHaler exactly as prescribed. Use SPIRIVA HandiHaler one time every day.
- Read the "Patient's Instructions for Use" at the end of this leaflet before you use SPIRIVA HandiHaler. Talk with your doctor if you do not understand the instructions.
- **Do not swallow SPIRIVA capsules.**
- **Only use SPIRIVA capsules with the HandiHaler device.**
- **Do not use the HandiHaler device to take any other medicine**.
- SPIRIVA HandiHaler comes as a powder in a SPIRIVA capsule that fits the HandiHaler device. Each SPIRIVA capsule, containing only a small amount of SPIRIVA powder, is one full dose of medicine.
- Separate one blister from the blister card. Then take out one of the SPIRIVA capsules from the blister package right before you use it.
- After the capsule is pierced, take a complete dose of SPIRIVA HandiHaler by breathing in the powder by mouth two times, using the HandiHaler device (take 2 inhalations from one SPIRIVA capsule). See the "Patient's Instructions for Use" at the end of this leaflet.
- Throw away any SPIRIVA capsule that is not used right away after it is taken out of the blister package. Do not leave the SPIRIVA capsules open to air; they may not work as well.
- If you miss a dose, take it as soon as you remember. Do not use SPIRIVA HandiHaler more than one time every 24 hours.
- If you use more than your prescribed dose of SPIRIVA HandiHaler, call your doctor or a poison control center.

What should I avoid while using SPIRIVA HandiHaler?

Do not let the powder from the SPIRIVA capsule get into your eyes. Your vision may get blurry and the pupil in your eye may get larger (dilate). If this happens, call your doctor.

What are the possible side effects of SPIRIVA HandiHaler?

SPIRIVA HandiHaler can cause serious side effects. If you get any of the following side effects, stop taking SPIRIVA HandiHaler and get medical help right away.

- **Allergic reaction.** Symptoms may include**:** itching, rash, swelling of the lips, tongue, or throat (trouble swallowing)
- **Sudden narrowing and blockage of the airways into the lungs (bronchospasm).** Your breathing suddenly gets worse.
- **New or worsened increased pressure in the eyes (acute narrow-angle glaucoma).** Symptoms of acute narrow-angle glaucoma may include: eye pain, blurred vision, seeing halos (visual halos) or colored images along with red eyes.
- **New or worsened urinary retention.** Symptoms of blockage in your bladder and/or enlarged prostate may include: difficulty passing urine, painful urination.

Other side effects with SPIRIVA HandiHaler include:

- upper respiratory tract infection
- dry mouth
- sinus infection
- sore throat
- non-specific chest pain
- urinary tract infection

- indigestion
- runny nose
- constipation
- increased heart rate
- blurred vision

These are not all the possible side effects with SPIRIVA HandiHaler. Tell your doctor if you have any side effect that bothers you or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store SPIRIVA HandiHaler?

- **Do not store SPIRIVA capsules in the HandiHaler device.**
- Store SPIRIVA capsules in the sealed blister package at room temperature between 68°F–77°F (20°–25°C).
- Keep SPIRIVA capsules away from heat and cold (do not freeze).
- Store SPIRIVA capsules in a dry place. Throw away any unused SPIRIVA capsules that have been open to air.

Ask your doctor or pharmacist if you have any questions about storing your SPIRIVA capsules.

Keep SPIRIVA HandiHaler, SPIRIVA capsules, and all medicines out of the reach of children.

General information about SPIRIVA HandiHaler

Medicines are sometimes prescribed for purposes other than those listed in Patient Information leaflets. Do not use SPIRIVA HandiHaler for a purpose for which it has not been prescribed. Do not give SPIRIVA HandiHaler to other people even if they have the same symptoms that you have. It may harm them.

For more information about SPIRIVA HandiHaler, talk with your doctor. You can ask your doctor or pharmacist for information about SPIRIVA HandiHaler that is written for health professionals.

For more information about SPIRIVA HandiHaler, you may call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257 or (TTY) 1-800-459-9906.

What are the ingredients in SPIRIVA HandiHaler?

Active ingredient: tiotropium
Inactive ingredient: lactose monohydrate

What is COPD (Chronic Obstructive Pulmonary Disease)?

COPD is a serious lung disease that includes chronic bronchitis, emphysema, or both. Most COPD is caused by smoking. When you have COPD, your airways become narrow. So, air moves out of your lungs more slowly. This makes it hard to breathe.

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Patient's Instructions for Use

Spiriva® HandiHaler®
(tiotropium bromide inhalation powder)

Do NOT swallow SPIRIVA capsules.

Step 1: Put the SPIRIVA capsule into the HandiHaler device.
Step 2: Inhale the medicine through your mouth.

<u>Important Information:</u> Do not swallow SPIRIVA capsules. SPIRIVA capsules should only be used with the HandiHaler device. SPIRIVA HandiHaler should only be inhaled through your mouth (oral inhalation).

First read the Patient Information that comes with SPIRIVA HandiHaler for important information about using SPIRIVA HandiHaler.

Read these Patient's Instructions for Use before you start to use SPIRIVA HandiHaler and each time you refill your prescription. There may be new information.

For more information, ask your doctor or pharmacist.

SPIRIVA HandiHaler comes with SPIRIVA capsules and a HandiHaler device. The HandiHaler device is an inhalation device that is for use only with SPIRIVA capsules. Do not use the HandiHaler device to take any other medicine.

Becoming familiar with SPIRIVA HandiHaler:

Figure A

Remove the HandiHaler device from the pouch and become familiar with its components. (Figure A)

1. dust cap
2. mouthpiece
3. mouthpiece ridge
4. base
5. green piercing button
6. center chamber
7. air intake vents

Figure B

Each SPIRIVA capsule is packaged in a blister. Each blister can be separated from the blister card by tearing along the perforation. (Figure B)

Figure C

Do not open the SPIRIVA capsule before you insert it into the HandiHaler device. If you open the SPIRIVA capsule, it may not work. Each SPIRIVA capsule contains only a small amount of powder. (Figure C) This is one full dose. The product was designed this way.

How do I inhale the contents of the SPIRIVA capsule using the HandiHaler device?

Taking your dose of medicine using the HandiHaler device has four main steps:

1. **Open** the HandiHaler device and the blister
2. **Insert** the SPIRIVA capsule
3. **Press** the green piercing button
4. **Breathe in (inhale)** your medicine

(See below for details)

Opening the HandiHaler device:

Figure 1

1. Open the dust cap by pressing the green piercing button. (Figure 1)

Figure 2

Pull the dust cap upwards to expose the mouthpiece. (Figure 2)

Figure 3

Open the mouthpiece by pulling the mouthpiece ridge upwards away from the base. (Figure 3)

Removing a SPIRIVA capsule:

Figure 4

Before removing a SPIRIVA capsule from the blister, separate one of the blisters from the blister card by tearing along the perforation. (Figure 4)

Do not swallow SPIRIVA capsules.

Always store SPIRIVA capsules in the sealed blisters. Remove only one SPIRIVA capsule from the blister right before use. Do not store SPIRIVA capsules in the HandiHaler device. Inhale the contents of the SPIRIVA capsule using the HandiHaler device right away after the blister packaging of an individual SPIRIVA capsule is opened, or else it may not work as well.

Figure 5

Right before you are ready to use your SPIRIVA HandiHaler:

Bend back and forth one of the corners of the blister that has an arrow and then with your finger separate the aluminum foil layers. Carefully peel back the printed foil until you can see the whole SPIRIVA capsule. (Figure 5)

Turn the blister upside down and tip the SPIRIVA capsule out, tapping the back of the blister, if needed.

Do not cut the foil or use sharp instruments to take out the SPIRIVA capsule from the blister.

If more SPIRIVA capsules are opened to air, they should not be used and should be thrown away.

Inserting the SPIRIVA capsule into the HandiHaler device:

Figure 6

2. Insert (put) the SPIRIVA capsule in the center chamber of the HandiHaler device. It does not matter which end of the SPIRIVA capsule you put in the chamber. (Figure 6)

Figure 7

Close the mouthpiece **until you hear a click**, but leave the dust cap open. (Figure 7)

Be sure that you have the mouthpiece sitting firmly against the gray base.

Taking your dose using the HandiHaler device:

Figure 8

Hold the HandiHaler device with the mouthpiece upright. It is important that you hold the HandiHaler device in an upright position (Figure 8) when pressing the green piercing button.

3. Press the green piercing button until it is flat (flush) against the base, and release. This is how you make holes in the SPIRIVA capsule so that you get the medicine when you breathe in.

Do not press the green button more than one time.

Figure 9

Breathe out completely. (Figure 9)

Important: Do not breathe (exhale) into the mouthpiece of the HandiHaler device at any time.

Figure 10

4. **Breathe in (inhale)**
   - Hold the HandiHaler device by the gray base. Do not block the air intake vents.
   - Raise the HandiHaler device to your mouth and close your lips tightly around the mouthpiece.
   - **Keep your head in an upright position. The HandiHaler device should be in a horizontal position.** (Figure 10)
   - Breathe in **slowly and deeply** so that you **hear or feel the SPIRIVA capsule vibrate.**
   - Breathe in until your lungs are full.
   - Hold your breath as long as is comfortable and at the same time take the HandiHaler device out of your mouth. Breathe normally again.

To make sure you get the full dose, you must breathe out completely, and inhale again as in step 4 above (Figure 10). ***Do not press the green piercing button again.***

Figure 11

If you do not hear or feel the SPIRIVA capsule vibrate, **do not press the green piercing button again.** Instead, hold the HandiHaler device in an upright position and tap the HandiHaler device gently on a table. (Figure 11)

Check to see that the mouthpiece is completely closed. Then, breathe in again – slowly and deeply.

If you still do not hear or feel the SPIRIVA capsule vibrate after repeating the above steps, throw away the SPIRIVA capsule. Open the base by lifting the green piercing button and check the center chamber for pieces of the SPIRIVA capsule (SPIRIVA capsule fragments). SPIRIVA capsule fragments in the center chamber can cause a SPIRIVA capsule not to vibrate. Turn the HandiHaler device upside down and gently tap to remove the SPIRIVA capsule fragments. Call your doctor for instructions.

Figure 12

After you finish taking your daily dose of SPIRIVA HandiHaler, open the mouthpiece again. Tip out the used SPIRIVA capsule and throw it away. (Figure 12)

Figure 13

Close the mouthpiece and dust cap for storage of your HandiHaler device. (Figure 13)

Do not store used or unused SPIRIVA capsules in the HandiHaler device.

When and how should I clean my HandiHaler device?

Figure 14

Clean the HandiHaler device one time each month or as needed. (Figure 14)

- Open the dust cap and mouthpiece.
- Open the base by lifting the green piercing button.
- Look at the center chamber for SPIRIVA capsule fragments or powder residue.
- Rinse the HandiHaler device with warm water. Check that any powder buildup or SPIRIVA capsule fragments are removed.
- Do not use cleaning agents or detergents.
- Do not place the HandiHaler device in the dishwasher for cleaning.
- Dry the HandiHaler device well by tipping the excess water out on a paper towel. Air-dry afterwards, leaving the dust cap, mouthpiece, and base open.
- Do not use a hair dryer to dry the HandiHaler device.
- **It takes 24 hours to air dry, so clean the HandiHaler device right after you use it so that it will be ready for your next dose.**
- Do not use the HandiHaler device when it is wet. If needed, you may clean the outside of the mouthpiece with a clean damp cloth.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-395/S029

SUMMARY REVIEW

Summary Review of Regulatory Action

Date	December 17, 2009
From	Sally Seymour, MD, Deputy Director for Safety
From	Badrul Chowdhury, MD, PhD, Division Director
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA# 21-395, SE8, S29
Applicant	Boehringer Ingelheim
Date of Submission	November 17, 2008
PDUFA Goal Date	December 17, 2009
Proprietary Name / Established (USAN) names	Spiriva HandiHaler Tiotropium bromide inhalation powder
Dosage forms / Strength	Inhalation powder
Proposed Indication(s)	Labeling claim and indication for reduction in COPD exacerbations; labeling claim for the long-term effects on lung function.
Recommended:	Approval

1. Introduction

Spiriva HandiHaler is a long acting anticholinergic that was approved on January 30, 2004, for the long term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. On November 17, 2008, Boehringer Ingelheim (BI) submitted an efficacy supplement for Spiriva HandiHaler to add the following labeling claims to the Clinical Studies Section of the product label:

- reduction in COPD exacerbations
- description of long-term effects on lung function
- reduction in mortality
- reduction in respiratory failure

To support the proposed labeling claims, BI submitted the results of a 4-year, placebo-controlled, parallel group trial in approximately 6000 patients with moderate-severe COPD. The trial is called Understanding Potential Long-term Impacts on Function with Tiotropium or UPLIFT (Study 205.235). In addition, BI referenced another clinical trial with Spiriva HandiHaler, a VA study (Study 205.266) that had been submitted and reviewed under NDA# 21-936 (Spiriva Respimat) to support the COPD exacerbation claim. Since Spiriva HandiHaler is a currently approved drug product, there were no new CMC, pharmacology/toxicology, or clinical pharmacology data submitted in this efficacy supplement.

On July 22, 2009, BI amended this efficacy supplement to remove the mortality claim to maintain consistency with global labeling. According to BI, there was no new Spiriva HandiHaler data contributing to this decision. The original PDUFA date for this application was September 17, 2009. However, on September 10, 2009, BI submitted the study report for an epidemiological study with Spiriva HandiHaler from Erasmus University. This additional

study report was considered a major amendment and the PDUFA date was extended until December 17, 2009. A Pulmonary Allergy Drugs Advisory Committee (PADAC) meeting was held on November 19, 2009, to discuss the COPD exacerbation claim as well as some safety concerns regarding stroke, myocardial infarction (MI), and cardiovascular death.

This memo will provide an overview of the Spiriva HandiHaler application with a focus on issues that warrant further discussion, including the COPD exacerbation claim, the safety issues of stroke, MI, and cardiovascular death, and the results of the PADAC meeting on November 19, 2009. This memo will also provide some safety information with a related investigational product, Spiriva Respimat, which is an inhalation solution of tiotropium delivered via a novel inhaler, the Respimat, currently under development by BI.

2. Background

Spiriva HandiHaler consists of tiotropium bromide in a dry powder formulation contained in capsules and administered with the HandiHaler inhalation device. Spiriva HandiHaler was approved on January 30, 2004, for the long term, once-daily, maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema. Tiotropium bromide is a long acting anticholinergic and is a bronchodilator medication. This efficacy supplement is for labeling claims in the Clinical Studies section of the product label. Only one other medication, Advair Diskus, currently has a labeling claim and indication for a reduction in COPD exacerbations. A new inhalation solution formulation of tiotropium bromide, Spiriva Respimat, is under development and some safety information from that program will be included in this memo. It is also important to note a related product, ipratropium bromide, which is a short acting anticholinergic that has been approved as a bronchodilator for patients with COPD since 1986. The safety profile of tiotropium is well-defined with known side effects related to the anticholinergic effects including dry mouth, constipation, and urinary retention. However, it is not unusual for safety signals to be identified post-marketing and recently several safety concerns with Spiriva HandiHaler have been raised as outlined below.

In November 2007, BI voluntarily submitted a document to the Agency that described a potential stroke safety signal with tiotropium. As part of routine safety monitoring, BI pooled safety data from clinical trials with tiotropium and noted a numerical increase in stroke adverse events. The pooled data included results from 29 controlled clinical trials – 25 with Spiriva HandiHaler and 4 with Spiriva Respimat, which reflected 13,544 patients contributing 4572 person years of exposure to tiotropium. Based upon BI's analysis, there was a numerical increase in the risk ratio for stroke of 1.37 (95% CI: 0.73, 2.56) with use of tiotropium. Although there is uncertainty of the risk, because of the seriousness of stroke and the Agency's commitment to inform the public about ongoing safety reviews, on March 18, 2008, the Agency released an Early Communication about an Ongoing Safety Review of Tiotropium (marketed as Spiriva HandiHaler) that described the preliminary information regarding stroke[1].

[1]http://www fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm070651.htm

In September 2008, a meta-analysis was published in the *Journal of the American Medical Association* evaluating cardiovascular risk of inhaled anticholinergics[2]. The inhaled anticholinergics included in the analysis were tiotropium and ipratropium. The authors analyzed 17 randomized, controlled clinical trials for the primary combined outcome of cardiovascular death, myocardial infarction (MI), or stroke, and showed a relative risk of 1.58 (95% CI 1.21, 2.06) for inhaled anticholinergics compared to placebo and concluded that inhaled anticholinergics are associated with a significantly increased risk of cardiovascular death, MI, or stroke.

Also of interest is the Lung Health Study, which the NIH initiated in 1986 to evaluate whether smoking intervention and use of inhaled bronchodilator (ipratropium bromide) could slow the rate of decline in FEV_1 in smokers. The Lung Health Study was a large, multicenter, randomized clinical trial, sponsored in 5887 smokers[3]. Patients were randomized to smoking intervention plus ipratropium, smoking intervention plus placebo, or usual care and were followed for years. One notable finding was a potential signal of an increase in cardiovascular deaths in the ipratropium group compared to the placebo group. However, there was no dose effect and the results were not adjusted for multiplicity. In addition, BI raised the issue that cardiovascular deaths were primarily noted in patients who were not compliant with study medication[4]. While the Lung Health Study was conducted with ipratropium, it is of interest because it is included in some of the published meta-analyses of inhaled anticholinergics.

Of relevance is NDA# 21-936 for Spiriva Respimat (submitted November 16, 2007), which is a new formulation of tiotropium bromide, an inhalation solution, delivered via a novel inhaler, the Respimat. This NDA is relevant because: 1) a mortality imbalance was noted in the phase 3 clinical trials with Spiriva Respimat and 2) a 6 month VA study with Spiriva HandiHaler was submitted in this NDA and provides data regarding COPD exacerbations. A Complete Response (CR) action was taken on this NDA due the mortality imbalance in the phase 3 clinical trials, which will be described in more detail in Section 8.

3. CMC/Device

There was no new CMC information submitted in this efficacy supplement because Spiriva HandiHaler is an approved product. However, a PLR version of the label was submitted and comments from the CMC were incorporated into the agreed upon labeling.

4. Nonclinical Pharmacology/Toxicology

There was no new nonclinical information submitted in this efficacy supplement because Spiriva HandiHaler is an approved product. However, a PLR version of the label was

[2] Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease – A systematic review and meta-analysis. JAMA 2008; 300(12): 1439-1450. Correction: JAMA 2009; 301(12): 1227-1230.
[3] Anthonisen, MR, Connett JE, et al. Hospitalizations and mortality in the Lung Health Study. Am J Respir Crit Care Med 2002; 166: 333-339.
[4] Lanes S, Golisch W, Mikl J. Correspondence - Ipratropium and lung health study. Am J Respir Crit Care Med 2003; 167(5): 801-802.

submitted and comments from the pharmacology/toxicology team were incorporated into the agreed upon labeling.

5. Clinical Pharmacology/Biopharmaceutics

There was no new clinical pharmacology information submitted in this efficacy supplement. However, a PLR version of the label was submitted and comments from the clinical pharmacology team were incorporated into the agreed upon labeling.

6. Clinical Microbiology

There was no clinical microbiology information submitted in this efficacy supplement.

7. Clinical/Statistical- Efficacy

7a. Overview of the Clinical Program

BI proposes to add the following labeling claims to the Spiriva HandiHaler product label: a) reduction in COPD exacerbations; b) description of long-term effects on lung function; and c) reduction in respiratory failure. To support the proposed labeling claims, BI submitted the results of a 4-year, placebo-controlled, parallel group trial in approximately 6000 patients with moderate-severe COPD. The trial is called Understanding Potential Long-term Impacts on Function with Tiotropium or UPLIFT (Study 205.235). In addition, BI referenced another clinical trial, a VA study (Study 205.266) that had been submitted and reviewed under NDA# 21-936 (Spiriva Respimat) to support the COPD exacerbation claim. The focus of the efficacy discussion will be UPLIFT and the VA Study will be summarized briefly.

Table 1 Summary of Clinical Program

Study No.	Description	Patients	Design	Dose	Duration	Endpoints
205.235 Worldwide Jan 2003- Feb 2008	P4 efficacy trial – Disease progression,COPD exacerbations **UPLIFT**	5992 patients with COPD	R, DB, PC	18 mcg Spiriva HandiHaler QD Placebo HandiHaler QD	4 years	-Rate of decline trough FEV1 - COPD exacerbations
205.266 United States Sept 2001- Feb 2003	P4 efficacy trial – COPD exacerbations **VA Study**	1829 patients with COPD	R, DB, PC	18 mcg Spiriva HandiHaler QD Placebo HandiHaler QD	6 months	- COPD exacerbations

7b. Design and Conduct of the Studies

<u>UPLIFT Study Design</u>

UPLIFT (Study 205.235) was a 4 year, randomized, double-blind, parallel group, placebo controlled trial to assess the rate of decline of lung function with Spiriva HandiHaler in patients with COPD. Patients were enrolled with a diagnosis of moderate to severe COPD, with the following pertinent entry criteria: a) 40 years of age and older; b) $FEV_1/FVC \leq 70\%$ and $FEV_1 \leq 70\%$; and c) current or ex-smokers with a smoking history of > 10 years. Patients

with a history of asthma or who were using oral corticosteroids in excess of 10mg of prednisone per day were excluded. Other pertinent exclusion criteria included: a) recent history of myocardial infarction; b) unstable or life-threatening cardiac arrhythmia; c) narrow angle glaucoma; and d) moderate to severe renal impairment. Unlike other clinical trials with Spiriva HandiHaler, many concomitant medications were allowed, including long-acting $beta_2$ adrenergic agonists, inhaled corticosteroids, chronic oxygen, and theophylline. The only medications not allowed during the treatment period were anticholinergic agents.

There were two co-primary endpoints: 1) the yearly rate of decline in trough FEV1 from day 30 (steady state) until completion of double-blind treatment and 2) the yearly rate in decline in FEV1 measured 90 minutes after inhalation of study drug and ipratropium (and 30 minutes after inhalation of salbutamol) from day 30 (steady state) until completion of double-blind treatment. Pertinent secondary endpoints included time to first COPD exacerbation, number of COPD exacerbations, and other types of COPD exacerbation variables as well as yearly rate of decline in St. George's Respiratory Questionnaire (SGRQ). Safety endpoints included adverse events and all cause mortality.

BI seeks a labeling claim for reduction of exacerbations in the product label. There is no standard, well-accepted definition of COPD exacerbation.[5] In Study 205.235, COPD exacerbation was defined as a an increase or new onset of more than one of the following of respiratory symptoms (cough, sputum, sputum purulence, wheezing, dyspnea) with a duration of three days of more requiring treatment with antibiotics and/or systemic steroids. Exacerbations were categorized as mild, moderate, and severe:

- mild – treated at home without visit to health care facility
- moderate – visit to outpatient facility or ER
- severe – hospital admission or ER visit greater than 24 hours

Clinic visits were held every 3 months, during which adverse events were recorded. PFTs were measured every 6 months. Patients recorded COPD exacerbations and hospitalizations. Study personnel reviewed the diaries during study visits and recorded exacerbations and hospitalizations on the case report form.

There were two protocol amendments that are important to note. There was an amendment to specify a Mortality Adjudication Committee (MAC) that centrally adjudicated all reported deaths. The committee had 3 members external to BI and not involved in the conduct of the study. In addition, BI amended the protocol for UPLIFT to collect vital status data for all prematurely discontinued patients.

<u>VA Study Design</u>

The VA Study (Study 205.266) was a phase 4, 6 month, randomized, double-blind, parallel group, placebo controlled trial in a Veteran's Affairs setting. The enrollment criteria were similar to UPLIFT. There were two co-primary endpoints: 1) the proportion of patients who experienced a COPD exacerbation and 2) the proportion of patients with a hospitalization associated with a COPD exacerbation during the 6 month period. In Study 205.266, COPD

[5] Cazzola M, MacNee W, et. al. Outcomes for COPD pharmacological trials: from lung function to biomarkers. *Eur Respir J* 2008; 31: 416-418.

exacerbation was defined as a complex of respiratory events/symptoms with a duration of three days of more requiring a change in treatment. A complex of respiratory events/symptoms means ≥ 2 of the following (increase of symptom or new onset): cough, sputum, wheezing, dyspnea, or chest tightness. A change in treatment included antibiotics and/or systemic corticosteroids and/or hospitalization. Exacerbations were categorized as mild, moderate, and severe:

- mild – treatment with antibiotics, no visit to health care facility
- moderate – visit to outpatient facility or treatment with corticosteroids
- severe – hospital admission or ER visit greater than 24 hours

COPD Exacerbation Definition

The definition of COPD exacerbation used in the VA Study and UPLIFT are slightly different. Although there is no well-accepted definition of COPD exacerbation, the definition used in both clinical trials is reasonable as it includes both symptoms and treatment and is consistent with definitions in the literature. One other product (Advair Diskus) has a labeling claim (and indication) for the reduction of COPD exacerbations, thus there is a regulatory pathway for this type of claim. While the definition used by BI is not exactly the same as used in the Advair clinical trials, the definition has many of the same elements.

7c. Efficacy Findings and Conclusions

In general, patients enrolled in UPLIFT and the VA Study were primarily white males with a mean age around 65 to 68 years and a baseline pre-bronchodilator FEV_1 of approximately 1 liter (~36% to 39% predicted). The demographic profile was generally balanced between treatment groups in the two trials. There was a difference in patient disposition between treatment groups because the placebo group had a higher percentage of patients who discontinued (Spiriva HandiHaler 37%, placebo 45%), the primary reason being worsening of COPD.

UPLIFT

Long Term Effects on Lung Function

The following table shows the results for the co-primary endpoints in UPLIFT. As shown below, there was no significant difference in rate of decline of FEV1 between the Spiriva HandiHaler and placebo treatment groups.

Table 2 Rate of Decline in Pre- and Post- Bronchodilator FEV1 in Study 205.235 (UPLIFT)

Mean	**Spiriva HandiHaler** ml/year	**Placebo** ml/year	**Difference** ml/year	**p value**
Pre-Bronchodilator FEV1	30 n=2557	30 n=2413	0	0.95
Post-Bronchodilator FEV1	42 n=2554	40 n=2410	2	0.21

The pre-bronchodilator trough FEV_1 over time is shown in the following figure. Although there is no difference in the rate of decline, there is a difference in trough FEV_1 between

treatment groups that is consistent over the 4 year period. The overall mean difference was 94 mL for pre-bronchodilator FEV_1 and 57 mL for post-bronchodilator FEV_1.

Figure 1 Mean Pre-Bronchodilator FEV1 in UPLIFT (Study 205.235)

Repeated measure ANOVA was used to estimate means. Means are adjusted for baseline measurements. Baseline trough FEV_1 (observed mean) = 1.116. Patients with ≥3 acceptable PFTs after day 30 and non-missing baseline value were included in the analysis.

BI performed subgroup analyses based upon age, gender, smoking status, concomitant medication use, race, BMI, and GOLD stage. It is notable, that based upon subgroup analysis of smokers (ex, sustained, intermittent) sustained smokers had the highest rate of decline of FEV1 (51 ml/yr) and sustained ex-smokers had the lowest rate of decline of FEV1 (23 ml/yr). BI noted that 72 and 74% of patients used LABA and ICS, respectively, and this may have confounded the effects of Spiriva HandiHaler.

The Applicant proposes to describe the PFT results of UPLIFT in the product label and state that the results for the co-primary endpoints were not significantly different between treatment groups and that the Spiriva HandiHaler group had sustained improvement in trough FEV1 throughout the 4 years of the study. This claim regarding sustained improvement is consistent with the current efficacy data described in the product label. Overall, the description of the results is accurate and is supported by the data submitted in this efficacy supplement.

COPD Exacerbations

The time to the first COPD exacerbation and time to first COPD exacerbation leading to hospitalization were key secondary endpoints in UPLIFT. From a statistical standpoint, since the primary endpoints did not win, using a step-down approach secondary endpoints should not be considered. The statistical team raised concern regarding support for the COPD exacerbation claim regarding this issue. However, COPD exacerbation is one of only several key secondary efficacy variables in this large, long-term trial and there is independent data for COPD exacerbations in the VA Study (described below). In addition, the results for the key secondary efficacy endpoints related to exacerbation are quite robust, thus, the clinical team believes it is reasonable to consider the COPD exacerbation claim.

The table below shows the pre-specified secondary efficacy endpoints of time to first COPD exacerbation and time to first COPD exacerbation leading to hospitalization (shaded) in

UPLIFT. Based on the estimated hazard ratio (using Cox model), there is evidence that treatment with Spiriva HandiHaler reduced the risk of COPD exacerbation by 14% compared with placebo. Furthermore, based on Kaplan-Meier estimates, the median time to first COPD exacerbation in the Spiriva HandiHaler group is 16.7 (95% CI 14.9, 17.9) months compared to 12.5 months (95% CI 11.5, 13.8) in the placebo group. This implies a four-month delay in the time to first exacerbation in the tiotropium-treated patients compared to placebo-treated patients.

Table 3 Select COPD Exacerbation Endpoints in UPLIFT (Study 205.235)

	Spiriva HandiHaler N=3006	Placebo N=2986	Ratio (p value) [95% CI]
Median time to first exacerbation (months)	16.7	12.5	0.86 (<0.0001) [0.81, 0.91]
Time to first exacerbation leading to hospitalization in 25% patients (months)	35.9	28.6	0.86 (0.0024) [0.78, 0.95]
Exacerbations per patient year*	0.73	0.85	0.86 (<0.0001) [0.81, 0.91]
Patients with exacerbations (%)	67	68	not calculated (0.35)
Patients hospitalized due to exacerbations	25	27	not calculated (0.18)

*Poisson model with adjustment for overdispersion

Other aspects of COPD exacerbation, including exacerbations per patient year, time to first exacerbation treated with steroids, time to first exacerbation treated with antibiotics, and number of exacerbation days were all in favor of Spiriva HandiHaler. However, the number of COPD exacerbations leading to hospitalization per patient year and number of days hospitalized due to exacerbation per patient year were not statistically significant.

VA Study

The following table shows the results for the co-primary endpoints (shaded) and some of the key secondary endpoints related to COPD exacerbation. The co-primary endpoints were the proportion of patients who experienced a COPD exacerbation and the proportion of patients with a hospitalization associated with a COPD exacerbation during the 6 month period.

Table 4 COPD Exacerbation Endpoints in VA Study (Study 205.266)

	Spiriva HandiHaler N=914	Placebo N=915	Odds† or Rate‡ Ratio (p value)
Proportion of patients with exacerbation (%)	27.9	32.3	0.81† (0.037)
Proportion of patients with hospitalizations due to exacerbation (%)	7.0	9.5	0.72† (0.056)
Median time to first COPD exacerbation (months)			0.83‡ (0.04)
Exacerbations per patient year*	0.71	0.88	0.81‡ (0.037)
Antibiotic days per patient year*	6.5	7.9	0.83‡ (0.105)
Corticosteroid days per patient year*	4.4	5.3	0.85‡ (0.375)

* adjusted for center and corrected for overdispersion, thus results are different than what is reported in the study report for Study 205.266

The second co-primary endpoint was not statistically significant. In this study, sequential testing was conducted only on the 'co-primary' endpoints. Multiplicity correction was not pre-specified in the secondary endpoints. The secondary endpoints related to COPD exacerbation were numerically supportive but were not uniformly statistically significant as shown in the table above. It is important to address the analysis of the data for the number of COPD exacerbations, antibiotic days, and corticosteroid days. Ideally, analysis of this data should account for the follow up time and the between-patient variability in the data[6]. Correction for follow up time or exposure is important as there is differential discontinuation between the active and placebo groups. Correction for over dispersion in the data is important because some patients may have different rates of events. Because of this issue, the results shown above are corrected for over-dispersion.

It is important to mention that there was a difference of opinion amongst the statistical review team with regards to this efficacy supplement. The issue in dispute was primarily regarding the COPD exacerbation claim. Three reviews were written by the statistical team, Dr. Joan Buenconsejo (primary reviewer), Dr. Qian Li (secondary reviewer), and Dr. Thomas Permutt (tertiary reviewer). Both Dr. Li and Dr. Buenconsejo contributed briefing documents for the PADAC background package so that the differing viewpoints were shared with the committee. Dr. Buenconsejo and Dr. Permutt both agreed that the COPD exacerbation claim in UPLIFT should not be considered statistically significant because of the pre-specified statistical analysis plan. Dr. Li noted that there because of collective evidence, including strong nominal significance, corroboration from the VA study, and the claim is related to known effects of tiotropium, the COPD exacerbation claim is supported. There was also some disagreement with regards to interpretation of the mortality data based upon differing interpretations of the hazard function. In general, however, all three statistical reviewers found the evidence for mortality equivocal.

PADAC

In both studies, there are statistical issues with consideration of an exacerbation claim. Because of this issue and other safety concerns, the UPLIFT and VA study data were discussed at a Pulmonary Allergy Drugs Advisory Committee (PADAC) meeting on November 19, 2009. One of the issues discussed was the adequacy of the data to support a COPD exacerbation claim. The AC members voted (11 yes, 1 no) that the data from UPLIFT and the VA study provided substantial and convincing evidence to support the claim that Spiriva HandiHaler reduces COPD exacerbations.

Efficacy Summary

In summary, the results of UPLIFT (Study 205.235) and the VA Study (Study 205.266) are supportive of a COPD exacerbation claim. BI proposes a claim regarding a delay in time to first exacerbation in the VA Study and a reduction in exacerbations and exacerbation related hospitalization in UPLIFT. In both studies, there are statistical issues with consideration of an exacerbation claim. However, the totality of the data is adequate to support a COPD exacerbation claim. This is consistent with the advice from the PADAC. BI has chosen different COPD exacerbation variables from each clinical trial to include in the label. The

[6] Suissa, S. Statistical treatment of exacerbations in therapeutic trials of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2006; 173: 842-846.

exact wording of the claim should be based upon the pre-specified primary and/or key secondary endpoints and should include the results whether statistically significant or not. In addition, the results support an indication for a reduction in COPD exacerbations, which would be consistent with the labeling for Advair Diskus for COPD.

In addition, the Applicant proposes to describe the PFT results of UPLIFT in the product label and state that the results for the co-primary endpoints were not significantly different between treatment groups and that the Spiriva HandiHaler group had sustained improvement in trough FEV1 throughout the 4 years of the study. This claim regarding sustained improvement is consistent with the current efficacy data described in the product label. Overall, the description of the results is accurate and is supported by the data submitted in this efficacy supplement.

8. Safety

8a. Safety Database

Since Spiriva HandiHaler is approved for patients with COPD, the safety of Spiriva HandiHaler in this population has been previously established. However, safety concerns regarding stroke, cardiovascular death, and MI have been raised recently as briefly described in Section 2. As UPLIFT is a large, 4 year, placebo controlled clinical trial in patients with COPD, the safety data are important to discuss, especially with regards to the aforementioned safety concerns. In the discussion of mortality data from UPLIFT, some data from the Spiriva Respimat program will be incorporated for completeness. UPLIFT provides a substantial safety database with a total of 5993 patients randomized: 3006 to Spiriva HandiHaler and 2986 to placebo (of note, one patient was randomized twice). With the submission of UPLIFT, the safety database for Spiriva HandiHaler is doubled.

In the VA Study a total of 1829 patients were randomized: 914 to Spiriva HandiHaler and 915 to placebo. While the VA Study provides data regarding the proposed COPD exacerbation claim, only a very brief summary of safety from that study is included because the safety assessments were not as rigorous.

8b. Safety Findings and Conclusions

<u>VA Study</u>

In the VA Study (Study 205.266), limited safety monitoring was performed in that only serious adverse events (SAEs) were reported. Non-serious adverse events, laboratories, and ECGs were not collected. This limited safety monitoring is acceptable because Spiriva HandiHaler is an approved drug product for patients with COPD. A total of 1829 patients were randomized: 914 to Spiriva HandiHaler and 915 to placebo. There was a difference in discontinuation between Spiriva HandiHaler (16%) vs. placebo (27%), primarily secondary to adverse events and worsening of COPD. There were a few more deaths in the Spiriva HandiHaler group (22, 2.4%) compared to placebo (19, 2.1%); however, the cause of death was generally balanced and the rate was not adjusted for the difference in exposure. The most common SAEs were COPD exacerbation, pneumonia, bronchitis, myocardial infarction, and congestive heart failure. These SAEs were generally balanced with the exception of bronchitis

which was more common in the Spiriva HandiHaler group (1.1%) compared to placebo (0.5%). These common SAEs are not unexpected in the COPD population. The safety data (SAEs) from Study 205.266 did not identify any new safety signal for Spiriva HandiHaler.

UPLIFT

In UPLIFT, throughout the four year treatment period, patients were seen approximately every 3 months. Adverse event (AE) data was collected during the treatment period and up to 30 days following the treatment period. Of the 5993 randomized, more patients discontinued in the placebo group (45%) compared to the tiotropium group (37%). The main reason for discontinuation was adverse events, the most common being worsening of COPD. The difference in discontinuation led to a difference in exposure between treatment groups - mean of 1128 days in the tiotropium group and mean of 1033 days in the placebo group. In terms of pertinent protocol violations 3.8% of patients in each treatment group used anticholinergic medications for at least two consecutive visits, while 17% of patients in both treatment groups use a short acting inhaled anticholinergic at least once during the treatment period. This may reflect use during a COPD exacerbation.

Before discussing the safety data from UPLIFT, it is important to note that BI collected safety data for the 4 year (1440 Days) treatment period and up to 30 days following the end of treatment, for a total of 1470 Days. For safety analyses, BI specified using the 1470 Day safety data. Overall AE results are shown in the table below, but these data do not take into account the difference in exposure between treatment groups.

Table 5 Adverse Events in UPLIFT (Study 205.235)*

	Tiotropium n = 3006	**Placebo n = 2986**
Any AE	93%	92%
AE leading to discontinuation	21%	25%
Serious AEs	52%	50%
Fatal Events	13%	14%

*4 year treatment period (1440 days) + 30 day washout

The most common AE was COPD exacerbation, which was more frequent in the placebo group. BI determined the rate ratio for Spiriva HandiHaler/placebo for AEs adjusting for exposure in patient years. For COPD exacerbation, the rate ratio was 0.84 (95% CI: 0.79, 0.89). The reduction in COPD exacerbation AEs is consistent with the efficacy data for COPD exacerbations. The following AEs were noted to have a rate ratio > 1 that was statistically significant: dry mouth (1.80, 95% CI: 1.37, 2.36) and insomnia (1.34, 95% CI: 1.02, 1.75). BI noted a significant decrease in respiratory failure with a rate ratio of 0.67 (95% CI 0.51, 0.89) and seeks a labeling claim for a reduction in respiratory failure. However, because respiratory failure was not a pre-specified event with an agreed upon definition and respiratory failure is one of a multitude of safety endpoints evaluated, a labeling claim is not supported.

In terms of SAEs, respiratory system disorders were the most common SAEs, primarily COPD exacerbations, which favored Spiriva HandiHaler (rate ratio of 0.84, 95% CI: 0.76, 0.94). Dr. Michele noted that intestinal obstruction adverse events occurred with a rate ratio of 5.55 (95%

CI: 1.24, 24.8) and for SAEs a rate ratio of 4.16 (95% CI: 0.90, 19.3). Intestinal obstruction may be related to the anticholinergic effects of tiotropium. Intestinal obstruction is listed in the current product label for Spiriva HandiHaler under the post-marketing adverse event section.

Stroke

In November 2007, BI voluntarily submitted a pooled analysis of 29 placebo controlled clinical studies with Spiriva HandiHaler (25 clinical trials) and Spiriva Respimat (4 clinical trials), which was performed as part of routine safety assessment. BI noted a numerical increase in risk of stroke (RR 1.37, 95% CI 0.73-2.56) in patients treated with tiotropium compared to placebo. These data reflected 13,544 patients contributing 4572 person years of exposure to tiotropium, but was not adjusted for multiplicity.

With the submission of UPLIFT, the safety database for Spiriva HandiHaler is doubled. Preferred terms for stroke were grouped similar to the grouping of terms for the pooled analysis. Adjusting for exposure in patient years, the hazard ratios for stroke adverse events in UPLIFT are as follows: stroke AEs 0.95 (95% CI 0.70, 1.29), stroke SAEs 0.97 (95% CI 0.69, 1.37), and fatal strokes (adjudicated) 0.85 (95% CI 0.39, 1.87). These data do not suggest an increase in stroke related adverse events with Spiriva HandiHaler compared to the placebo group, but the uncertainty of the confidence intervals is noted.

The potential stroke safety signal and the safety data from UPLIFT were discussed at the PADAC meeting on November 19, 2009. One of the issues discussed was whether the data from UPLIFT were adequate to address the potential safety signal of stroke events. The AC members voted (11 yes, 1 no) that the data from UPLIFT adequately addressed the potential safety signal of stroke events.

Fatal Adverse Events

Because UPLIFT is a large, long term controlled clinical trial, the mortality data is of interest. Two protocol amendments specified obtaining vital status on patients who discontinued and established an independent adjudication committee. These amendments make the mortality data in UPLIFT more robust. Because of the collection of vital status data, there are several datasets for the mortality data. BI analyzed the fatal adverse event data in multiple ways – on treatment (deaths on treatment) vs. vital status (all deaths including discontinuation vital status data), and Day 1440 (4 years) vs. Day 1470 (4 years + 30 day washout) vs. all (no cut-off). BI was able to obtain vital status on 97-98% of patients.

The hazard ratio for fatal adverse events on treatment Day 1440 (4 years) is 0.83 (95% CI 0.72, 0.95). The results for the other analysis of fatal adverse events (on treatment, vital status, Day 1440, Day 1470) were generally similar, e.g. Day 1470 Vital Status 0.89 (95% CI: 0.79, 1.02). Below is the Kaplan-Meier curve for the probability of no all cause mortality using the vital status data at Day 1470. The curves appear to separate around 12 months.

Figure 2 Kaplan Meier estimate of probability of no all cause mortality at Day 1470

The most common causes of death were COPD exacerbation, lung neoplasm, and unknown cause. Importantly, since BI seeks a labeling claim for COPD exacerbation, the rate ratio for death from COPD exacerbation was 0.79 (95% CI: 0.60, 1.02), using the vital status Day 1470 data. For lung neoplasm and unknown cause the rate ratios were: 1.02 (95% CI: 0.73, 1.43) and 0.74 (95% CI: 0.46, 1.21), respectively. Cardiovascular deaths are of interest. Using the same dataset, the rate ratio for death due to cardiovascular disorder was 0.81 (95% CI 0.48, 1.36) and for death due to MI was 1.00 (95% CI 0.43, 2.30). The number needed to treat (NNT) was calculated by Dr. Joan Buenconsejo and depending upon the dataset used, the NNT with Spiriva HandiHaler over a 4 year period to prevent one death was between 63 (Vital Status, Day 1470) and 111 (treatment, all).

Cardiovascular death and myocardial infarction

As discussed in Section 2, in September 2008, a meta-analysis was published in *JAMA* evaluating cardiovascular risk associated with inhaled anticholinergics[1]. For the primary combined outcome of cardiovascular death, myocardial infarction (MI), or stroke, the authors reported a relative risk of 1.58 (95% CI 1.21, 2.06) for tiotropium and ipratropium compared to placebo and concluded that inhaled anticholinergics are associated with a significantly increased risk of cardiovascular death, MI, or stroke.

To evaluate this potential safety signal, the Office of Surveillance and Epidemiology (OSE) reviewed this meta-analysis as well as other relevant literature regarding the safety of tiotropium and ipratropium. In Dr. Simone Pinheiro's review, she noted limitations of the aforementioned meta-analysis, including study selection bias, and lack of discontinuation information and failure to use person-time data. Dr. Pinheiro also noted the limitations of other published observational studies[7,8,9]. She noted that the Singh meta-analysis disagreed

[7] Lee TA, Pickard AS, Au DH, Bartle B, Weiss KB. Risk for death associated with medications for recently diagnosed chronic obstructive pulmonary disease. Ann Intern Med 2008; 149(6): 380-90.
[8] Macie C, Wooldrage K, Manfreda J, Anthonisen N. Cardiovascular morbidity and the use of inhaled bronchodilators. Int J Chron Obstruct Pulmon Dis 2008; 3(1): 163-9.
[9] Ogale SS, Lee TA, Au DH, Boudreau DM, Sullivan SD. Cardiovascular events associated with ipratropium bromide in COPD. Chest 2009; prepublished online April 10, 2009.

with the findings of other published meta-analyses [10,11,12,13] and disagreed with the results of UPLIFT, all of which did not suggest an association between anticholinergics and cardiovascular events or mortality. Dr. Pinheiro concluded that the currently available data implicating tiotropium and ipratropium in increasing risk of cardiovascular death, myocardial infarction, and stroke is not compelling.

Because of the safety concern of MI and cardiovascular death, cardiac events in UPLIFT are of interest. The rate ratio for death due to cardiovascular disorder was 0.81 (95% CI 0.48, 1.36) and for death due to MI was 1.00 (95% CI 0.43, 2.30). Adjusting for exposure in patient years, overall cardiac SAEs were more common in the placebo group with a rate ratio of 0.84 (95% CI: 0.73, 0.98). In terms of specific SAEs, MI occurred with a rate ratio of 0.71 (95% CI: 0.52, 0.99) and angina occurred with a rate ratio of 1.44 (95% CI: 0.91, 2.26). The rate ratio for other adverse events such as coronary artery disease (0.58, 95% CI: 0.33, 1.01) favored Spiriva HandiHaler. The AE data for cardiac events of interest showed similar findings.

The potential cardiovascular event safety signal and the safety data from UPLIFT were discussed at the PADAC meeting on November 19, 2009. One of the issues discussed was whether the data from UPLIFT were adequate to address the potential safety signal of cardiovascular events. The AC members voted (11 yes, 1 abstain) that the data from UPLIFT adequately addressed the potential safety signal of cardiovascular events.

Spiriva Respimat

The data from UPLIFT suggests that there is a benefit of Spiriva HandiHaler on mortality and this is primarily driven by a decrease in deaths from COPD exacerbation. However, it is relevant to note a safety concern regarding mortality with another formulation of tiotropium under development, Spiriva Respimat. As mentioned in Section 2, Spiriva Respimat is a new inhalation solution formulation of tiotropium bromide delivered via a novel inhaler, the Respimat. BI has evaluated two doses of Spiriva Respimat in three, 48-week, double blind, placebo controlled, phase 3 clinical trials (Studies 205.254, 205.255, and 205.372) in patients with COPD. The nominal doses for Spiriva Respimat are 5mcg and 10mcg, which are different than Spiriva HandiHaler (18mcg) because of the difference in formulations/devices. Pharmacokinetic comparisons of the two formulations show that Spiriva Respimat 5mcg and Spiriva HandiHaler 18mcg have similar exposures.

The results of all 3 trials show that Spiriva Respimat both 5mcg and 10mcg are statistically superior to placebo for trough FEV_1 at 48 weeks. The trials also show a numerical imbalance in mortality favoring placebo. The results for fatal adverse events in the 48 week, Spiriva Respimat clinical trials are shown in the table below. At the suggestion of the Agency, BI retrospectively obtained vital status on patients who discontinued and the numerical imbalance

[10] Kesten S, Jara M, Wentworth C, Lanes S. Pooled clinical trial analysis of tiotropium safety Chest 2006; 130(6): 1695-703.
[11] Barr RG, Bourbeau J, Camargo CA, Ram FS. Tiotropium for stable chronic obstructive pulmonary disease: A meta-analysis Thorax 2006; 61(10): 854-62.
[12] Salpeter SR, Buckley NS. Systematic review of clinical outcomes in chronic obstructive pulmonary disease: beta-agonist use compared with anticholinergics and inhaled corticosteroids. Clin Rev Allergy Immunol 2006; 31(2-3): 219-30.
[13] Wilt TJ, Niewoehner D, MacDonald R, Kane RL. Management of stable chronic obstructive pulmonary disease: a systematic review for a clinical practice guideline. Ann Intern Med 2007; 147(9): 639-53.

may be partially explained by differences in discontinuation. However, the results are most striking in Study 205.255, in which there were no deaths in the placebo group. The causes of death were reviewed and are discussed in detail in Dr. Michele's review. The most common causes were unknown and neoplasm, primarily lung cancer, followed by COPD exacerbation and myocardial infarction. Based upon review of cause of death, there was no obvious pattern that could explain the imbalance.

Table 6 Fatal Adverse Events in 48 Week Clinical Trials with Spiriva Respimat

Number Fatal Adverse Events (%)*	Tiotropium 5 mcg	Tiotropium 10 mcg	Placebo	Relative Risk vs. Placebo (95% CI)**	
				Tiotropium 5 mcg	Tiotropium 10 mcg
Study 254 (n)	332	332	319		
Within Study	7 (2.2%)	8 (2.4%)	5 (1.9%)	1.2 (0.4, 3.8)	1.4 (0.4, 4.2)
With Vital Status	8 (2.5%)	8 (2.1%)	7 (2.3%)	1.1 (0.4, 3.0)	1.1 (0.4, 2.9)
Study 255 (n)	338	335	334		
Within Study	5 (1.6%)	8 (2.7%)	0 (0.0%)	undefined	undefined
With Vital Status	7 (1.8%)	10 (2.8%)	2 (0.6%)	3.4 (0.7, 16.5)	5.0 (1.1, 22.9)
Study 372 (n)	1952		1965		
Within Study	30 (1.5%)		19 (1.0%)	1.5 (0.9, 2.7)	NA
With Vital Status	52 (2.7%)		38 (1.9%)	1.4 (0.9, 2.1)	NA

*Kaplan Meier estimates at 48 weeks
**Estimated by Cox proportional hazards regression with treatment as independent variable, stratified by study for pooled analysis

The mortality data from UPLIFT and the Spiriva Respimat trials were discussed at the PADAC meeting on November 19, 2009. While a question for voting was not asked, the committee was asked to comment on the data. In general, the committee noted that the mortality data from UPLIFT suggests that there is not an increase in mortality, but there were concerns about the Spiriva Respimat data and this issue should be further explored.

9. Advisory Committee Meeting

A Pulmonary Allergy Drugs Advisory Committee (PADAC) meeting was held on November 19, 2009 for this efficacy supplement because of the COPD exacerbation claim and outstanding safety concerns regarding stroke, myocardial infarction (MI), and cardiovascular death. While the feedback from the AC is included in the relevant sections of this memo, a brief overview of the PADAC is included here. The AC meeting included members of the PADAC and members of the Drug Safety and Risk Management Advisory Committee.

In general, the committee voted that the UPLIFT results adequately addressed the potential safety signals of stroke and cardiovascular events. The committee also voted that the data from UPLIFT and the VA Study were adequate to support a COPD exacerbation claim. The mortality data were discussed and while the committee noted that the data from UPLIFT were compelling, there was concern regarding the Respimat data. There were five questions posed to the committee: two non-voting and three voting questions. The questions and voting/discussion are outlined below.

1. Please comment on the mortality data from Spiriva HandiHaler trial 205.235 (UPLIFT).

The UPLIFT trial data suggests that there is no increase in mortality. One member raised concern on whether the population studied is truly representative of the real world population.

2. Please comment on the mortality data from the Spiriva Respimat Phase 3 trials (205.254, 205.255, and 205.372).

The committee indicated it was unclear as to what the Respimat data suggested and voiced concerns of a possible dose response and cardiovascular effects. Further data, including quality of life, was suggested.

3. Do the data from trials 205.235 (UPLIFT) and 205.266 (VA study) provide substantial and convincing evidence to support the claim that Spiriva HandiHaler reduces COPD exacerbations? (voting question)

yes=11, no=1, abstain=0

4. Do the data from trial 205.235 (UPLIFT) adequately address the potential safety signal of stroke events? (voting question)

yes=11, no=1, abstain=0

5. Do the data from trial 205.235 (UPLIFT) adequately address the potential safety signal of adverse cardiovascular outcomes? (voting question)

yes=11, no=0, abstain=1

10. Pediatrics

BI was granted a waiver for pediatric studies in the January 30, 2004, Approval letter for Spiriva HandiHaler, because Spiriva HandiHaler is indicated for COPD, which is a disease of adults. BI requested a pediatric waiver for this efficacy supplement for the same reason, which is acceptable.

11. Other Relevant Regulatory Issues

11a. DSI Audit

A DSI audit was requested for UPLIFT since this efficacy supplement proposed a new COPD exacerbation labeling claim. There were 7 inspections for UPLIFT: Dr. Rodolfo Posada-Valay in Monterrey, Mexico; Dr. Wanchai Dejsomritrutai in Bangkok, Thailand; Dr. Jiri Erban in Czech Republic; Dr. Kota Gunnayya Chetty in Long Beach, CA; Dr. William Bailey in Birmingham, AL; Dr. Donald Tashkin in Los Angeles, CA; and Dr. Gary Greenwald in Rancho Mirage, CA. While there were issues noted at some of the sites, the data obtained appeared to be reliable. The only issue noted of potential concern was the use of prohibited concomitant medication periodically over the 4 year treatment period, primarily for the treatment of COPD exacerbations. A previous DSI audit was conducted for the VA Study and while there were some minor issues noted, the efficacy data were deemed reliable.

11b. Financial Disclosure

Financial disclosure was reviewed for both the VA and UPLIFT trials. The majority of investigators did not report significant financial interests—there were only (b) investigators in the VA trial and (b) (6) in the UPLIFT trial with financial interests. DSI audited (b) (4) investigator in the VA trial and (b) (4) in the UPLIFT trial who reported financial interests and also were high enrollers. No data integrity issues were identified at these sites. Because efficacy or safety findings were not driven by only one or a few sites, it is unlikely that financial conflicts could have altered the results of the studies.

12. Labeling

12a. Proprietary Name

Spiriva HandiHaler is an approved product and there is no proposal for change to the proprietary name.

12b. Physician Labeling

BI submitted the Spiriva HandiHaler label in the PLR format. While four claims were initially sought: a) reduction in COPD exacerbations; b) description of long-term effects on lung function; c) reduction in mortality; and d) reduction in respiratory failure, BI withdrew the mortality claim. As discussed in this memo, there is adequate support for the COPD exacerbation claim and the long term effects on lung function claim. There is not adequate support for the respiratory failure claim. While the data from UPLIFT suggest a benefit of Spiriva HandiHaler with regards to mortality, the mortality data will not be included in the product label because of the outstanding mortality issues with Spiriva Respimat.

12c. Carton and Immediate Container Labels

Spiriva HandiHaler is an approved product and there is no proposal for change to the carton and container labels.

12d. Patient Labeling and Medication Guide

The currently approved labeling for Spiriva HandiHaler has a patient package insert and patient's instruction for use. There is no Medication Guide, nor is one required. The patient labeling has been updated to include the new information regarding reduction in COPD exacerbations. In addition, figures have been added to instruct patients not to swallow the Spiriva capsules.

13. Recommendations/Risk Benefit Assessment

13a. Regulatory Action

The recommended regulatory action is **Approval**. The submitted data from the VA Study and UPLIFT are adequate to support the proposed exacerbation labeling claim and indication. The submitted data from UPLIFT are adequate to support the long term pulmonary function claim. Because the proposed respiratory failure claim is not supported, this claim has been removed from the agreed upon labeling.

13b. Risk Benefit Assessment

Spiriva HandiHaler is currently approved for the long term, once-daily, maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema (i.e. a bronchodilator for patients with COPD) and has been deemed to have a favorable risk benefit assessment for that indication. The proposed labeling claim is for the same population (COPD patients) and would not change the risk benefit assessment. The safety concerns regarding stroke, myocardial infarction (MI), and cardiovascular death have been adequately addressed by this large, 4 year, placebo controlled clinical trial, UPLIFT. The results do not support/suggest these safety signals occur with Spiriva HandiHaler in long-term use and actually suggest a potential mortality benefit for Spiriva HandiHaler. Thus, the risk benefit assessment is favorable.

13c. Post-marketing Risk Management Activities

There are no recommendations for postmarketing risk management activities. Spiriva HandiHaler is currently approved for COPD patients and the proposed labeling claim is for the same population (COPD patients) and would not warrant new risk management activities.

13d. Post-marketing Study Commitments

There are no recommendations for postmarketing study commitments.

SUMMARY REVIEW OF REGULATORY ACTION

Date:	November 13, 2008
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary and Allergy Products, CDER, FDA
Subject:	Division Director Summary Review
NDA Number:	21-395, SE8, S24
Applicant Name:	Boehringer Ingelheim Pharmaceuticals, Inc.
Date of Submission:	January 11, 2008
Date of Receipt:	January 14, 2008
PDUFA Goal Date:	November 14, 2008
Proprietary Name:	Spiriva HandiHaler
Established Name:	Tiotropium bromide
Dosage form:	Inhalation Powder – Spiriva capsule to be used with HandiHaler device
Strength:	18 mcg tiotropium per Spiriva capsule
Proposed Indications:	Labeling claim for reduction of exacerbations in patients with chronic obstructive pulmonary disease (COPD)
Action:	Complete response

1. Introduction

Boehringer Ingelheim Pharmaceuticals submitted this 505(b)(1) application as an efficacy supplement for Spiriva HandiHaler to add a labeling claim for reduction of exacerbation in patients with chronic obstructive pulmonary disease (COPD). The proposal is to add labeling language in the Clinical Studies section of the product label, but not as a separate indication in the Indications and Usage section. The application is based on clinical efficacy and safety studies. This summary review will provide an overview of the application, with a focus on the clinical efficacy and safety studies.

2. Background

There are several drug classes approved for maintenance treatment of airflow obstruction in patients with COPD. These include beta-adrenergic agents, anticholinergic agents, combination products containing beta-adrenergic agents and anticholinergic agents, combination of long-acting beta-adrenergic agents and corticosteroids, and methylxanthines. Advair Diskus (fluticasone propionate and salmeterol) is also approved for reducing exacerbations in patients with COPD.

Tiotropium bromide is a long-acting anticholinergic with specificity for muscarinic receptors that is currently approved as Spiriva HandiHaler (tiotropium bromide inhalation powder) for long-term maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema. Spiriva HandiHaler was approved on January 30, 2004 (NDA 21-395). The approved product consists of a dry powder

containing tiotropium bromide in the Spiriva capsule, and the inhalation device, the HandiHaler, which is used to deliver the dry powder from the capsule. The recommended dose is inhalation of one Spiriva capsule, once-daily, with the HandiHaler inhalation device. One Spiriva capsule contains 18 mcg tiotropium, which is equivalent to 22.5 mcg tiotropium bromide monohydrate. With this application Boehringer Ingelheim proposes to add a labeling claim for reduction of COPD exacerbation for Spiriva HandiHaler. Advair Diskus is the only drug that has a reduction of exacerbation indication in COPD patients.

3. Chemistry, Manufacturing, and Controls

Spiriva HandiHaler is an approved product and there are no CMC issues.

4. Nonclinical Pharmacology and Toxicology

No new pharmacology and toxicology studies were submitted with this application. The pharmacology and toxicology data were reviewed in the original Spiriva HandiHaler application (NDA 21-395).

5. Clinical Pharmacology and Biopharmaceutics

The general clinical pharmacology and biopharmaceutic consideration for tiotropium bromide were addressed in the original Spiriva HandiHaler application (NDA 21-395).

6. Clinical Microbiology

Spiriva HandiHaler is an approved product and there are no clinical microbiology issues.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

Some characteristics of the studies that form the basis of review and regulatory decision for this application are shown in Table 1. The sole pivotal study submitted by Boehringer Ingelheim to support the labeling claim is study 266. Boehringer Ingelheim refers to studies 254, 255, 249, and 250 submitted to the Spiriva Respimat NDA (NDA 21-936, submitted November 16, 2007) as supporting evidence. Studies 254 and 255 use Spiriva Respimat, a different delivery device, which is not directly relevant to an efficacy claim for Spiriva HandiHaler. Studies 249 and 250 are submitted as an attempt to demonstrate a link between Spiriva HandiHaler and Spiriva Respimat. The design and conduct of these studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in the following section.

Table 1. Selected clinical studies

ID	Study type	Study duration	Patient Age, yr	Treatment groups*	N (ITT)	Study Year#	Countries
266	Efficacy and safety Parallel-group	6 month	≥ 40	SH 18 mcg QD Pbo	914 915	2003	US
254	Efficacy and safety Parallel-group	48 week	≥ 40	SR 5 mcg QD SR 10 mcg QD Pbo QD	332 332 319	2005	US, Canada, EU
255	Efficacy and safety Parallel-group	48 week	≥ 40	SR 5 mcg QD SR 10 mcg QD Pbo QD	338 335 334	2005	US, Canada, EU, Africa, Australia
249	Efficacy and safety Phase 3 Cross-over	4 week	≥ 40	SR 5 mcg QD SR 10 mcg QD SH 18 mcg QD Pbo QD	131 131 131 131	2004	US, Canada
250	Efficacy and safety Phase 3 Cross-over	4 week	≥ 40	SR 5 mcg QD SR 10 mcg QD SH 18 mcg QD Pbo QD	76 76 76 76	2003	Belgium, Netherlands

* SR = Spiriva Respimat; SH: Spiriva HandiHaler; Pbo = Placebo;
# Year study subject enrollment ended

b. Design and conduct of the studies

Study 266 was randomized, double-blind, placebo-controlled, parallel-group in design, conducted in patients with moderate-to-severe COPD in a Veterans Affairs Hospital setting. Unlike many other studies with Spiriva, many concomitant COPD treatments, such as long-acting beta agonists, inhaled corticosteroids, chronic oxygen, and theophylline were allowed in the study. The study had an initial screening period, followed by 6-month double-blind treatment period. The study had two co-primary efficacy variables: the proportion of patients who experienced a COPD exacerbation and the proportion of patients with a hospitalization associated with a COPD exacerbation. Secondary efficacy variables included others aspects of COPD exacerbation and spirometric measures. Safety assessments included serious adverse event recording, vital signs, and physical examination. Non-serious adverse events, clinical laboratory measures, and ECGs were not collected.

Studies 254 and 255 were randomized, double-blind, placebo-controlled, parallel group in design, conducted in patients with moderate-to-severe COPD. The studies had a 2-week run-in period followed by 48-week randomized treatment period, and then a 3-week follow-up period. The studies had four co-primary efficacy endpoints pre-declared to be tested sequentially (in order to control the type I error for multiple endpoints) as follows: trough FEV1 at the end of 48-week treatment period, total SGRQ score at the end of 48-week treatment period, Mahler TDI at the end of 48-week treatment period, and number of COPD exacerbations occurring during the year of randomized treatment. The protocol specified that trough FEV1 and SGRQ were to be analyzed separately for each study, and Mahler TDI and COPD exacerbation to be analyzed by pooling the studies. Boehringer Ingelheim stated that the Mahler TDI was included for the purpose of registration in EU and that no claims were being requested based on the SGRQ. Therefore, for the purpose

of US review, the endpoints for consideration are trough FEV1 and COPD exacerbation. The protocol specified that demonstration of statistical significance with the first primary endpoint (FEV1) would be adequate for demonstration of efficacy. This was acceptable to the Agency. Safety assessments included recording of adverse events, vital signs, physical examinations, clinical laboratory measures, ECG and 24-hour Holter monitoring in a subset of patients.

COPD exacerbation in studies 266, 254, and 255 were defined as "a complex of respiratory events or symptoms with duration of 3 days or more requiring treatment." A complex of respiratory events/symptoms means ≥ 2 of the following (increase of symptom or new onset): shortness of breath/dyspnea/shallow, rapid breathing, sputum production (volume), occurrence of purulent sputum, cough, wheezing, and chest tightness. A change in or requirement of treatment included the following: prescription antibiotics and/or systemic corticosteroids, and/or a significant change of the prescribed respiratory medication (bronchodilators including theophylline). There is no generally accepted definition of COPD exacerbations, but it usually includes some combination of symptoms and a change of treatment. The definition used in these studies is as precise as practical and generally closely follows the definitions used in the literature.[1]

Studies 249 and 250 were randomized, double-blind, double-dummy, active- and placebo-controlled, parallel group in design, conducted in patients with moderate-to-severe COPD. The studies had four randomized 4-week treatment periods separated by 4-week washout periods. The primary efficacy endpoint was trough FEV1 at the end of each 4-week treatment period. Trough FEV1 was defined as FEV1 measured at -10 minutes at the end of the 24-hour dosing interval. Serial blood samples and urine were collected for pharmacokinetic analyses. Safety assessments included recording of adverse events, vital signs, physical examinations, clinical laboratory measures, and ECG.

c. Efficacy findings and conclusions

The sole clinical study submitted to support the labeling claim is study 266 that used the Spiriva HandiHaler device. The supporting studies 254 and 255 are not relevant to support the labeling claim because these studies used Spiriva Respimat, which is a different delivery device. Although Spiriva HandiHaler and Spiriva Respimat deliver the same active moiety, tiotropium, the two products are different because the two products use different delivery devices and efficacy from one product cannot be extrapolated to the other product.

The submitted data failed to show substantial evidence to support a reduction of COPD exacerbation claim for Spiriva HandiHaler. Results of the co-primary efficacy variables for study 266 are shown in Table 2. One of the two co-primary efficacy variables was met in this study and the other efficacy variable showed positive trend. Secondary efficacy variable generally trended in the right direction, but the results were not consistent (data not shown in this review). This study, while it may be considered

[1] Cazzola M, MacNee W, Martinez FJ, et al. ATS/ERS Task Force Report: Outcomes for COPD pharmacological trials, from lung function to biomarkers. Eur Resp J 2008; 31: 416-468.

positive, is not sufficiently robust to support approval of the labeling claim. A second placebo-controlled study demonstrating a benefit with Spiriva HandiHaler will be required to support a reduction of COPD exacerbation claim. Boehringer Ingelheim has recently concluded a 6000 patient 4-year study with Spiriva HandiHaler in COPD patients (The UPLIFT Study – Understanding Potential Long-term Impacts on Function with Tiotropium). [2] This study may provide the necessary evidence and replicate finding to support a reduction in COPD exacerbation claim for Spiriva HandiHaler.

Study 266 had a large number of protocol violations and relatively poor compliance with study drug. The enrollment criteria and study conduct were described as "real world." Despite these factors, which would tend to bias efficacy against the drug, the exacerbation data was in the right direction, and the spirometry data (not shown in this review) were in line with what is typically seen in a relatively tightly controlled studies.

Table 2. Percentage of patients with COPD exacerbation, study 266

	Spiriva HandiHaler (n=914)	Placebo (n=915)	Odds Ratio	P-value
Protocol defined exacerbation	27.9	32.3	0.806	0.0368
Hospitalization due to exacerbation	7.0	9.5	0.718	0.0557

Boehringer Ingelheim refers to studies 254 and 255 submitted to the Spiriva Respimat NDA (NDA 21-936, submitted November 16, 2007) as supporting evidence. This is not acceptable for reasons stated above. Nevertheless, results of these two studies are shown in Table 3. These two studies were not adequate to (b) (4) for Spiriva Respimat (b) (4) mcg. (b) (4) Only one of the two studies showed statistically significant superiority for Spiriva Respimat over placebo (Table 3). Although pre-specified combined analyses of the two studies shows statistical significance (data not shown), this is (b) (4) a (b) (4) because the pooled studies are considered as one study.

Table 3. Mean COPD exacerbations data

Treatment groups		Exacerbation Rate per patient	Exacerbation rate ratio versus placebo Point estimate	p-value*
Study 254				
Spiriva Respimat 5 mcg QD	332	0.8	-1.1	0.20
Spiriva Respimat 10 mcg QD	332	0.8	-1.1	0.07
Placebo	319	1.9		
Study 255				
Spiriva Respimat 5 mcg QD	338	1.1	-0.9	0.003
Spiriva Respimat 10 mcg QD	335	1.2	-0.8	0.004
Placebo	334	2.0		

* p-value determine using the Wilcoxon-Mann-Whitney test

[2] Tashkin DP, Celli B, Senn S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. New Eng J Med 2008; 359:1543-1554.

Boehringer Ingelheim refers to studies 249 and 250 submitted to the Spiriva Respimat NDA (NDA 21-936, submitted November 16, 2007) as an attempt to demonstrate link between Spiriva HandiHaler and Spiriva Respimat. This is not an accepted approach because for efficacy claims these are considered as separate products. This approach also has scientific limitations. Results of these two studies are shown in Table 4 to point out the limitation of such an approach to link products. In these studies, both 5 mcg and 10 mcg doses were statistically significantly superior to placebo, and both doses provided numerically similar trough FEV1 response over placebo. Both doses of Spiriva Respimat were at least nearly noninferior to Spiriva HandiHaler (with a noninferiority margin of 0.05L) and in fact provided slightly larger numerical response compared to Spiriva HandiHaler 18 mcg. In study 249 both doses of Spiriva Respimat provided slightly larger numerical response compared to Spiriva HandiHaler 18 mcg. These data are invalid to establish similarity among either dose of Spiriva Respimat to Spiriva HandiHaler 18 mcg because the data are not even sensitive enough to differentiate doubling doses of Spiriva Respimat. The data rather shows insensitivity of such an approach to establish link between two products.

Table 4. Mean trough FEV1 (L) treatment differences between Spiriva Respimat and the comparators at the end of treatment periods from two comparative studies

Treatment groups	Difference from placebo			Difference from HandiHaler		
	Point estimate	95% CI	p-value*	Point estimate	95% CI	p-value†
Study 249						
Spiriva Respimat 5 mcg QD	0.12	0.08, 0.15	<0.001	0.05	0.01, 0.08	<0.001
Spiriva Respimat 10 mcg QD	0.13	0.09, 0.16	<0.001	0.06	0.02, 0.09	<0.001
Spiriva HandiHaler 18mcg QD	0.07	0.04, 0.10	<0.001			
Study 250						
Spiriva Respimat 5 mcg QD	0.13	0.09, 0.17	<0.001	0.00	-0.04, 0.04	0.006
Spiriva Respimat 10 mcg QD	0.12	0.08, 0.16	<0.001	-0.10	-0.51, 0.03	0.028
Spiriva HandiHaler 18mcg QD	0.13	0.09, 0.17	<0.001			

* superiority; p-values are one-sided
† non-inferiority; p-values are one sided

8. Safety

a. Safety database

The safety monitoring in study 266 was limited in that only serious adverse events were recorded. Non-serious adverse events, clinical laboratory measures, and ECGs were not collected. While this level of safety monitoring is not ideal, it is acceptable for this specific application because Spiriva HandiHaler in an approved product for use in COPD patients and safety in this population is known.

b. Safety findings and conclusion

The Agency has previously concluded that tiotropium bromide administered by the inhalation route is safe for use in COPD patients, which was the basis for approval of

Spiriva HandiHaler. No new safety signals were identified in study 266. There were 22 deaths in the Spiriva HandiHaler treatment arm and 19 deaths in the placebo treatment arms. The number of deaths and cause of the deaths were generally expected in this older population with COPD. The common serious adverse events were COPD exacerbation, pneumonia, bronchitis, myocardial infarction, and congestive heart failure. These are also expected findings in this older population with COPD.

There are two major safety issues with tiotropium that are still unresolved. These are increased frequency of death seen in Spiriva Respimat 48-week studies and increased frequency of stroke seen in Spiriva HandiHaler and Spiriva Respimat studies. The safety findings of death and stroke are discussed in the following sections.

Death

The two 48-week clinical studies conducted with Spiriva Respimat showed a mortality imbalance against Spiriva Respimat (Table 5).

Table 5. Death in 48 week studies with Spiriva Respimat

	Spiriva Respimat		Placebo	Relative risk vs placebo (95% CI)	
	5 mcg	10 mcg		5 mcg	10 mcg
Study 254 (n)	332	332	319		
Within study period	7 (2.2%)	8 (2.4%)	5 (1.9%)	1.2 (0.4, 3.8)	1.4 (0.4, 4.2)
With retrospective follow-up	8 (2.5%)	8 (2.1%)	7 (2.3%)	1.1 (0.4, 3.0)	1.1 (0.4, 2.9)
Study 255 (n)	338	335	334		
Within study period	5 (1.6%)	8 (2.7%)	0 (0.0%)	undefined	undefined
With retrospective follow-up	7 (1.8%)	10 (2.8%)	2 (0.6%)	3.4 (0.7, 16.5)	5.0 (1.1, 22.9)
Study 254 + 255 (n)	670	667	653		
Within study period	12 (1.9%)	16 (2.5%)	5 (0.9%)	2.1 (0.7, 5.9)	2.9 (1.1, 8.0)
With retrospective follow-up	15 (2.1%)	18 (2.5%)	9 (1.4%)	1.6 (0.7, 3.6)	1.9 (0.9, 4.3)

Boehringer Ingelheim made the Division aware of the mortality imbalance seen in the two 48-week studies in November 2005, well before submitting this application. The Division presented the finding to the Drug Safety Oversight Board (DSOB) on June 15, 2006. At that time data from within the study period were available and the retrospective follow-up data were not available (Table 5). The DSOB was not overly concerned because the overall death signal was driven largely by no death in the placebo arm in one study. No death in a large COPD study is highly unlikely. Also, there was an imbalance of discontinuation between the two treatment arms with approximately 30% of patients discontinuing from the placebo arm and approximately 20% patients discontinuing from each Spiriva Respimat arm. On the Division's advice, Boehringer Ingelheim subsequently set up study 392 to obtain retrospective follow up data from patients discontinued from these two 48-week studies. Boehringer Ingelheim was remarkably successful in their effort and obtained vital status on approximately 97% of discontinued patients. The additional death numbers modify the finding, but the mortality imbalance against Spiriva Respimat remains (Table 5).

Review of the cases of death seen in the Spiriva Respimat 48-week studies did not point to a particular cause or organ system. The causes of death were generally what would be expected in older patients with COPD, such as cardiac and respiratory system diseases. Death is expected to be related to systemic effect of tiotropium, and should occur with both Spiriva Respimat and Spiriva HandiHaler, and also with the short-acting anticholinergic ipratropium. From a mechanistic standpoint one could theorize that an anticholinergic drug may have cardiac effects that can result in mortality. This theory is supported by finding of the US Lung Health Study that evaluated the effects of smoking on decline in FEV1 and mortality or morbidity. Results of the study were suggestive of a possible link between use of inhaled ipratropium and increased cardiovascular death.[3] A meta-analyses of placebo controlled clinical studies with ipratropium and tiotropium did not show an increase in deaths.[4] The recently concluded 6000 patient 4-year study with Spiriva HandiHaler in COPD patients (The UPLIFT Study) is claimed to show no imbalance in death between Spiriva HandiHaler treated patients and placebo treated patients.[2] However, a more recent meta-analysis suggests a link between inhaled anticholinergic drugs and major adverse cardiovascular events in patients with COPD.[5] A review of the placebo controlled clinical studies with Spiriva HandiHaler submitted to the Agency did not show an increase in mortality. The finding of increased death in the two 48-week clinical studies with Spiriva Respimat is difficult to discard as a chance finding, but is also difficult to explain based on negative data from other sources.

The Division discussed the mortality data at an internal CDER Regulatory Briefing on July 18, 2008. The general opinion expressed by senior CDER staff was that the mortality signal seen in the two 48-week clinical studies are difficult to discard as a chance event or accept as real and additional clinical data are necessary to sort this out. Boehringer Ingelheim has recently concluded a 6000 patient 4-year study with Spiriva HandiHaler in COPD patients (The UPLIFT Study – Understanding Potential Long-term Impacts on Function with Tiotropium).[2] This study will provide a large safety database for review. The signal of death with tiotropium is an open issue and will likely be the subject of a future advisory committee meeting once the Agency has reviewed the UPLIFT study formally in the context of an industry submission.

Stroke

In November 2007, Boehringer Ingelheim submitted a pooled analyses of 29 placebo-controlled clinical studies with Spiriva HandiHaler (25 clinical studies) and Spiriva Respimat (4 studies) that showed an increased risk of stroke (Table 6). The analysis was performed as part of routine safety monitoring for tiotropium. The Agency issued an

[3] Anthonisen NR, Connett JE, et al. Hospitalization and mortality in the Lung Health Study. Am J Respir Crit Care Med 2002; 166:333-339.
[4] Salpeter SR, Buckley NS, Salpeter EE. Meta-analysis: Anticholinergics, but not beta-agonists, reduce severe exacerbations and respiratory mortality in COPD. J Gen Intern Med 2006; 21:1011-1019.
[5] Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease. A systematic review and meta-analysis. JAMA 2008; 300:1439-1450.

Early Communication regarding this potential serious safety signal in March 2008. [6] Specific detailed review of the studies submitted with this application for Spiriva Respimat do not show a stroke signal. As with the death signal discussed above, the stroke signal is also an open issue at this time. Review of the UPLIFT study, that will provide substantial safety data, will help address the stroke signal as well as the death signal.

Table 6. Risk of stroke in pooled clinical studies with tiotropium

Event	Spiriva patients with event per 1000 patients treated for one year	Placebo patients with event per 1000 patients treated for one year	Excess events expressed per 1000 patients treated for one year period	Risk Ratio (95% confidence interval)
Any Stroke	8	6	2	1.4 (0.7, 2.6)
Serious Stroke	7	5	2	1.6 (0.9, 3.1)

c. REMS/RiskMAP

Not relevant because this efficacy supplement for Spiriva HandiHaler will not be approved in this cycle. A final decision will be made later prior to approval.

9. Advisory Committee Meeting

An advisory committee meeting was not convened for this application because the submitted data is not adequate for approval. A second placebo-controlled study demonstrating a reduction in COPD exacerbations with Spiriva HandiHaler will be required to support a reduction of COPD exacerbation claim.

10. Pediatric

COPD is an adult disease, therefore, specific pediatric studies would not be required that relate to this action specific to COPD.

11. Other Relevant Regulatory Issues

a. DSI Audits

A DSI audit was requested of the CRO that performed the data entry and management functions of study 266 and two other sites that enrolled high number of patients. Audit of these sites did not show any major irregularities. Review of the application did not identify any irregularities that would raise concerns regarding data integrity. No ethical issues were present. All studies were conducted in accordance with accepted ethical standards.

b. Financial Disclosure

Boehringer Ingelheim submitted acceptable financial disclosure statements. A total of 19 investigators had significant financial interest in Boehringer Ingelheim or Pfizer (co-marketer for Spiriva). The number of subjects that these investigators enrolled was not

[6] Early Communication about an Ongoing Safety Review of Tiotropium.
Http://www fda.gov/cder/drug/early_comm/tiotropium.htm

large enough to alter the outcome of any study. Furthermore, the multi-center nature of the studies makes it unlikely that these financial interests could have influenced or biased the results of these studies.

c. Others

There are no outstanding issues with consults received from DDMAC, DMETS, or from other groups in CDER.

12. Labeling

a. Proprietary Name

There is no issue with the proprietary name as the root name Spiriva was previously reviewed and found to be acceptable, and HandiHaler is the accepted name for the delivery device.

b. Physician Labeling

The labeling was not reviewed in detail and not discussed with Boehringer Ingelheim during review of this application because the application cannot be approved due to lack of efficacy finding as discussed in section 7 above. To support the proposed labeling change, Boehringer Ingelheim will need to show efficacy in a second study, and revise the labeling to include the results of a second efficacy study. It will be more useful to do a comprehensive label review and have discussions with the applicant with a label that is expected to be final or close to final.

c. Carton and Immediate Container Labels

Not relevant because Spiriva HandiHaler is an approved product.

d. Patient Labeling and Medication Guide

Not relevant because Spiriva HandiHaler is an approved product and this application will not be approved in this review cycle. There is no Medication Guide proposed for this product.

13. Action and Risk Benefit Assessment

a. Regulatory Action

The application will not be approved in this review cycle. The submitted data has failed to provide substantial evidence of efficacy to support labeling claim for reduction of exacerbation in patients with COPD.

The comments below are for the action letter. Comment 1 identifies the deficiency that precludes approval of this application. Comment 2 is an additional comment, which is not a deficiency that precludes approval of this application.

1. The submitted data do not provide substantial evidence of efficacy to support the labeling claim for reduction of exacerbation in COPD patients. Replicate findings from two adequate and well controlled studies are necessary to support a COPD

exacerbation labeling claim. The results from combined analysis of clinical studies 205.254 and 205.255 are not acceptable for replication because these studies were conducted with Spiriva Respimat, which is a distinct product in terms of efficacy.

To support the proposed claim of reduction of COPD exacerbation, provide data from an adequate and well controlled clinical study that shows statistically significant reduction in COPD exacerbation with Spiriva HandiHaler compared to placebo.

2. Increased frequencies of stroke were observed in patients treated with tiotropium bromide compared to placebo in a pooled analysis of clinical study data with Spiriva HandiHaler and Spiriva Respimat. Provide data from an adequate and well-controlled study to address the concerns of stroke. The study should be of adequate duration and power that will allow evaluation of the safety concern.

b. Risk Benefit Assessment

Risk-benefit assessment specific to this application is not relevant because substantial evidence of efficacy to support the labeling claim of reduction of exacerbation in COPD patients has not been shown with Spiriva HandiHaler. Spiriva HandiHaler is already approved for long-term maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema, and has been deemed to have a favorable risk-benefit profile. Addition of a reduction of COPD exacerbation will not negatively change the risk-benefit assessment of Spiriva HandiHaler.

c. Post-marketing Risk Management Activities

Not relevant because the application will not be approved.

d. Post-marketing Study Commitments

Not relevant because the application will not be approved.

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/s/

Badrul Chowdhury
11/13/2008 11:39:50 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-395/S029

OFFICER/EMPLOYEE LIST

Officer/Employee List
Application: sNDA 21395 S-0-29

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified on this list:

Barnes, Sandra L.
Buenconsejo,Joan
Chowdhury, Badrul A.
Duer, Robin
Iyasu, Solomon
Li, Qian
Michele, Theresa
Pei, Luqi
Pinheiro, Simone
Permutt, Thomas
Purohit-Sheth, Tejashari
Ragavachari, Ramesh
Raggio, Miranda
Roy, Partha
Seymour, Sally
Shea, Molly
Skariah, Samuel
Wu, Jean
Xu, Yun
Vidra, James D.
Volpe, Carolyn

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-395/S029

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	October 31, 2008
From	Sally Seymour, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA# 21-395, SE8, S24
Applicant	Boehringer Ingelheim
Date of Submission	January 11, 2008
PDUFA Goal Date	November 14, 2008
Proprietary Name / Established (USAN) names	Spiriva HandiHaler Tiotropium bromide inhalation powder
Dosage forms / Strength	Inhalation powder
Proposed Indication(s)	Labeling claim for reduction in COPD exacerbations
Recommended:	Complete Response

1. Introduction

On January 11, 2008, Boehringer Ingelheim (BI) submitted an efficacy supplement for Spiriva HandiHaler to add the following labeling claim to the Clinical Studies Section of the product label:

> "In a 6-month clinical trial of COPD patients in a Veterans Affairs setting, Spiriva HandiHaler significantly reduced the proportion of COPD patients who experienced exacerbations compared to placebo and significantly delayed the time to first exacerbation. These findings are supported by a pre-specified combined analysis of two one-year clinical trials using Spiriva Respimat."

Spiriva HandiHaler Inhalation Powder is a long acting anticholinergic approved on January 30, 2004, for the long term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

To support this application, BI submitted the results of one 6-month clinical trial with Spiriva HandiHaler and the results of two combined 48 week clinical trials with Spiriva Respimat, which is an inhalation solution formulation of tiotropium bromide that is not currently approved in the US. All of these studies were submitted under NDA# 21-936 for Spiriva Respimat and cross-referenced in this NDA. Since Spiriva HandiHaler is a currently approved drug product, there was no new CMC, pharmacology/toxicology, or clinical pharmacology data submitted in this efficacy supplement. This memo will provide an overview of the application with a focus on issues that warrant further discussion. The PDUFA date for this application is November 14, 2008.

2. Background

Tiotropium bromide is a long acting anticholinergic, with specificity for muscarinic receptors that is currently approved as Spiriva HandiHaler. Spiriva HandiHaler is an inhalation powder approved for the long term, once-daily, maintenance treatment of bronchospasm associated

with COPD, including chronic bronchitis and emphysema (i.e. a bronchodilator for patients with COPD). This efficacy supplement is for a labeling claim in the Clinical Studies section of the product label. Only one other medication, Advair Diskus, currently has a labeling claim for a reduction in COPD exacerbations.

Of relevance is the Pre-NDA meeting held on April 20, 2005, for Spiriva Respimat in which BI posed a question regarding its plan (b) (4) The Division responded as follows: (b) (4) *Whether 205.266 provides adequate data to substantiate the finding will be a review issue. In addition, the exact wording in the product label will be a review issue.*

On November 16, 2007, BI submitted an NDA (NDA# 21-936) for Spiriva Respimat, which is a new formulation of tiotropium bromide, an inhalation solution, delivered via a novel inhaler, the Respimat. In this NDA, BI proposed that Spiriva Respimat (b) (4) (b) (4) BI submitted the results of two combined 48-week, placebo controlled clinical trials with Spiriva Respimat. To replicate the COPD exacerbation finding, BI submitted the results of the VA study with Spiriva HandiHaler (205.266). Because the VA study was conducted with a different drug product, the results were not adequate for replication of the efficacy findings for the COPD exacerbation claim. In addition, there was a mortality imbalance favoring placebo noted in the phase 3 clinical trials. While the efficacy findings were sufficient for approval of the bronchodilator indication, a Complete Response action was taken on the Spiriva Respimat application on September 16, 2008, because of two safety signals – mortality and stroke (see below).

On November 30, 2007, the Applicant submitted a document to the IND for Spiriva HandiHaler (IND# 46,687) that described a potential stroke safety signal found in a routine safety analysis of pooled data from controlled Spiriva HandiHaler and Spiriva Respimat clinical trials. Based upon BI's analysis of 29 pooled clinical trials, there was an increased risk of stroke with use of tiotropium bromide with a risk ratio of 1.37 (95% CI: 0.73, 15.6). Additional patient level data was requested from BI and the status of this analysis is described in Section 8. Because of the Agency's commitment to inform the public about ongoing safety reviews, on March 18, 2008, the Agency released an Early Communication about an Ongoing Safety Review of Tiotropium (marketed as Spiriva HandiHaler) that described the preliminary information regarding stroke and Spiriva. This safety signal remains unresolved at the time of finalization of this review.

3. CMC/Device

There was no new CMC information submitted in this efficacy supplement because Spiriva HandiHaler is an approved product.

4. Nonclinical Pharmacology/Toxicology

There was no new nonclinical information submitted in this efficacy supplement because Spiriva HandiHaler is an approved product.

5. Clinical Pharmacology/Biopharmaceutics

There was no new clinical pharmacology information submitted in this efficacy supplement because Spiriva HandiHaler is an approved product.

6. Clinical Microbiology

There was no clinical microbiology information submitted in this efficacy supplement.

7. Clinical/Statistical- Efficacy

To support the proposed labeling claim, BI submitted the results of one 6 month, placebo controlled clinical trial with Spiriva HandiHaler, Study 205.266, and the combined results from two 48-week, clinical trials with Spiriva Respimat. Also referenced was the comparison between Spiriva Respimat and Spiriva HandiHaler, including two 4 week cross-over studies. The focus of the efficacy discussion will be Study 205.266 as the Spiriva Respimat trials were addressed in the review for NDA# 21-936.

Table 1 Summary of Clinical Program

Study No.	Description	Subjects	Design	Dose	Duration	Endpoints
205.266 United States Sept 2001- Feb 2003	P4 efficacy trial – COPD exacerbations	1829 subjects with COPD	R, DB, PC	18 mcg Spiriva HandiHaler QD Placebo HandiHaler QD	6 months	COPD exacerbations
205.249 United States Canada Nov 2002- Apr 2004	P3 cross over comparison of tiotropium inhalation powder and inhalation spray	131 subjects with COPD	R, DB, DD, AC, PC, XO trial	5mcg Tio Respimat QD 10mcg Tio Respimat QD 18 mcg Spiriva HandiHaler QD Placebo Respimat QD Placebo HandiHaler QD	4 weeks	Trough FEV1 (non-inferiority)
205.250 Netherlands Belgium Aug 2002 – July 2003	P3 cross over comparison of tiotropium inhalation powder and inhalation spray	76 subjects with COPD	R, DB, DD, AC, PC, XO trial	5mcg Tio Respimat QD 10mcg Tio Respimat QD 18 mcg Spiriva HandiHaler QD Placebo Respimat QD Placebo HandiHaler QD	4 weeks	Trough FEV1 (non-inferiority)
205.254 Multinational Feb 2003 – June 2005	P3 48 week safety and efficacy trial	983 subjects with COPD	R, DB, PC, //	5mcg Tio Respimat QD 10mcg Tio Respimat QD Placebo Respimat QD	48 week	Trough FEV1, SGRQ, TDI, exacerbations (combined)
205.255 Multinational Mar 2003 – June 2005	P3 48 week safety and efficacy trial	1007 subjects with COPD	R, DB, PC, //	5mcg Tio Respimat QD 10mcg Tio Respimat QD Placebo Respimat QD	48 week	FEV1, SGRQ, TDI exacerbations (combined)

Phase 3 Efficacy Design

Study 205.266 was a phase 4, 6 month, randomized, double-blind, parallel group, placebo controlled trial in a Veteran's Affairs setting. Patients were enrolled with a diagnosis of moderate to severe COPD, with the following pertinent entry criteria: a) 40 years of age and older; b) $FEV_1/FVC \leq 70\%$ and $FEV_1 \leq 60\%$; and c) current or ex-smokers with a smoking history of > 10 years. Patients with a history of asthma or who were using oral corticosteroids in excess of 20mg of prednisone per day were excluded. Other pertinent exclusion criteria included: a) recent history of myocardial infarction; b) unstable or life-threatening cardiac arrhythmia; c) narrow angle glaucoma; and d) moderate to severe renal impairment. Unlike other clinical trials with Spiriva HandiHaler, many concomitant medications were allowed, including long-acting $beta_2$ adrenergic agonists, inhaled corticosteroids, chronic oxygen, and theophylline. The only medications not allowed during the treatment period were anticholinergic agents.

There were two co-primary endpoints: 1) the proportion of patients who experienced a COPD exacerbation and 2) the proportion of patients with a hospitalization associated with a COPD exacerbation during the 6 month period. Secondary endpoints included other aspects of COPD exacerbation including: time to first COPD exacerbation, time to first hospitalization for COPD exacerbation, number of days on corticosteroids for exacerbation, and number of days on antibiotics. In addition, spirometry measurements were also secondary endpoints, including trough FEV_1 and trough FVC.

BI seeks a labeling claim for reduction of exacerbations in the product label. There is no standard, well-accepted definition of COPD exacerbation.[1] In Study 205.266, COPD exacerbation was defined as a complex of respiratory events/symptoms with a duration of three days of more requiring a change in treatment. A complex of respiratory events/symptoms means ≥ 2 of the following (increase of symptom or new onset): cough, sputum, wheezing, dyspnea, or chest tightness. A change in treatment included antibiotics and/or systemic corticosteroids and/or hospitalization. Exacerbations were categorized as mild, moderate, and severe:

- mild – treatment with antibiotics, no visit to health care facility
- moderate – visit to outpatient facility or treatment with corticosteroids
- severe – hospital admission or ER visit greater than 24 hours

Patients recorded COPD exacerbation symptoms daily in diaries. In addition, patients recorded any treatment for exacerbations or visit to health care providers. Study personnel reviewed the diaries during study visits and interim telephone calls. Events that met the protocol definition of exacerbation were recorded in a specific section of the case report form.

Although there is no well-accepted definition of COPD exacerbation, the definition used in this clinical program is reasonable as it includes both symptoms and treatment and is consistent with definitions in the literature. This definition is also consistent with the definition of COPD exacerbation used for the Spiriva Respimat program.

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[1] Cazzola M, MacNee W, et. al. Outcomes for COPD pharmacological trials: from lung function to biomarkers. *Eur Respir J* 2008; 31: 416-418.

One other product (Advair Diskus) has a labeling claim (and indication) for the reduction of COPD exacerbations, thus there is a regulatory pathway for this type of claim. While the definition used by BI is not exactly the same as used in the Advair clinical trials, the definition has many of the same elements. It should be noted that to support the COPD exacerbation claim, BI submitted Study 205.266 with Spiriva HandiHaler, which is described in this section. In addition, BI submitted the results of two 48 week clinical trials with Spiriva Respimat (Studies 205.254 and 205.255). The use of efficacy data from Spiriva Respimat is not acceptable for substantiation of the findings of COPD exacerbation as the Respimat is a different drug product. Because the dose, formulation, and delivery system are all very different for this locally acting product, extrapolation of efficacy is not acceptable.

Phase 3 Efficacy Results

In general, patients enrolled in Study 205.266 were primarily white males with a mean age around 68 years and a baseline pre-bronchodilator FEV_1 of approximately 1 liter (~36% predicted). The demographic profile was generally balanced between treatment groups in the trials. There was a difference in patient disposition between treatment groups because the placebo group had a higher percentage of patients who discontinued, the primary reason being worsening of COPD.

The following table shows the results for the co-primary endpoints (shaded) and some of the key secondary endpoints related to COPD exacerbation. One point is worth noting - the second co-primary endpoint was not statistically significant.

Table 2 COPD Exacerbation Endpoints in Study 205.266

	Spiriva HandiHaler N=914	Placebo N=915	Odds Ratio (p value)
Percentage of patients with exacerbation	27.9	32.3	0.81 (0.037)
Percentage of patients with hospitalizations due to exacerbation	7.0	9.5	0.72 (0.056)
Exacerbations per patient year*	0.71	0.88	0.81 (0.037)
Antibiotic days per patient year*	6.5	7.9	0.83 (0.105)
Corticosteroid days per patient year*	4.4	5.3	0.85 (0.375)

* adjusted for center and corrected for overdispersion, thus results are different than what is reported in the study report for Study 205.266

The secondary endpoints related to COPD exacerbation were numerically supportive but were not uniformly statistically significant. The Applicant proposes a claim regarding a delay in time to first exacerbation, based upon a secondary endpoint. Claims based upon secondary endpoints typically are not encouraged due to multiplicity concerns. However, the secondary endpoint, time to first COPD exacerbation, is not expected to be independent of the primary efficacy analyses and it was selected from a relatively limited number of pre-specified secondary endpoints, therefore, the risk of a Type I error due to inadequate multiplicity correction is low. Thus, this claim, based upon a secondary endpoint, may potentially be considered. In Study 205.266, the time to first exacerbation was statistically significant compared to placebo (RR 0.83, p=0.04). While the finding needs to be replicated to consider

as a labeling claim, the exact wording of the exacerbation claim will need to be carefully considered as the secondary endpoints assessed many aspects of COPD exacerbation.

It is important to address the analysis of the data for the number of COPD exacerbations, antibiotic days, and corticosteroid days. Ideally, analysis of this data should account for the follow up time and the between-patient variability in the data.[2] Correction for follow up time or exposure is important as there is differential discontinuation between the active and placebo groups. Correction for over dispersion in the data is important because some patients may have different rates of events. Because of this issue, the Division requested that BI re-analyze the data correcting for over dispersion, which accounts for the variability of the data between patients. These corrected results are shown in the above table and are not as robust as what is reported in the original study report. As has been illustrated, analyses of these types of endpoints are sensitive to the statistical methods chosen so that careful consideration of these issues and further exploration of the statistical methods involved would be warranted in planning future studies with these types of "counts-of-events" endpoints particularly if the endpoints were intended to serve as the primary efficacy endpoints.

The other key secondary endpoints were spirometry measurements. For trough FEV_1 and FVC, Spiriva HandiHaler was statistically significant compared to placebo on Day 1 and end of study (Day 150). For FEV_1 the treatment group difference was 130mL and 170mL on Day 1 and Day 150, respectively.

Two issues identified during the review period are worth brief discussion: protocol violations and missing data. A large number of protocol violations were noted with the most common being visits outside the examination window, prohibited medication use and improper medication washout. Prohibited medication use was primarily use of ipratropium bromide. Dr. Michele determined that these protocol violations are unlikely to affect the results of the study and I concur. However, another issue identified during the review period was the handling of missing COPD exacerbation data. The Division requested clarification regarding handling of the missing COPD exacerbation data and had a teleconference with BI to further discuss this issue. The Applicant indicated that if a patient missed a clinic visit the diary data regarding exacerbations was collected since the last clinic visit and transcribed onto the CRF at the next clinic visit. Thus, even though 23% of patients had missing examination data, the COPD exacerbation data was captured at the next visit, which is acceptable.

In summary, the results of Study 205.266 are supportive of a COPD exacerbation claim, but replication of the findings is necessary to support the COPD exacerbation labeling claim. The combined results from Studies 205.254 and 205.255 with Spiriva Respimat are not adequate for replication of findings since these studies were conducted with Spiriva Respimat, which is a different product and efficacy cannot be extrapolated.

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[2] Suissa, S. Statistical treatment of exacerbations in therapeutic trials of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2006; 173: 842-846.

8. Safety

In Study 205.266, limited safety monitoring was performed in that only serious adverse events (SAEs) were reported. Non-serious adverse events, laboratories, and ECGs were not collected. While this level of safety monitoring is not ideal, it is acceptable because Spiriva HandiHaler is an approved drug product indicated for patients with COPD, and the safety in this population has been established.

Review of the safety data (SAEs) from Study 205.266 did not identify any new safety signal for Spiriva HandiHaler. There were a few more deaths in the Spiriva HandiHaler group (22, 2.4%) compared to placebo (19, 2.1%); however, the cause of death was generally balanced and not unexpected in this older population. The most common SAEs were COPD exacerbation, pneumonia, bronchitis, myocardial infarction, and congestive heart failure. These SAEs were generally balanced with the exception of bronchitis which was more common in the Spiriva HandiHaler group (1.1%) compared to placebo (0.5%). These common SAEs are not unexpected in the COPD population.

No new safety signals were identified in Study 205.266, but two outstanding safety issues with tiotropium warrant a brief discussion.

In November 2007, BI submitted a pooled analysis of 29 placebo controlled clinical studies with Spiriva HandiHaler (25 clinical trials) and tiotropium Respimat (4 clinical trials), which was performed as part of routine safety. BI noted an increased risk of stroke (RR 1.37, 95% CI 0.73-1.56) in patients treated with tiotropium compared to placebo. This analysis is not adjusted for multiplicity. While the results are not statistically significant, the Division issued an Early Communication regarding this potential serious safety signal in March 2008.[3] In the Early Communication, it was noted that the Applicant recently completed a large, 4 year, placebo controlled clinical trial with Spiriva HandiHaler – Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) in 6000 patients with COPD. Data from UPLIFT will be helpful to further evaluate the potential stroke safety signal with Spiriva HandiHaler. BI submitted preliminary results from UPLIFT during the review period, which did not show an increase in stroke with Spiriva HandiHaler; however, the final study has not been submitted for review, but is expected in November 2008. In this efficacy supplement, there was no increase in stroke with Spiriva HandiHaler in Study 205.266. The issue of stroke is not a deficiency for this efficacy supplement, but it is an outstanding safety issue that needs to be addressed and a comment will be conveyed to the Applicant.

The second outstanding safety issue with tiotropium is an increase in deaths compared to placebo which was noted in the two 48-week phase 3 studies in the Spiriva Respimat program, which was the reason a Complete Response action was taken on this NDA. No increase in death has been noted with Spiriva HandiHaler based upon the original program supporting approval and a pooled analysis of studies with Spiriva HandiHaler.[4] This issue is not a

[3] Early Communication about an Ongoing Safety Review of Tiotropium
http://www fda.gov/cder/drug/early_comm/tiotropium.htm
[4] Kesten S, Jara M, et. al. Pooled clinical trial analysis of tiotropium safety. *Chest*. 2006; 130: 1695-1703.

deficiency for this efficacy supplement, but it is an outstanding safety issue that needs to be addressed for the Spiriva Respimat NDA.

9. Advisory Committee Meeting

An advisory committee meeting was not held for this efficacy supplement because the supplement is not adequate for approval as the Division requires replication of the efficacy findings to support a COPD exacerbation labeling claim.

10. Pediatrics

BI was granted a waiver for pediatric studies in the January 30, 2004, Approval letter for Spiriva HandiHaler, because Spiriva HandiHaler is indicated for COPD, which is a disease of adults. BI requested a pediatric waiver for this efficacy supplement for the same reason, which is acceptable.

11. Other Relevant Regulatory Issues

A DSI audit was requested since this efficacy supplement proposed a new COPD exacerbation labeling claim. Two clinical sites and the Duke Clinical Research Institute, which performed the data entry and management functions for Study 205.266, were selected for audit. As of the date of finalization of this review, DSI audit of two of the investigational sites have been performed. The two clinical sites, Dr. Claudia Cote (Bay Pines VAMC, St. Petersburg, FL) and Dr. Daniel Paulson (McGuire VAMC, Richmond, VA) were chosen because they had high enrollment. DSI audit showed that there were some minor issues with both sites. The efficacy data was deemed reliable. One site enrolled 6 patients that had a history of asthma and the DSI audit report suggested analyzing the data without these 6 subjects. However, in this large trial, data from 6 patients is unlikely to alter the conclusions. DSI audit of the CRO was limited in that the only records at the Duke Clinical Research Institute CRO were the contract records and correspondence between the CRO and BI. Preliminary findings did not note any deviations in the standard operating procedures.

12. Labeling

BI submitted the Spiriva HandiHaler label in the PLR format. Because the decision is to not approve this efficacy supplement, labeling negotiations were not conducted with the Applicant.

13. Recommendations/Risk Benefit Assessment

- Recommended regulatory action

The recommended regulatory action is **Complete Response**. The submitted data are not adequate to support the proposed exacerbation labeling claim. While Study 205.266 supports a COPD exacerbation labeling claim, replication of the findings is necessary to support the labeling claim. The combined results from Studies 205.254 and 205.255 with Spiriva Respimat are not adequate for replication of findings since these studies were conducted with Spiriva Respimat, which is a different product and efficacy cannot be extrapolated. No new safety signals were indentified in Study 205.266, but there is an outstanding safety issue of stroke with tiotropium that should also be addressed.

- Risk Benefit Assessment

Spiriva HandiHaler is currently approved for the long term, once-daily, maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema (i.e. a bronchodilator for patients with COPD) and has been deemed to have a favorable risk benefit assessment for that indication. The proposed labeling claim is for the same population (COPD patients) and would not change the risk benefit assessment.

- Recommendation for Postmarketing Risk Management Activities

This section is not applicable since the recommended regulatory action is **Complete Response**.

- Recommendation for other Postmarketing Study Commitments

This section is not applicable since the recommended regulatory action is **Complete Response**.

- Recommended Comments to Applicant

Deficiency

The submitted data do not provide substantial evidence that Spiriva HandiHaler is sufficiently effective for the proposed claim that "Spiriva HandiHaler significantly reduced the proportion of COPD patients who experienced exacerbations compared to placebo and significantly delayed the time to first COPD exacerbation." Replication of the findings is necessary to support the COPD exacerbation labeling claim. The combined results from Studies 205.254 and 205.255 with Spiriva Respimat are not adequate for replication of findings since these studies were conducted with Spiriva Respimat, which is a different product and efficacy cannot be extrapolated.

Information Needed to Resolve the Deficiency

To support approval of Spiriva HandiHaler for the proposed COPD exacerbation labeling claim, provide data from an adequate and well-controlled study with Spiriva HandiHaler to replicate the efficacy findings in Study 205.266.

Additional Comment

Increased frequencies of stroke were observed in patients treated with tiotropium bromide compared to placebo in a pooled analysis of clinical study data with Spiriva HandiHaler and Spiriva Respimat. Provide data from an adequate and well-controlled study to address the concerns of stroke. The study should be of adequate duration and power that will allow evaluation of this safety concern.

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/s/

Sally Seymour
10/31/2008 09:44:50 AM
MEDICAL OFFICER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21395	SUPPL-29	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	SPIRIVA HANDIHALER

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/s/

SALLY M SEYMOUR
12/17/2009

BADRUL A CHOWDHURY
12/17/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-395/S029

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA supplement
Submission Number	21-395
Submission Code	SE 08, S029
Letter Date	November 17, 2008
Stamp Date	November 17, 2008
PDUFA Goal Date	December 17, 2009
Reviewer Name	Theresa M. Michele, MD
Review Completion Date	November 30, 2009
Established Name	tiotropium bromide
(Proposed) Trade Name	Spiriva HandiHaler
Therapeutic Class	anticholinergic bronchodilator
Applicant	Boehringer Ingelheim
Priority Designation	S
Formulation	inhalation powder
Dosing Regimen	18 mcg QD
Indication	labeling claim for reduction in COPD exacerbations and respiratory failure
Intended Population	adults with COPD

Table of Contents

1 EXECUTIVE SUMMARY 7

1.1 RECOMMENDATION ON REGULATORY ACTION 7
1.2 RECOMMENDATION ON POSTMARKETING ACTIONS 8
1.2.1 Risk Management Activity 8
1.2.2 Required Phase 4 Commitments 8
1.2.3 Other Phase 4 Requests 8
1.3 SUMMARY OF CLINICAL FINDINGS 8
1.3.1 Brief Overview of Clinical Program 8
1.3.2 Efficacy 9
1.3.3 Safety 11
1.3.4 Dosing Regimen and Administration 13
1.3.5 Drug-Drug Interactions 13
1.3.6 Special Populations 13

2 INTRODUCTION AND BACKGROUND 13

2.1 PRODUCT INFORMATION 13
2.2 CURRENTLY AVAILABLE TREATMENT FOR INDICATIONS 14
2.3 AVAILABILITY OF PROPOSED ACTIVE INGREDIENT IN THE UNITED STATES 14
2.4 IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED PRODUCTS 14
2.5 PRESUBMISSION REGULATORY ACTIVITY 16
2.6 OTHER RELEVANT BACKGROUND INFORMATION 17

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES 17

3.1 CMC (AND PRODUCT MICROBIOLOGY, IF APPLICABLE) 17
3.2 ANIMAL PHARMACOLOGY/TOXICOLOGY 17

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY 17

4.1 SOURCES OF CLINICAL DATA 17
4.2 TABLES OF CLINICAL STUDIES 18
4.3 REVIEW STRATEGY 18
4.4 DATA QUALITY AND INTEGRITY 18
4.4.1 Division of Scientific Investigation audits 18
4.4.2 Other audits 22
4.5 COMPLIANCE WITH GOOD CLINICAL PRACTICES 22
4.6 FINANCIAL DISCLOSURES 22

5 CLINICAL PHARMACOLOGY 23

6 INTEGRATED REVIEW OF EFFICACY 23

6.1 EFFECTS ON LUNG FUNCTION 23
6.1.1 Methods 24
6.1.2 General Discussion of Lung Function Endpoints 24
6.1.3 Study Design 27
6.1.4 Lung Function Efficacy Findings 27
6.1.5 Clinical Microbiology 34
6.1.6 Lung Function Efficacy Conclusions 34
6.2 EFFECTS ON COPD EXACERBATIONS 35
6.2.1 Methods 35
6.2.2 General Discussion of COPD Exacerbation Endpoints 35
6.2.3 Study Design 37
6.2.4 COPD Exacerbation related Efficacy Findings 37

6.2.5 Clinical Microbiology 45
6.2.6 COPD Exacerbation Efficacy Conclusions 45

7 INTEGRATED REVIEW OF SAFETY 45

7.1 METHODS AND FINDINGS 45
7.1.1 Deaths 46
7.1.2 Other Serious Adverse Events 55
7.1.3 Dropouts and Other Significant Adverse Events 57
7.1.4 Other Search Strategies 60
7.1.5 Common Adverse Events 61
7.1.6 Less Common Adverse Events 68
7.1.7 Laboratory Findings 70
7.1.8 Vital Signs 70
7.1.9 Electrocardiograms (ECGs) 70
7.1.10 Immunogenicity 70
7.1.11 Human Carcinogenicity 70
7.1.12 Special Safety Studies 71
7.1.13 Withdrawal Phenomena and/or Abuse Potential 71
7.1.14 Human Reproduction and Pregnancy Data 71
7.1.15 Assessment of Effect on Growth 72
7.1.16 Overdose Experience 72
7.1.17 Postmarketing Experience 72
7.2 ADEQUACY OF PATIENT EXPOSURE AND SAFETY ASSESSMENTS 73
7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety 73
7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety 77
7.2.3 Adequacy of Overall Clinical Experience 81
7.2.4 Adequacy of Special Animal and/or In Vitro Testing 81
7.2.5 Adequacy of Routine Clinical Testing 81
7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup 81
7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study 82
7.2.8 Assessment of Quality and Completeness of Data 82
7.2.9 Additional Submissions, Including Safety Update 84
7.3 SUMMARY OF SELECTED DRUG-RELATED ADVERSE EVENTS, IMPORTANT LIMITATIONS OF DATA, AND CONCLUSIONS 84
7.4 GENERAL METHODOLOGY 86
7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence 86
7.4.2 Explorations for Predictive Factors 86
7.4.3 Causality Determination 87

8 ADDITIONAL CLINICAL ISSUES 87

8.1 DOSING REGIMEN AND ADMINISTRATION 87
8.2 DRUG-DRUG INTERACTIONS 87
8.3 SPECIAL POPULATIONS 88
8.4 PEDIATRICS 88
8.5 ADVISORY COMMITTEE MEETING 88
8.6 LITERATURE REVIEW 89
8.7 POSTMARKETING RISK MANAGEMENT PLAN 89
8.8 OTHER RELEVANT MATERIALS 89

9 OVERALL ASSESSMENT 89

9.1 CONCLUSIONS 89
9.2 RECOMMENDATION ON REGULATORY ACTION 93

9.3 RECOMMENDATION ON POSTMARKETING ACTIONS 94
9.3.1 Risk Management Activity....94
9.3.2 Required Phase 4 Commitments 94
9.3.3 Other Phase 4 Requests....94
9.4 LABELING REVIEW....94
9.4.1 PLR format....94
9.4.2. New language....96
9.5 COMMENTS TO THE APPLICANT 96

10 APPENDICES....97

10.1 REVIEW OF INDIVIDUAL STUDY REPORTS: 205.235 97
10.1.1 Protocol 97
10.1.2 Results....115
10.1.3 Summary and conclusions....153
10.2 LINE-BY-LINE LABELING REVIEW 155
10.2.1 PLR format....155
10.2.2. New language....157

REFERENCES 158

List of Tables

Table 1: Currently available drugs for the treatment of COPD 14
Table 2: Spiriva HandiHaler clinical studies submitted for this supplement....18
Table 3: Protocol 205.235 domestic sites proposed for inspection 19
Table 4: Protocol 205.235 international sites proposed for inspection....21
Table 5: Protocol 205.235 rate of decline in FEV1 (random effects model)....28
Table 6: Protocol 205.235 rate of decline in FEV1 by smoking status 29
Table 7: Protocol 205.235 FEV1 31
Table 8: Protocol 205.235 COPD related events endpoints 41
Table 9: Protocol 205.235 subgroup analysis of COPD exacerbation: number (%) of patients with an exacerbation and median time to first exacerbation (in months) 43
Table 10: Protocol 205.235 fatal event summary 46
Table 11: Protocol 205.235 on-treatment adjudicated cause of death occurring in ≥ 10 patients in either treatment group 48
Table 12: Protocol 205.235 subgroup analysis of pneumonia deaths....49
Table 13: Protocol 205.235 number needed to treat for mortality....50
Table 14: Protocol 205.235 subgroup analysis of on-treatment deaths (all) 51
Table 15: Protocol 205.235 serious adverse events occurring in ≥ 1% of patients in either treatment group (as reported by applicant) 56
Table 16: Protocol 205.235 adverse events leading to discontinuation occurring in ≥ 10 patients overall 58
Table 17: Protocol 205.235 stroke adverse events....59
Table 18: Protocol 205.235 combined stroke definition....62
Table 19: Protocol 205.235 frequency and incidence rates (per 100 patient years) of patients with AEs occurring in >3% of either treatment group....67
Table 20: Protocol 205.235 frequency and incidence rates (per 100 patient years) of patients with AEs with a risk ratio of ≥3 69
Table 21: Protocol 205.235 patient demographic and disease characteristics....74

Table 22: Protocol 205.235 baseline PFT data 75
Table 23: Protocol 205.235 summary of treatment exposure 76
Table 24: Patient-years of exposure across the tiotropium program 78
Table 25: Pooled analysis results for major adverse cardiac events 78
Table 26: Singh, et al. anticholinergic meta-analysis results 80
Table 27: Protocol 205.235 protocol violations 83
Table 28: Protocol 205.235 treatment compliance 84
Table 29: Protocol 205.235 study flow chart 102
Table 30: Protocol 205.235 patient disposition 116
Table 31: Protocol 205.235 unblinded patients 117
Table 32: Protocol 205.235 patient demographic and disease characteristics 119
Table 33: Protocol 205.235 baseline PFT data 120
Table 34: Protocol 205.235 protocol violations 121
Table 35: Protocol 205.235 treatment compliance 122
Table 36: Protocol 205.235 concomitant pulmonary medications used at least once during the study 123
Table 37: Protocol 205.235 patients included in the analysis of rate of decline of PFT and SGRQ 124
Table 38: Protocol 205.235 rate of decline in FEV1 (random effects model) 125
Table 39: Protocol 205.235 rate of decline in FEV1 by smoking status 126
Table 40: Protocol 205.235 rate of decline in FEV1 modeled for different slopes during ICS/LABA use and non-use 127
Table 41: Protocol 205.235 rate of decline in FEV1 by baseline LABA or ICS use 127
Table 42: Protocol 205.235 FEV1 131
Table 43: Protocol 205.235 overall mean SGRQ scores 134
Table 44: Protocol 205.235 COPD related events endpoints 135
Table 45: Protocol 205.235 summary of treatment exposure 138
Table 46: Protocol 205.235 overall adverse event summary 139
Table 47: Protocol 205.235 fatal event summary 140
Table 48: Protocol 205.235 on-treatment adjudicated cause of death occurring in ≥ 10 patients in either treatment group 142
Table 49: Protocol 205.235 serious adverse events occurring in ≥ 1% of patients in either treatment group (as reported by applicant) 145
Table 50: Protocol 205.235 stroke adverse events 146
Table 51: Protocol 205.235 adverse events leading to discontinuation occuring in ≥ 10 patients overall 147
Table 52: Protocol 205.235 frequency and incidence rates (per 100 patient years) of patients with AEs occurring in >3% of either treatment group 149
Table 53: Protocol 205.235 frequency and incidence rates (per 100 patient years) of patients with AEs with a risk ratio of ≥3 150

List of Figures

Figure 1: Protocol 205.235 mean pre-bronchodilator FEV1 28
Figure 2: Protocol 205.235 pre-bronchodilator FEV1 over time by smoking status 29
Figure 3: Protocol 205.235 post-bronchodilator FEV1 over time by smoking status 30

Figure 4: Study 205.235 Kaplan-Meier estimates of the probability of no exacerbation.....38
Figure 5: Protocol 205.235 Kaplan-Meier estimates of the probability of no exacerbation leading to hospitalization 39
Figure 6: Protocol 205.235 Kaplan-Meier estimates of probability of no all cause mortality [adjudicated on treatment deaths censored at Day 1470] 47
Figure 7: Protocol 205.235 mortality subgroup analysis Forest plot.....54
Figure 8: Protocol 205.235 mean pre-bronchodilator FEV1 125
Figure 9: Study 205.235 Kaplan-Meier estimates of the probability of no exacerbation....128
Figure 10: Protocol 205.235 Kaplan-Meier estimates of the probability of no exacerbation leading to hospitalization 129
Figure 11: Protocol 205.235 Kaplan-Meier estimates of probability of no all cause mortality [adjudicated on treatment deaths censored at Day 1470] 141

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Tiotropium bromide dry powder inhaler (HandiHaler inhalation device, 18 mcg tiotropium) was approved on January 30, 2004 (NDA 21-395) for the long-term, once-daily maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. Tiotropium is a specific antagonist at muscarinic acetylcholine receptors, often called anticholinergic. The Applicant, Boehringer Ingelheim Pharmaceuticals, Inc., now seeks additional efficacy claims for the HandiHaler with an additional 3 years of marketing exclusivity. Requested efficacy claims included in the clinical trials section of the label are: 1) description of the long-term effects on lung function, 2) reduction in exacerbations, 3) reduction in mortality, and 4) reduction in respiratory failure.

To support this application, BI submitted a 4-year, placebo-controlled, parallel group trial enrolling nearly 6000 patients with moderate-severe COPD. The short title of this trial is UPLIFT: Understanding Potential Long-term Impacts on Function with Tiotropium (Protocol 205.235). In addition, BI referenced trial 205.266 (submitted under S024) to support the COPD exacerbation claim. On July 22, 2009, BI withdrew the mortality claim. According to BI, there were no new Spiriva HandiHaler data contributing to this decision. From an efficacy perspective, the applicant has provided sufficient data to support two of the proposed claims: long-term effects on lung function and reduction in exacerbations. Reduction in respiratory failure is not supported because the improvement is marginally significant and is not predefined.

From a safety perspective, there have been potential safety signals of stroke and cardiovascular events associated with Spiriva HandiHaler reported in the public domain recently. The UPLIFT trial did not show an increase in mortality, stroke, or cardiovascular events in the tiotropium group relative to placebo. In fact, the results suggest a decrease in mortality and cardiovascular events with Spiriva HandiHaler, but the upper bounds of the confidence intervals for stroke were greater than one. However, concerns regarding a numeric increase in mortality relative to placebo with another formulation of tiotropium (Spiriva Respimat) complicate the mortality evaluation for Spiriva HandiHaler. Results of the UPLIFT study along with the Respimat data were discussed at a Pulmonary and Allergy Drug Advisory Committee (PADAC) meeting held November 19, 2009. Potential safety signals of stroke and cardiovascular events previously identified as part of pooled analyses and meta-analyses were also discussed at the meeting. The committee voted in favor of support of the exacerbation claim and that the UPLIFT trial adequately addressed potential safety signals of stroke and cardiovascular events.

The clinical recommendation for this application is that the lung function and reduction of exacerbation claims are adequately supported. The respiratory failure claim is not

adequately supported. The clinical recommendation is approval pending agreed upon labeling.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Risk Management activity is not recommended for this application.

1.2.2 Required Phase 4 Commitments

There are no required Phase 4 commitments for this application.

1.2.3 Other Phase 4 Requests

There are no other Phase 4 requests for this application.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

To support the proposed claims, the applicant submitted the results of Protocol 205.235 (UPLIFT) and Protocol 205.266 (VA study). With 5992 patients enrolled over a 4 year treatment period, the UPLIFT trial doubles the size of the tiotropium safety database. Mortality for this trial was collected both on-treatment and for discontinued patients out to the time of their scheduled exit date from the study (vital status). Cause of death was adjudicated in a blinded fashion by an independent committee.

This application cross references Protocol 205.266, a 6-month, placebo controlled trial evaluating the effect of Spiriva HandiHaler on COPD exacerbations in a US Veterans Affairs setting. Protocol 205.266 was previously reviewed under Spiriva HandiHaler NDA 21-395, S-024. Refer to Medical Officer Review NDA 21-395, S024, dated September 22, 2008.

The Applicant initially requested four efficacy claims included in the clinical trials section of the label: 1) description of the long-term effects on lung function, 2) reduction in exacerbations, 3) reduction in mortality, and 4) reduction in respiratory failure. The claims for lung function and exacerbations are discussed under Section 1.3.2 Efficacy, and the claims for reduction in mortality and respiratory failure are discussed under Section 1.3.3 Safety.

1.3.2 Efficacy

Protocol 205.235 was a multicenter, randomized, double-blind, placebo-controlled, parallel group trial to determine the effect of tiotropium 18 mcg capsule dry powder inhaler (tio HH18) on disease progression over 4 years in 5992 patients with COPD. The two co-primary endpoints were the yearly rate of decline in trough FEV1 from day 30 until completion of double blind treatment and the yearly rate of decline in FEV1 90 minutes after study drug and bronchodilator administration from day 30 until completion of double blind treatment. A number of secondary endpoints included other spirometry endpoints, COPD exacerbation-related endpoints, and the St. George Respiratory Questionnaire (SGRQ). For the purposes of the UPLIFT trial, a COPD exacerbation was defined as "an increase or new onset of more than one respiratory symptoms (cough, sputum, sputum purulence, wheezing, dyspnea) with a duration of three days or more requiring treatment with antibiotics and/or systemic (oral, intramuscular, or intravenous) steroids." Although there is no well-accepted definition of COPD exacerbation, the definition used in this clinical program is reasonable as it includes both symptoms and treatment and is consistent with definitions in the literature.

The UPLIFT trial showed no significant difference between treatment groups in the primary endpoints of rate of decline in pre- and post-bronchodilator FEV1. There was a loss of 30 ml per year of pre-bronchodilator FEV1 in both the placebo and tio HH18 groups and a loss of 42 (placebo) versus 40 ml (tio HH18) per year in post-bronchodilator FEV1. In a subgroup analysis, patients who were sustained quitters from smoking did experience a significant decrease in rate of decline in FEV1 compared to sustained smokers. This effect was observed across both treatment groups and provides internal validation for the trial.

For the key secondary endpoints of time to first COPD exacerbation and time to first COPD exacerbation leading to hospitalization, tiotropium showed a significant difference compared to placebo. For COPD exacerbations, patients in the tio HH18 group had a significantly longer time to event than patients in the placebo group ($p<0.0001$, RR 0.86, 95% CI 0.81-0.91). The median time to first exacerbation was 12.5 months in the placebo group and 16.7 months in the tio HH18 group. Patients in the tio HH18 group also had a statistically significantly longer time to first hospitalization due to COPD exacerbation compared to placebo ($p= 0.0024$, RR 0.86, 95% CI 0.78, 0.95). The lower quartile for time to first exacerbation requiring hospitalization was 28.6 months in the placebo group and 35.9 months in the tio HH group. The UPLIFT trial adjusted for multiplicity using a step-wise approach, i.e. allowing testing of secondary endpoints only if the primary endpoints were met. From a statistical viewpoint, the trial could be considered "failed" for the exacerbation endpoints. This issue of multiplicity was discussed at the PADAC meeting on November 19, 2009.

A significant improvement in most of the additional COPD exacerbation-related endpoints was also observed. These included the number of COPD exacerbations, time to first exacerbation treated with steroids, time to first exacerbation treated with antibiotics, number of exacerbations treated with steroids, number of exacerbation days, number of COPD

exacerbations leading to hospitalization, and number of days hospitalized due to exacerbation per patient year.

Spirometry endpoints included trough FEV1, FVC, and SVC response and 90 minute FEV1, FVC, and SVC response. Endpoints were measured every six months throughout the four-year treatment period. Consistent with the known bronchodilator properties of the drug, the tio HH18 group generally demonstrated a significant improvement ($p<0.0001$) over placebo for all endpoints and time points tested. These data are supportive of the description of spirometry outcomes for the trial the Applicant proposes for the label. Based upon review of the pulmonary function data, the Applicant's proposed claim regarding lung function is generally supported. It is reasonable to describe UPLIFT in the product label and note that the primary endpoints were not significantly different. Regarding the sustained improvement in trough FEV1, this is consistent with the current indication and efficacy data in the product label and would also be reasonable to include in the description of the outcomes of UPLIFT in the product label.

SGRQ endpoints included rate of SGRQ deterioration, as well as total and component SGRQ scores. There were no differences in rate of decline in SGRQ scores from month 6 until completion of treatment for the activity component, impact component, or total scores. The mean SGRQ scores showed a statistically significant but not clinically important decrease across all domains and timepoints for the tio HH18 group compared to placebo, with a treatment difference ranging from -2.30 to -3.35 ($p<0.0001$) for the total SGRQ score.

Protocol 205.266 (VA trial, submitted under NDA 21-395, S-024) was a multicenter, 6-month, randomized double-blind, placebo controlled trial of tio HH18 mcg in COPD patients in a Veteran's Affairs setting. The enrollment criteria were similar to UPLIFT. There were two co-primary endpoints: 1) the proportion of patients who experienced a COPD exacerbation and 2) the proportions of patients with a hospitalization associated with a COPD exacerbation during the 6 month period. The definition of COPD exacerbation used in this clinical trial is also reasonable as it includes both symptoms and treatment and is consistent with definitions in the literature.

The results of the VA study demonstrated that fewer patients in the tio HH18 group compared to placebo (27.9% versus 32.3%, $p=0.037$) experienced a COPD exacerbation over the 6 months of the trial. In addition, there were significantly fewer exacerbations per patient year. This evidence from Protocol 205.266, in conjunction with data from the UPLIFT trial, are supportive of an exacerbation claim. The exact wording of the claim will need consideration as various aspects of exacerbation were measured in this trial.

On November 19, 2009, the PADAC voted that the UPLIFT and VA trials provide substantial and convincing evidence to support the claim that Spiriva HandiHaler reduces COPD exacerbations.

1.3.3 Safety

The safety discussion for this application is complex because there are several potential safety signals that have recently been indentified for Spiriva HandiHaler. These potential safety signals include stroke, myocardial infarction, and cardiovascular death. Because of its size, duration, and randomized, placebo-controlled design, the UPLIFT trial (Protocol 205.235) is particularly useful to address these potential safety signals.

Mortality is an important outcome to address. The Applicant made protocol amendments to UPLIFT to provide more robust mortality data. Mortality was collected both on-treatment and for discontinued patients out to the time of their scheduled exit date from the study (vital status). Cause of death was adjudicated in a blinded fashion by an independent committee. While the Applicant has withdrawn their initial proposal for a mortality benefit claim, a detailed discussion of mortality is still warranted. In addition, when considering the mortality data from UPLIFT, it is of interest to briefly discuss an issue with the mortality data from a tiotropium product under development, Spiriva Respimat. Spiriva Respimat is a completely new inhalation solution formulation of tiotropium. The Applicant has conducted 3 one year clinical trials with Spiriva Respimat in patients with COPD that show a numerical imbalance in mortality, favoring placebo. There is no consistent cause of death. A review of the mortality data from the Spiriva Respimat program is available under NDA 21-936 and IND (b) (4)

In UPLIFT (Protocol 205.235), the total number of deaths during treatment (including the last day of study drug plus 30 days) was 792; 411 (13.7%) in the placebo group and 381 (12.8%) in the tiotropium group. Vital status information was known for 98% of tio HH18 treated patients and 97% of placebo treated patients including discontinued patients out to at least 45 months post-randomization. Compared to the on-treatment mortality, an additional 149 deaths were collected for patients who discontinued. The risk ratio for death from any cause (tiotropium/placebo) on treatment was 0.84 [95% CI (0.73, 0.97)]. The risk ratio for death remains significantly or nearly significantly different from placebo regardless of the cut off used or inclusion of vital status data.

The primary cause of each death in the UPLIFT trial was adjudicated by an independent committee. The most common causes (adjudicated) of death both on-treatment and including vital status were COPD exacerbation, lung cancer, and death of unknown cause. Combining the preferred terms of sudden death, sudden cardiac death, and death of unknown cause, 127 patients died with sudden or unknown causes of death. Of these, 70 (2.3%) were in the placebo group and 57 (1.9%) were in the tio HH18 group [RR=0.75, 95% CI (0.53, 1.06)].

Overall, these data are supportive of a mortality claim, as UPLIFT is a major study that doubles the size of the safety database, prespecified mortality endpoints and vital status collection were appropriately collected and adjudicated, and the salutary effect on mortality is robust across multiple different analyses. In addition, the mortality benefit was driven by a reduction in fatal COPD exacerbations, suggesting a plausible mechanism of action. However, outstanding issues with regards to mortality with Spiriva Respimat temper such a claim. Also, the mortality benefit was observed in only a single, albeit very large, trial. The

Pulmonary and Allergy Drugs Advisory Committee (PADAC), in their meeting on November 19, 2009, concluded that UPLIFT was a compelling and important study, demonstrating generally beneficial effects on mortality. However, the Respimat results were felt to be somewhat concerning and additional data are needed.

Serious adverse events (SAEs) occurred in 50.9% of the overall study population, including 51.6% of the tio HH18 group and 50.2% of the placebo group. The most common SAEs were COPD exacerbation, pneumonia, and respiratory failure. SAEs were generally balanced between treatment groups, although COPD exacerbations were significantly reduced in the tio HH18 group compared to placebo [RR 0.86, 95% CI (0.76, 0.94), p=0.0014). While the incidence of SAEs of respiratory failure is reduced in the tio HH18 group, the difference is marginally significant and there are multiple related preferred terms that have been analyzed separately. Multiplicity is also an issue. Unlike mortality, which is a hard endpoint and was pre-specified in the protocol as an event of interest (including vital status collection and an independent adjudication committee), the term "respiratory failure" is undefined and subject to investigator interpretation. There is insufficient evidence to justify a specific claim that Spiriva HandiHaler reduces respiratory failure.

There were 618 (20.7%) patients in the tio HH18 group and 735 (24.5%) patients in the placebo group who discontinued prematurely due to an adverse event. The most frequent AEs leading to discontinuation were all lower respiratory events—COPD exacerbation, dyspnea, pneumonia, and respiratory failure. A reduced number of patients in the tio HH18 group discontinued due to COPD exacerbations and dyspnea compared to the placebo group.

The most frequently reported AEs were COPD exacerbation, pneumonia, dyspnea, nasopharyngitis, and upper respiratory tract infection. If evaluated by exposure adjusted rates, COPD exacerbation, dyspnea, and respiratory failure occurred significantly less frequently in the tio HH18 group compared to placebo. In contrast, dry mouth and insomnia occurred significantly more frequently in the tio HH18 group. Dry mouth is a known anticholinergic side effect of tiotropium. In addition, although the numbers were small, intestinal obstruction occurred significantly more frequently in the tio HH18 group and could represent an anticholinergic side effect related to constipation.

Stroke is an adverse event of interest based on a potential safety signal observed in an analysis of combined tiotropium HandiHaler and Respimat trials. Stroke-related adverse events (AEs, SAEs, or fatal events) were not increased in the tio HH18 group relative to placebo (Risk Ratio of 0.95, 0.97, and 0.85, respectively).

Cardiovascular events are also adverse events of interest based on a potential safety signal observed in a meta-analysis literature report. There was no increase in adverse events of myocardial infarction in the tiotropium group compared to placebo, with a Risk Ratio of 0.71, 95% CI (0.52, 0.99). Overall, there was a borderline significant decrease in AEs in the cardiac SOC [RR 0.84, 95% CI (0.73, 0.98)], driven by a decrease in congestive heart failure and MI. Likewise, there was no increase in deaths due to cardiac disorders, sudden cardiac death, sudden death, or death due to unknown cause.

The PADAC voted that the UPLIFT trial adequately addressed potential safety signals of stroke and cardiovascular events for Spiriva HandiHaler.

1.3.4 Dosing Regimen and Administration

Spiriva HandiHaler is approved at a dose of 18 mcg for once daily inhalation. No modifications to the approved dose are proposed in this Application.

1.3.5 Drug-Drug Interactions

Patients in the UPLIFT trial (205.235) were permitted to be on any pulmonary medication other than anticholinergic bronchodilators. Approximately 72% of patients used concomitant long-acting beta-agonists (LABAs) and 74% used inhaled corticosteroids at least once during the trial. In a post-hoc analysis, tio HH18 was shown to reduce the rate of decline in FEV1 for patients not taking LABAs or ICS. However, the UPLIFT design was considerably strengthened by its "real world" approach to inclusion of multiple concomitant medications, similar to the situation encountered in the COPD population in the United States. Thus, one can conclude that in the setting of high-quality COPD care, the addition of tiotropium is unlikely to significantly impact the natural history of disease. Concomitant medication use did not show a difference for other trial endpoints.

No formal drug-drug interaction studies were submitted with this program.

1.3.6 Special Populations

No new data regarding special populations is submitted as part of this application.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

This efficacy supplement is submitted in support of Spiriva HandiHaler (tiotropium bromide) inhalation powder. Tiotropium is a specific antagonist at muscarinic acetylcholine receptors, often called anticholinergic.

Spiriva HandiHaler was approved on January 30, 2004 (NDA 21-395) for the long-term, once-daily maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema in adults. Spiriva HandiHaler consists of a capsule dosage form containing a dry powder formulation of tiotropium bromide intended for oral inhalation only with the HandiHaler inhalation device.

2.2 Currently Available Treatment for Indications

There are several drug classes available for relief of bronchospasm in patients with COPD. These include beta-adrenergic agents, anticholinergic agents, combination beta-agonists/anticholinergics, methylxanthines, and combination corticosteroid/long-acting beta-agonists. See Table 1 for a list of currently available products. Only one product, Advair Diskus, is currently approved for reduction in COPD exacerbations. Only a single dose of Advair Diskus (250/50 mcg) is approved for the chronic treatment of COPD, whereas three doses are approved for asthma.

Table 1: Currently available drugs for the treatment of COPD

Drug class	Generic name	Brand name	Formulation	Dosing frequency
Beta-agonists (short-acting)	albuterol	many	MDI/inhalation solution	Q 4-6 hr
Beta-agonists (long acting)	salmeterol	Serevent Diskus	DPI	BID
	formoterol	Foradil Aerolizer	DPI	BID
	formoterol	Brovana	inhalation solution	BID
anticholinergic (short acting)	ipratropium	Atrovent and others	MDI/inhalation solution	QID
anticholinergic (long-acting)	tiotropium	Spiriva HandiHaler	DPI	QD
methylxanthine	theophylline	many	tablet/ extended release capsule/ oral elixir/ oral syrup/ injectable	QD
combination products	ipratropium/albuterol	Combivent	MDI	QID
	ipratropium/albuterol	Duoneb and others	inhalation solution	QID
	fluticasone/salmeterol	Advair Diskus	DPI	BID

2.3 Availability of Proposed Active Ingredient in the United States

Spiriva HandiHaler was approved on January 30, 2004, for the long-term, once daily treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema. Spiriva HandiHaler is marketed in the US, Japan and EU, as well as many other countries worldwide.

2.4 Important Issues with Pharmacologically Related Products

Tiotropium is a long-acting, antimuscarinic agent, which is often referred to as an anticholinergic bronchodilator. It is manufactured by Boehringer Ingelheim (the Applicant) and is approved for use in patients with COPD as Spiriva HandiHaler. Spiriva HandiHaler

consists of a capsule dosage form containing a dry powder formulation of tiotropium bromide intended for oral inhalation only with the HandiHaler inhalation device. It is intended as a once-daily maintenance treatment for COPD and is not indicated for the initial treatment of acute episodes of bronchospasm, i.e. rescue therapy. According to the product label for Spiriva HandiHaler, the product may worsen symptoms and signs associated with narrow-angle glaucoma, prostatic hyperplasia, or bladder-neck obstruction and should be used with caution in patients with any of these conditions. As a predominantly renally excreted drug, patients with moderate to severe renal impairment treated with Spiriva HandiHaler should be monitored closely. In addition, immediate hypersensitivity reactions and paradoxical bronchospasm are listed in the warnings section of the Spiriva HandiHaler label. The most common adverse events occurring in patients in 1-year placebo and active controlled trials were upper respiratory tract infection (41-43%), dry mouth (12-16%), accidents (5-13%), pharyngitis (7-9%), non-specific chest pain (5-7%), and urinary tract infection (4-7%). In March 2008, the Agency released an Early Communication regarding a potential stroke signal with tiotropium. This is discussed in detail in Section 7.1.6.

On November 16, 2007, the Applicant submitted an NDA (NDA #21-936) for another tiotropium bromide formulation, Spiriva Respimat. Spiriva Respimat is an inhalational spray delivered via the Respimat device. Although sufficient efficacy was demonstrated with tiotropium Respimat to support approval, a complete response action was taken on NDA 21-936 due to outstanding safety issues. This was primarily due to a potential adverse mortality signal demonstrated in the 1-year Phase 3 trials. In addition, a potential stroke signal with tiotropium was identified from controlled clinical trials with Spiriva HandiHaler. The Division determined that additional safety data from a long-term placebo-controlled clinical trial are required to support approval of tiotropium Respimat. In June 2009, Boehringer Ingelheim submitted the results of a one year, placebo controlled, parallel group trial (Protocol 205.372) in 3,991 patients with moderate-severe COPD. Review of this trial also demonstrates a small mortality imbalance in favor of placebo. (See Appendix NDA 21-936 and IND (b) (4) for reviews.)

Ipratropium bromide is a short-acting, anticholinergic bronchodilator that is also manufactured by Boehringer Ingelheim and is approved for use in patients with COPD. The drug substance is marketed as a metered dose inhaler in two formulations: as the sole active agent (Atrovent HFA) and as a combination product with albuterol sulfate (Combivent Inhalation Aerosol). Ipratropium bromide is also approved as an inhalation solution and a nasal spray. According to the product label for Atrovent HFA, the product should be used with caution in patients with narrow-angle glaucoma, prostatic hypertrophy, or bladder neck obstruction. These precautions are based on the potential systemic anticholinergic effects of the drug, and cases of precipitation or worsening of narrow-angle glaucoma and acute eye pain have been reported. Cases of hypotension and allergic-type reactions have also been reported. The most common adverse events occurring in a 1-year active-controlled trial were upper respiratory tract infection (34%), bronchitis (23%), COPD exacerbation (23%), sinusitis (11%), urinary tract infection (10%), influenza-like symptoms (8%), back pain (7%), headache (7%), and dyspnea (7%).

In September 2008, the *Journal of the American Medical Association* published a meta-analysis by Singh, Loke, and Furberg evaluating cardiovascular risk of inhaled anticholinergics[1]. After screening 103 published articles, the authors analyzed 17 literature reports of trials of tiotropium or ipratropium enrolling 14,783 patients for the primary combined outcome of cardiovascular death, myocardial infarction (MI), or stroke. Singh et al. reported a relative risk of 1.58 (95% CI 1.21, 2.06) for anticholinergics compared to placebo and concluded that inhaled anticholinergics are associated with a significantly increased risk of cardiovascular death, MI, or stroke. The effect was primarily demonstrated in the six studies of ≥ 6 months duration (total patients 7267). Of note, 3923 of these patients were drawn from the Lung Health Study, which compared ipratropium to placebo over 5 years. In the Lung Health Study, there was a known and reported imbalance in mortality favoring placebo. This imbalance was investigated by a blue ribbon committee sponsored by the National Institutes of Health, which concluded that the imbalance was a statistical anomaly due to poor compliance with medication.

2.5 Presubmission Regulatory Activity

On November 30, 2007, the Applicant submitted a document to the IND for Spiriva HandiHaler (IND# 46,687) that described a potential stroke safety signal found in a routine safety analysis of pooled data from controlled Spiriva HandiHaler and Spiriva Respimat clinical trials. Based upon BI's analysis of 29 pooled clinical trials, there was an increased risk of stroke with use of tiotropium bromide with a risk ratio of 1.37 (95% CI: 0.73, 15.6). Because of the Agency's commitment to inform the public about ongoing safety reviews, on March 18, 2008, the Agency released an Early Communication about an Ongoing Safety Review of Tiotropium (marketed as Spiriva HandiHaler) that described the preliminary information regarding stroke and Spiriva. This communication was updated on October 7, 2008 with preliminary results from UPLIFT. See Section 7.1.6.

On November 16, 2007, the Applicant submitted a related NDA application (NDA 21-936) for Spiriva Respimat, which is a new inhalation solution formulation of tiotropium bromide administered with a novel Respimat device. In the pivotal 1-year studies for the Spiriva Respimat Application, an imbalance in deaths was noted upon unblinding. The Applicant submitted a summary of mortality data from these trials to the FDA in November 2005, two years prior to the NDA. Because there was a marketed product containing the same drug substance (tiotropium HandiHaler), this issue was reviewed by the Drug Safety Oversight Board on June 15, 2006. The committee concluded that "the potential safety signal for Spiriva Respimat is weak because the signal is present in one of two very similar studies (study 255) and the rate of death in the placebo group of study 255 was zero, a very unusual finding in a COPD population. The difference in mortality seen in study 255 is likely due to this unusually low mortality rate in the placebo group. The causes of death show no sensible pattern and the HandiHaler data are reassuring."

The mortality issue was reviewed again in an internal Regulatory Briefing meeting held on July 18, 2008 once complete follow up data for the 1-year trials (205.254 and 205.255) were submitted as part of NDA 21-936. The committee concluded that while a portion of the

mortality signal could be explained by differential drop out, additional data are required to determine if the potential signal represents a true safety issue. Based on the two potential safety signals of mortality and stroke, the Agency took an action of Complete Response for NDA 21-936, pending additional data from a clinical trial of adequate duration and power to evaluate fatal and stroke adverse events.

Boehringer Ingelheim submitted additional data pertinent to this application in (b) (4) under IND (b) (4) consisting of a one year, placebo controlled, parallel group trial (Protocol 205.372) in 3,991 patients with moderate-severe COPD. Review of this trial also demonstrates a small mortality imbalance in favor of placebo (See Appendix 10 for an abbreviated review and complete review under IND (b) (4) The mortality data from all 3 Respimat trials in conjunction with the data from UPLIFT (Spiriva HandiHaler Protocol 205.235) was reviewed at the Pulmonary and Allergy Drugs Advisory Committee (PADAC) meeting held on November 19, 2009. The PADAC concluded that UPLIFT was a compelling and important study, demonstrating generally beneficial effects on mortality. Although the Respimat results were felt to be somewhat concerning and additional data are needed, the Respimat results do not necessarily convey to the HandiHaler.

2.6 Other Relevant Background Information

There is no other relevant background information.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

No additional CMC data were submitted as part of this supplement since Spiriva HandiHaler is an approved drug product.

3.2 Animal Pharmacology/Toxicology

No additional animal pharmacology or toxicology data were submitted as part of this supplement since Spiriva HandiHaler is an approved drug product.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Protocol 205.235 is submitted as part of this NDA supplement, NDA 21-395, S029. Protocol 205.266 is cross referenced from the recently submitted Spiriva Respimat NDA (NDA 21-936) dated November 16, 2007, and may be found as part of that application. However, because it more appropriately pertains to Spiriva HandiHaler, it is reviewed under

NDA 21-395, S024. Spiriva Respimat mortality data are reviewed under NDA 21-936 (November 16, 2007) and under IND (b) (4)

4.2 Tables of Clinical Studies

Studies referenced in this NDA supplement are displayed in Table 2.

Table 2: Spiriva HandiHaler clinical studies submitted for this supplement

ID #	Study type	Study duration	Patient age	Treatment groups	N (ITT)	Study Year	Countries
205.266	efficacy for COPD exacerbations	6 mo	≥40 yrs	tio HH18 QD placebo	914 915	2003†	US (VA)
205.235	Efficacy and safety COPD	4 years	≥40 yrs	tio HH18 QD placebo	2986 3006	2008	EU N America Africa Australia

†Year patient enrollment ended
tio HH18 = tiotropium HandiHaler 18 mcg

4.3 Review Strategy

Protocol 205.235 is reviewed as part of this efficacy supplement (S029). Where appropriate, data from Protocol 205.266, reviewed under efficacy supplement S024, are mentioned in this review. Protocol 205.266 was a placebo controlled trial evaluating the effect of Spiriva HandiHaler on COPD exacerbations; thus, it provides evidence from a second trial to support the COPD exacerbation claim requested in S029.

Because the mortality data from Spiriva Respimat is relevant to this NDA and was discussed at the PADAC meeting November 19, 2009, abbreviated reviews of relevant Spiriva Respimat studies are provided in the Appendix (Section 10). Complete reviews of the Spiriva Respimat studies are available under NDA 21-936 and IND (b) (4)

4.4 Data Quality and Integrity

4.4.1 Division of Scientific Investigation audits

The clinical team requested FDA Division of Scientific Investigation (DSI) audits of 3 to 4 domestic and 3 to 4 international sites for this application (total 6 to 8 sites) from trial #205-235 (UPLIFT). Audits were previously conducted for Protocol 205.266 under S024. A larger number of sites were identified so that DSI could choose based on resourcing and any

potential audit triggers identified by DSI. Given the size and importance of the trial, DSI audited a larger number of sites than are typically audited for most applications.

The medical officer reviewed sites for audit selection based on the following criteria: 1) enrollment, 2) region, 3) previous audit (BI or FDA), 4) death, 5) protocol violations, and 6) financial disclosure. Enrollment was a primary criterion; only sites with 20 or more treated patients were included for consideration and sites were rank ordered by country, region, domestic/international, and for the trial as a whole. An effort was made to include at least one site from each region, particularly as the majority of the mortality benefit was observed in Latin America and Asia. Next, sites audited in 2008 by FDA for the Spiriva program were excluded. Sites audited by Boehringer Ingelheim (BI) for this trial were excluded unless there were significant deaths or protocol violations. No site had a particular imbalance in deaths; however, sites with a mortality rate of >20% were considered for audit (overall vital status mortality for the trial was 16.4%). No site had a particular imbalance in deaths; however, sites with a mortality rate of >20% were considered for audit (overall vital status mortality for the trial was 16.4%). Sites with >10% protocol violations were also considered for audit.

In addition to the criteria used by the medical officer for site selection, Dr. Joan Buenconsejo, FDA statistician for this application, reviewed sites for outliers based on mortality and FEV1. No particular outlier sites were identified.

The selected sites are provided in Table 3 for domestic sites and Table 4 for international sites. Sites that were actually audited are highlighted.

Table 3: Protocol 205.235 domestic sites proposed for inspection

Site Location (city, state)	Site #	Subjects Enrolled/Treated	Rationale for Selection
Los Angeles, CA	3800	145/98	-high enroller (#1 US/#1 trial) -protocol violations 14.3% (b) (4) -PI for entire trial
Birmingham, AL	3708	125/84	-high enroller (#2 US/#2 trial) -protocol violations 18.6% (b) (4)
Detroit, MI	3732	127/74	-high enroller (#3 US/#3 trial) -not audited by BI or FDA
Cleveland, OH	3701	78/51	-high enroller (#6 US/#6 trial) -protocol violations 13.7% -not audited by BI or FDA
Rancho Mirage, CA	3741	58/46	-high enroller (#7 US/#7 trial) -deaths 34.8% -not audited by BI or FDA
Long Beach, CA	3812	35/26	-high enroller (#9 US/#21 trial) -protocol violations 30.8% -deaths 23.1% -not audited by BI or FDA

Table 4: Protocol 205.235 international sites proposed for inspection

Site Location (city, country)	Site #	Subjects Enrolled/Treated	Rationale for Selection
Budapest, Hungary	1310	51/41	-high enroller (#2 E Eur/#2 Int/ #9 trial) -protocol violations 22% -deaths 22%
Bangkok, Thailand	3404	22/20	-high enroller (#2 Asia) -protocol violations 35% -deaths 45%
Kaunas, Lithuania	1802	36/30	-high enroller (#4 E Eur/#4 Int/ #12 trial) -not audited by BI or FDA
Monterrey, Mexico	2004	32/27	-high enroller (#1 Latin Am/ #8 Int/#16 trial) -not audited by BI or FDA -protocol violations unknown
Vienna, Austria	0301	31/27	-high enroller (#1 W Eur/#9 Int/ #17 trial) -not audited by BI or FDA
Praha, Czech Republic	0707	30/27	-high enroller (#7 E Eur/#10 Int/ #18 trial) -22% deaths -not audited by BI or FDA

The conduct of the UPLIFT study at 7 identified clinical study sites was audited between 11 May and 24 July 2009. DSI statistical analysis indicated that if unacceptable GCP were not found at any of 7 sites, the GCP compliance rate could be determined to be >80% (sites with unacceptable GCP < 20% of all sites) with 80% confidence.

DSI confirmed adequate adherence to applicable GCP regulations and standards at all 7 sites. GCP deficiencies were observed at 4 of the 7 sites, but the deficiencies were unlikely to have importantly affected site-specific study outcomes. The FDA inspections confirmed acceptable GCP at the clinical sites inspected, and more importantly, validated the sponsor's more extensive internal monitoring performed periodically for all study sites while the study was on-going. The data from the UPLIFT study appear to be reliable as reported under the NDA supplement.

4.4.2 Other audits

In the statistical analysis plan for UPLIFT, the Applicant notes that fraudulent data were reported for an investigator site (#1106) in Germany:

> "**Fraudulent PFT data:** a BI audit revealed the lack of data integrity at one of the investigator sites. The PFT data for the following patients and visits are deemed as fraudulent, and will be removed from the analyses: patient 18956 visits 9 and 10, patient 18933 visit 9, patient 18974 visits 7 and 9, patient 18932 visits 3 and 5."

[m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/16109f1-statistical-methods-interim-analysis-pln/page 22]

Further data provided by the Applicant shows that the investigator for this site contacted BI, indicating a suspicion of fraud committed by one of his subinvestigators after finding that two visits had been documented for a patient after he had died. A for-cause audit by BI substantiated serious fraud at this site. The integrity of the data could not be confirmed for several subjects. The FDA statistician for this application, Dr. Joan Buencosejo, analyzed the efficacy data with and without all subjects from Site #1106, comparing the outcome with that provided by the Applicant (in which only data specifically noted to be fraudulent on the audit were excluded). Exclusion of all data from this site does not change the outcome of the trial.

Reviewer comment:

While the issue of fraudulent data at a site is always taken very seriously, in this case exclusion of the data does not change the outcome of the trial. Further, BI was very cooperative with FDA inquiries as to the nature of the fraud, and provided their internal audit report in which appropriate compliance with GCP and ICH guidelines regarding the audit were followed. Because this site has already been audited and the data excluded from the trial, further audits of this site by DSI are unlikely to be helpful.

4.5 Compliance with Good Clinical Practices

The Applicant states that the reviewed trial (Protocol 205.235) was conducted using Good Clinical Practices. In addition, it approved by the appropriate IRB and followed ICH guidelines. [m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/0202-0235-01-15-study-report-body.pdf/page 41] The Applicant also provides debarment certification. [m1/us/debar-certification.pdf]

4.6 Financial Disclosures

Because Spiriva is co-marketed by Pfizer, the Applicant requested financial disclosure pertaining to both Boehringer Ingelheim and Pfizer for the UPLIFT trial.

The majority of primary investigators for the UPLIFT trial provided financial disclosure statements. A total of 28 primary investigators, all in the United States, did not provide

financial disclosure. Excluding the 24 investigators who did not enroll patients, there were only 4 sites of 490 with enrollment for whom the primary investigator did not provide financial disclosure. Of these, two investigators enrolled only one patient, one investigator is deceased and one was lost to follow up. The original primary investigator at site #3737, which enrolled 14 patients, was reported as lost to follow up. However, this site is located in New Orleans, Louisiana, and the UPLIFT trial was conducted at the time of Hurricane Katrina (2005). The primary investigator at site #3737 who was lost to follow up was replaced prior to conclusion of the trial, and the new PI reported no financial interests.

Of those investigators providing financial disclosure, the majority did not report financial interests requiring disclosure. There were a total (b) (4)

Because efficacy and safety was not driven by only one site or a few sites, it is unlikely that a single site significantly altered the results of the trial.

[m1/us/financial-cert-and-disclosure.pdf]

5 CLINICAL PHARMACOLOGY

There were no new clinical pharmacology data submitted as part of this Application since Spiriva HandiHaler is an approved drug product.

6 INTEGRATED REVIEW OF EFFICACY

The Applicant proposes two efficacy claims—lung function and COPD exacerbations. Each of these efficacy variables will be discussed separately. The lung function efficacy variables are discussed in Section 6.1 and the COPD exacerbations efficacy variables are discussed in Section 6.2. Mortality and respiratory failure are discussed under safety, as they were not prespecified efficacy endpoints.

6.1 Effects on Lung Function

Boehringer Ingelheim (BI) proposes including a figure of trough FEV1 over 48 months in addition to the following labeling claim in the Clinical Studies section of the product label:

> "The co-primary efficacy endpoints, yearly rate of decline in pre- and post-bronchodilator FEV_1, were not significantly different between the two groups.

SPIRIVA HandiHaler maintained improvements in pulmonary function throughout 4 years. Specifically, SPIRIVA HandiHaler sustained improvements in trough (pre-dose) FEV_1 (adjusted means over time: 87-103 mL) throughout the 4 years of the study."

6.1.1 Methods

To support this application, BI submitted the UPLIFT trial, a 4-year randomized, double-blind, placebo controlled trial evaluating the efficacy of Spiriva HandiHaler in a population of patients with moderate to severe COPD.

6.1.2 General Discussion of Lung Function Endpoints

The primary endpoints for Study 205.235 were:

- The yearly rate of decline in trough FEV1 from day 30 (steady state) until completion of double blind treatment. Trough FEV1 is the pre-dose value measured approximately 24 hours after the previous dose of study drug
- The yearly rate of decline in FEV1 90 minutes after study drug and ipratropium administration (including 30 minutes post albuterol) from day 30 (steady state) until completion of double blind treatment

Secondary endpoints related to lung function included:

- Yearly rate of decline in trough FVC and slow vital capacity (SVC)
- Yearly rate of decline in trough FVC and slow vital capacity (SVC) from day 30 until completion of double-blind treatment. Trough FVC and SVC are the pre dose values measured approximately 24 hours after the previous dose of study drug.
- Yearly rate of decline in FVC and SVC measured 90 minutes after inhalation of study drug and ipratropium (and 30 minutes after albuterol) from day 30 until completion of double-blind treatment.
- Yearly rate of decline in FEV_1, FVC, and SVC prior to ipratropium and albuterol inhalation from day 1 until completion of the trial (30 days post study drug treatment).
- Yearly rate of decline in FEV_1, FVC, and SVC measured 90 minutes after inhalation of ipratropium (and 30 minutes after inhalation of albuterol) from day 1 until completion of the trial (30 days post study drug treatment).
- Estimated mean pre- and post-bronchodilator FEV_1, FVC, and SVC from day 30 until completion of double-blind treatment.

[m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/0202-0235-01-15-study-report-body.pdf/page 55]

Trough FEV_1 was defined as the FEV_1 measured at the -5 minute time point at the end of the dosing interval 24 hours post drug administration. Trough FEV_1 response was defined as the change from baseline in trough FEV_1. Baseline FEV_1 was the pre-treatment FEV_1 value measured at Visit 2 in the morning 5 minutes prior to administration of the first dose of study medication.

FEV1, FVC, and SVC measurements were obtained through pulmonary function testing at screening (Visit 1), baseline (Visit 2), after 30 days (Visit 3) and every 6 months thereafter until the end of the double-blind treatment period (Visits 5, 7, 9, 11, 13, 15, 17, and 19). PFTs were also performed at the final visit after being off study drug (on open-label ipratropium) for 30 days. PFTs were performed using standardized spirometry equipment provided by the applicant and calibrated by study staff on all test days. A calibration log was maintained for the spirometry equipment. Equipment and techniques conformed to American Thoracic Society (ATS) criteria.

Patients were instructed to arrive at the clinic approximately 1 hour prior to the time they were scheduled to take study drug having abstained from medications as specified in the protocol. Spirometric measurements commenced at approximately the same time at all visits. If a patient arrived for a visit without adequate washout, the visit was postponed (once).

The following medications were appropriately restricted prior to PFT testing:

- inhaled corticosteroids (withhold morning dose)
- short-acting theophylline (at least 24 hour washout)
- long-acting theophylline (at least 48 hour washout)
- short-acting beta-adrenergic bronchodilators (at least 8 hour washout)
- long-acting beta-adrenergics (LABA) or combination LABA/inhaled steroid products (at least 24 hour washout)
- study medications (not to be taken prior to test-day pre-dose PFTs)
- ipratropium (at least 8-hour washout prior to the final visit)

In addition, patients were to refrain from strenuous exercise, smoking, caffeinated or ice-cold beverages, cold temperatures, dust, and environmental smoke the morning prior to spirometry.

If an oral corticosteroid burst occurred prior to PFT days, the visit was postponed for at least one, but no more than 2 weeks after the last increased or additional dose was given. The use of antibiotics was not restricted. Antibiotics were used as medically necessary for exacerbations and other infections. If antibiotics were prescribed for a respiratory illness prior to pulmonary function testing days, the visit was postponed for at least one, but no more than 2 weeks after the last dose was given. If an increase in or addition of theophylline

dose occurred prior to PFT days, the visit was postponed for at least one, but no more than 2 weeks after the last increased dose was given.

PFTs were performed with the patient in a seated position. Slow vital capacity (SVC) by slow exhalation maneuver was the first spirometric maneuver performed. The forced maneuvers, FEV_1 and forced vital capacity (FVC) were done in triplicate after obtaining the SVC. The best of three efforts was recorded in the case report form (CRF). The best of three efforts was defined as the highest FEV_1 and the highest FVC each obtained on any of three blows (even if not from the same curve) meeting the ATS criteria (with a maximum of five attempts).

At screening (Visit 1), spirometry was performed at the 90-minute post-bronchodilator timepoint (after administration of 4 inhalations of ipratropium [80 mcg] and 4 inhalations of albuterol [400 mcg]). For this visit, washout of respiratory medications was not required. At the randomization visit (Visit 2) and the end of trial visit (30 days after completion of study medication), washout of restricted medications was required and spirometry was performed pre-bronchodilator and at the 90 minute post-bronchodilator timepoint (after administration of 4 inhalations of ipratropium [80 mcg] and 4 inhalations of albuterol [400 mcg]). For visits at Day 30 (Visit 3) and then every 6 months until the end of treatment (Visits 5, 7, 9, 11, 13, 15, 17, and 19), washout of restricted medications was required and spirometry was performed pre-bronchodilator and at the 90 minute post-bronchodilator timepoint (after administration of study drug, 4 inhalations of ipratropium [80 mcg], and 4 inhalations of albuterol [400 mcg]).

nSpire Health Inc. centrally managed spirometry including providing spirometry equipment and training, and ensuring uniformity of the spirometry testing across all participating sites. All staff performing PFTs were required to have at least 6 months of experience performing spirometry and to have performed at least 120 PFTs over the last 6 months. All individuals performing spirometry tests were required to complete training including practice tests. Training on spirometry systems was provided at each investigator meeting. All spirometry technicians during the 4 years were required to demonstrate competency with the spirometer through completing a training checklist and submitting practice maneuvers for approval prior to study maneuvers being performed. The practice spirometry tests were reviewed for overall quality, protocol compliance, and integrity.

Standardized spirometry testing was completed via identical spirometers with secure access features (username and password). Custom software for use by the sites was designed and validated specifically for the study. This software incorporated both ATS criteria for acceptability, and criteria for calculating predicted values as specified by the Standardized Lung Function Testing of the European Community of Coal and Steel (ECCS).

Sites were expected to transmit spirometry data on each day of testing. Centralized quality review and data collection were performed by nSpire Health Inc. Spirograms were reviewed by nSpire Health Inc. technical staff for overall quality, morphology, and artifacts in accordance with the ATS criteria for acceptability, vendor quality assurance review standards, and protocol-specific quality review standard guidelines. Spirograms not meeting quality review standards were queried within 3 business days of receipt. The investigator signed copies of all spirometric reports to approve the data.

[m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/0202-0235-01-15-study-report-body.pdf/pages 66-69, 80-81]

Reviewer comment:

FEV1 is an established endpoint for COPD trials. Methodology for pulmonary function testing and collection of spirometry data was appropriate in the UPLIFT trial.

6.1.3 Study Design

The UPLIFT trial was a 4-year, multicenter, multinational, randomized, double-blind, placebo-controlled, parallel group study comparing the rate of decline in forced expiratory volume in one second (FEV1) in patients with COPD receiving tiotropium HandiHaler 18 mcg (tio HH18) to those receiving placebo in addition to their usual care for COPD. Usual care included short- and long-acting inhaled beta-agonists, steroids, and theophyllines but excluding inhaled anticholinergics. Following an initial screening period of 14-30 days, qualifying patients were randomized to tiotropium or placebo. Patients were seen after 1 month of treatment, at 3 months, and then every 3 months until study drug termination at 4 years. At study drug termination, patients received open-label ipratropium for 30 days. The final visit occurred approximately 30 days post-treatment.

[m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/0202-0235-01-15-study-report-body.pdf/page 57]

Reviewer comment:

The enrollment criteria for this trial represent a "real world" population of patients with COPD. In contrast to studies leading to approval of a COPD exacerbation claim for Advair Diskus in which the patient population was enriched for exacerbation by inclusion of patients with a history of recent exacerbation, Protocol 205.235 did not exclude patients based on lack of exacerbation history.

6.1.4 Lung Function Efficacy Findings

There were two co-primary endpoints for this study, rate of decline of pre- and post-bronchodilator FEV1 from Day 30 (steady state) until completion of double-blind treatment. The endpoints did not achieve statistical significance, thus the applicant reported p-values as unadjusted for multiple comparisons.

There was no significant difference between treatment groups for rate of decline in either pre- or post-bronchodilator FEV1. The sponsor reports that sensitivity analyses including patients with at least one measurement and including center as a random effect also showed no significant treatment difference. Likewise, adjusting for baseline covariates of post-bronchodilator FEV1, age, sex, height and smoking status did not change significance. Pre-specified subgroups of age, gender, smoking status, baseline ICS use, baseline ICS/LABA combination use, baseline anticholinergic use, GOLD stage, race, region, reversibility, and

BMI were evaluated. No significant treatment by subgroup interaction was detected. See Table 5 and Figure 1.

Table 5: Protocol 205.235 rate of decline in FEV1 (random effects model)

	Placebo		Tio HH18		Difference		
	N	Mean (SE) ml/yr	N	Mean (SE) ml/yr	Mean (SE) ml/yr	95%CI	p-value
Pre-BD	2413	30 (1)	2557	30 (1)	0 (2)	(-4, 4)	0.9524
Post-BD	2410	42 (1)	2554	40 (1)	2 (2)	(-6, 2)	0.2074

Figure 1: Protocol 205.235 mean pre-bronchodilator FEV1

Treated set with at least 3 measurements after and including Day 30. Estimated based on repeated measure ANOVA model. Model adjusted for baseline measurement. Day 1 (baseline) value is overall mean, not estimated from the mixed model.

An evaluation of the association between smoking status and rate of decline in FEV1 demonstrated that in both treatment groups, sustained smokers had the highest mean rate of decline in FEV1, sustained ex-smokers had the lowest rate, and intermittent smokers were in between. Smokers were distributed evenly between the groups, and rate of decline was comparable between treatment groups for all smoker subgroups. See Table 6, Figure 2, and Figure 3. The figures were generated by Dr. Joan Buenconsejo, FDA statistical reviewer.

Table 6: Protocol 205.235 rate of decline in FEV1 by smoking status

	Placebo		Tio HH18			Difference	
	N	Mean (SE) ml/yr	N	Mean (SE) ml/yr	Subgroup treatment interaction p-value	Mean (SE) ml/yr	p-value
Pre-BD					0.8889		
Sustained ex-smoker	1438	23 (2)	1486	23 (2)		0 (2)	0.8465
Sustained smoker	303	51 (4)	313	51 (4)		0 (5)	0.9865
Intermittent smoker	672	36 (2)	758	35 (2)		2 (3)	0.6493
Post-BD					0.8424		
Sustained ex-smoker	1432	36 (2)	1484	36 (2)		3 (2)	0.1909
Sustained smoker	305	59 (4)	312	59 (4)		0 (5)	0.9807
Intermittent smoker	673	48 (3)	754	46 (2)		2 (3)	0.5731

Figure 2: Protocol 205.235 pre-bronchodilator FEV1 over time by smoking status

Figure 3: Protocol 205.235 post-bronchodilator FEV1 over time by smoking status

[m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/0202-0235-01-15-study-report-body.pdf/pages 106-107]

Reviewer comment:

This study failed on the primary endpoint, rate of decline of FEV1. However, it is important to note that the difference between treatment groups is maintained throughout the study, suggesting that tiotropium does not lose bronchodilator efficacy with prolonged use (see subsequent discussion of FEV1 at each timepoint). It is well-accepted in the COPD literature that sustained smoking causes a more rapid decline of lung function compared to patients who are able to quit smoking, in whom the rate of decline returns to similar slope as that of never smokers[2, 3]. The UPLIFT trial demonstrates this fact nicely, providing internal validation for the FEV1 measurements in the study.

FEV1 endpoints

Mean pre- and post-bronchodilator FEV1 at each visit was estimated using a repeated measure ANOVA model with visit as a discrete variable and baseline value as a covariate. The tio HH18 group had a significantly higher pre- and post-bronchodilator FEV1 compared to placebo at all timepoints. Pre-bronchodilator FEV1 was a trough level performed after wash-out of appropriate pulmonary medications (see section on PFT measurements). For mean pre-bronchodilator FEV1, the estimated mean difference between tio HH18 and placebo groups ranged from 87 to 103 ml ($p<0.0001$), with an overall mean difference of 94

ml. See Table 7. Post bronchodilator FEV1 was measured after four puffs of albuterol, four puffs of ipratropium and administration of study drug. For post-bronchodilator FEV1, the treatment difference ranged from 47 to 65 ml (p<0.0001), with an overall mean difference of 57 ml.

Table 7: Protocol 205.235 FEV1

Test Day	Broncho-dilator	Placebo [L]	Tio HH18 [L]	Treatment difference [L]	p-value	95% CI
Day 1	Pre	1.116	1.116			
	Post	1.347	1.347			
Month 1	Pre	1.134	1.221	0.087	<0.0001	0.077, 0.098
	Post	1.372	1.418	0.047	<0.0001	0.037, 0.057
Month 6	Pre	1.126	1.225	0.099	<0.0001	0.087, 0.110
	Post	1.365	1.423	0.058	<0.0001	0.047, 0.069
Month 12	Pre	1.111	1.213	0.103	<0.0001	0 091, 0.115
	Post	1.345	1.398	0.054	<0.0001	0.042, 0.065
Month 18	Pre	1.101	1.192	0.091	<0.0001	0.078, 0.104
	Post	1.326	1.379	0.053	<0.0001	0.040, 0.066
Month 24	Pre	1.079	1.173	0.094	<0.0001	0.081, 0.107
	Post	1.294	1.356	0.062	<0.0001	0.049, 0.075
Month 30	Pre	1.061	1.156	0.095	<0.0001	0.081, 0.109
	Post	1.274	1.335	0.061	<0.0001	0.047, 0.075
Month 36	Pre	1.045	1.144	0.099	<0.0001	0.085, 0.114
	Post	1.250	1.315	0.065	<0.0001	0.051, 0.080
Month 42	Pre	1.034	1.129	0.095	<0.0001	0.080, 0.110
	Post	1.236	1.297	0.061	<0.0001	0.045, 0.076
Month 48	Pre	1.024	1.112	0.088	<0.0001	0.073, 0.103
	Post	1.219	1.268	0.049	<0.0001	0.033, 0.065
Overall mean	Pre	1.080	1.174	0.094	<0.0001	0.084, 0.105
	Post	1.298	1.354	0.057	<0.0001	0.046, 0.067

Pre-BD N=2363 placebo, N=2494 tio HH18; Post-BD N=2374 placebo, N=2516 tio HH18
Mean and 95% CI estimated using repeated measured ANOVA adjusted for D1 baseline overall mean value.

[m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/0202-0235-01-15-study-report-body.pdf/page 109-111]

The FDA statistical reviewer for this application, Dr. Joan Buenconsejo, also evaluated FEV1 in terms of a responder analysis. Responders were defined as an improvement of 15% from baseline in trough (pre-bronchodilator) FEV1. Patients who discontinued from the study were considered non-responders. Using these criteria, at Month 1, 33% of patients in the tio HH18 group were responders compared to 16% in the placebo group. At Month 48, 16% of the tio HH18 group were responders compared to 9% of the placebo group. The proportion of responders in the tio HH18 group was also higher than placebo at all visits for

post-bronchodilator FEV1. See Statistical Review NDA 21-395, S-029, Dr. Joan Buenconsejo.

Reviewer comment:

Bronchodilatory effect of tio HH18 is slightly lower than that observed in both the Spiriva HandiHaler and Spiriva Respimat Phase 3 programs. For Spiriva HandiHaler Phase 3 pivotal trials the FEV_1 trough response was 0.110-0.130L. For Spiriva Respimat Phase 3 pivotal trials (205.251 and 205.252), the trough response was 0.109-0.124L. Overall, however, the results are comparable. The spirometry results from this study demonstrate bronchodilator efficacy in a more "real world" patient population in which there was high use of concomitant respiratory medications. In addition, the results (trough FEV1 treatment difference of 0.09-0.10L) are similar to that observed in Spiriva HandiHaler Protocol 205.266, a Phase 3 trial conducted in a Veteran's Affairs setting (NDA 21-395, S024), with similar "real world" inclusion criteria.

While the proportion of patients considered responders is relatively low, tio HH18 showed a significant and sustained improvement over placebo at all visits throughout the study. The UPLIFT trial did not have an inclusion criteria for bronchodilator responsiveness. Less than half of patients were considered responders to maximal bronchodilation (4 puffs of albuterol and 4 puffs of ipratropium). Counting missing data (including discontinued patients) as non-responders and evaluation at the end of the dosing interval also contributes to the relatively low percentage of patients with a 15% FEV1 response to therapy. As such, these numbers should not be construed to mean that only 1/6 of patients received benefit from tiotropium after 4 years of therapy. In addition, it is important to put this analysis into context of the study population, who had a baseline pre-bronchodilator FEV1 of only 1.096L. A 15% increase in this population is approximately 164ml, a very large bronchodilator improvement for COPD. Patients who did not demonstrate this large of an increase likely received some benefit. Overall, the responder analysis is supportive of a sustained bronchodilator effect compared to placebo over the course of the study.

The proposed claim regarding lung function "...SPIRIVA HandiHaler sustained improvements in trough (pre-dose) FEV_1 (adjusted means over time: 87-103 mL) throughout the 4 years of the study" is supported by the UPLIFT data. This claim was not specifically discussed at the PADAC meeting, although both the Applicant and FDA presented the data.

FVC measurements

Mean pre- and post-bronchodilator FVC values were significantly increased in the tio HH18 group compared to placebo at all time points from Day 30 to Month 48, with treatment differences for pre-bronchodilator (trough) values ranging from 0.17-0.20 ($p<0.0001$). The overall mean pre-bronchodilator difference was 0.19L ($p<0.0001$). The differences for post-bronchodilator (peak) values ranged from 0.03-0.07L ($p=0.04$, $p<0.0001$), with an overall mean difference of 0.05L ($p<0.0001$).

[m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/0202-0235-01-15-study-report-body.pdf/page 112-113]

SVC measurements

Mean pre-bronchodilator (trough) SVC values were significantly increased in the tio HH18 group compared to placebo at all time points from Day 30 to Month 48, with treatment differences ranging from 0.15 to 0.19L ($p<0.0001$). The overall mean pre-bronchodilator difference was 0.17L ($p<0.0001$). The mean post-bronchodilator (peak) SVC values were significantly increased in the tio HH18 group compared to placebo out to Month 36, becoming non significant at months 42 and 28. The differences ranged from 0.03-0.05L. The overall mean post-bronchodilator SVC difference was 0.035L ($p=0.0006$).

[m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/0202-0235-01-15-study-report-body.pdf/pages 114-115]

Lung function efficacy subgroup analysis

Subgroup analyses were performed for the primary endpoints of rate of decline in pre- and post-bronchodilator FEV1 from Day 30 until the end of treatment. The following subgroup parameters were investigated:

- Age (<55, ≥55-<65, ≥65-<75, ≥75 years)
- Gender (male/female)
- Smoking status (active smoker/ex-smoker)
- Race (white/black/Asian)
- Baseline long-acting ß-agonist use (yes/no)
- Baseline inhaled corticosteroid use (yes/no)
- Baseline LABA and ICS combination use (yes/no)
- Anticholinergic use (yes/no)
- GOLD stage (I or II/III/IV)
- Region (Asia/Eastern Europe/Latin America/USA/Western Europe)
- Reversibility (yes/no)
- Body mass index (<20/ ≥20-<25/ ≥25-<30/ ≥30)

There were no subgroup by treatment interactions, i.e. the same treatment effect (no change in disease progression over time compared to placebo) was observed in each subgroup. As noted previously, current smokers in both treatment groups had a larger loss of lung function over time than did ex-smokers. In addition, younger patients and patients with more preserved lung function at baseline (GOLD Stage I/II) in both treatment groups had a greater loss in lung function over time. See statistical review by Dr. Joan Buenconsejo for a table of all subgroup analyses for both pre- and post-bronchodilator FEV1.

Reviewer comment:

It makes physiologic sense for younger patients (more likely to be GOLD Stage I/II) and patients with GOLD Stage I/II to lose more lung function (in ml) over time, as the starting point allows a greater loss. In patients with Stage IV disease (FEV1 at baseline of <1L), a loss of even a small amount may represent a clinically important decline. If the numbers were expressed as % predicted rather than absolute slope, a more linear curve would be expected (ref Fletcher, 1977).[3] *In addition, it is possible that smoking status may have confounded the age and GOLD stage evaluations, because younger patients with better lung function may be more likely to be active smokers.*

6.1.5 Clinical Microbiology

No clinical microbiology data is applicable to this NDA.

6.1.6 Lung Function Efficacy Conclusions

The UPLIFT study showed no significant difference between treatment groups in the primary endpoints of rate of decline in pre- and post-bronchodilator FEV1. In a subgroup analysis, patients who were sustained quitters from smoking did experience a significant decrease in rate of decline in FEV1 compared to sustained smokers. This effect was observed across both treatment groups.

The applicant offers two plausible explanations for the failure of the UPLIFT trial to demonstrate a difference in long-term rate of decline in FEV1, confounding by concomitant disease-modifying therapy and differential discontinuation biasing against tiotropium. While these effects may be real, the UPLIFT design overall was significantly strengthened by its "real world" approach to inclusion of multiple concomitant medications, similar to the situation encountered in the COPD population in the United States. Thus, one can conclude that in the setting of high-quality COPD care, the addition of tiotropium is unlikely to impact the natural history of disease.

Spirometry endpoints included trough FEV_1, FVC, and SVC response and 90 minute FEV_1 FVC, and SVC response. Endpoints were measured every six months throughout the four year treatment period. Consistent with the known bronchodilator properties of the drug, the tio HH18 group generally demonstrated a significant improvement ($p<0.0001$) over placebo for all endpoints and time points tested.

Based upon review of the pulmonary function data, the Applicant's proposed claim is generally supported. It is reasonable to describe UPLIFT in the product label and note that the primary endpoints were not significantly different. Regarding the sustained improvement in trough FEV1, this is consistent with the current indication and efficacy data in the product label and would also be reasonable to include in the description of the outcomes of UPLIFT in the product label.

6.2 Effects on COPD Exacerbations

Boehringer Ingelheim (BI) proposes a labeling claim related to COPD exacerbations in the Clinical Studies section of the product label with the following language:

> "In a 6-month clinical trial of COPD patients in a Veterans Affairs setting, SPIRIVA HandiHaler significantly reduced the proportion of COPD patients who experienced exacerbations compared to placebo and significantly delayed the time to first exacerbation. These findings are supported by a pre-specified combined analysis of two one-year clinical trials using SPIRIVA RESPIMAT.
>
> Exacerbations were evaluated as a secondary outcome in the 4-year multicenter trial. In this trial, COPD exacerbations were defined as an increase or new onset of more than one of the following respiratory symptoms (cough, sputum, sputum purulence, wheezing, dyspnea) with a duration of three or more days requiring treatment with antibiotics and/or systemic (oral, intramuscular or intravenous) steroids. SPIRIVA HandiHaler reduced the risk of an exacerbation by 14% (Hazard Ratio 0.86, 95% CI = 0.81, 0.91, p<0.001) and exacerbation-related hospitalization by 14% (Hazard Ratio 0.86, 95% CI = 0.78, 0.95, p<0.002) compared to placebo. Improvement in symptom scores was also seen in patients treated with SPIRIVA HandiHaler compared to placebo."

6.2.1 Methods

To support this application, BI submitted the UPLIFT trial, a 4-year randomized, placebo controlled trial evaluating the efficacy of Spiriva HandiHaler in a population of patients with moderate to severe COPD. In addition, the Veterans Affairs trial mentioned in the proposed labeling (Protocol 205.266) was previously reviewed under NDA 21-395, S024. The two Spiriva Respimat trials were previously reviewed under NDA 21-936.

Reviewer comment:

Because Spiriva Respimat and Spiriva HandiHaler are different drug products, the Respimat data cannot be used to support an efficacy claim for Spiriva HandiHaler. As such, the clinical team recommends removing the statement regarding (b) (4) *from the label claim.*

6.2.2 General Discussion of COPD Exacerbation Endpoints

COPD exacerbations were recorded on an ongoing basis throughout the study. As an aid to recall, patients were given a Patient Daily Record book that was reviewed at each visit.

For the purposes of the UPLIFT trial, a COPD exacerbation was defined as "an increase or new onset of more than one respiratory symptoms (cough, sputum, sputum purulence, wheezing, dyspnea) with a duration of three days or more requiring treatment with antibiotics and/or systemic (oral, intramuscular, or intravenous steroids." The onset of the

COPD exacerbation was defined by the onset of the first recorded symptom. The end of the COPD exacerbation was recorded as defined by the investigator.

Exacerbation events were derived based on the adverse event (AE) records on the exacerbation AE CRF page. All events included on the exacerbation AE CRF were included in the efficacy analysis whether or not BI determined that they met all components of the protocol exacerbation definition. In addition to standard AE reporting, total days on antibiotics, total days on systemic steroid bursts, and number of hospitalized days (broken into regular ward and intensive care unit) were also collected for all COPD exacerbation events. Overlapping exacerbations were collapsed into one exacerbation. Two exacerbations were considered distinct events if there were at least 7 exacerbation-free days between the end of one event and the start of the next one.

Exacerbations were categorized as mild, moderate, and severe according to the following definitions:

- mild: treated at home without seeing a health care provider
- moderate: visit with a health care provider (e.g., home visit, visit to an outpatient facility or an emergency department) but not requiring admission to hospital
- severe: hospitalization (emergency room visits >24 hours were considered hospitalizations

[m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/0202-0235-16101-protocol-or-amendment.pdf/pages 26-27] [m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/0202-0235-16102-sample-case-report-form.pdf/pages 33-35] [m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/0202-0235-16109f1-statistical-methods-interim-analysis-pln.pdf/pages 34-36]

Reviewer comment:

The definition of COPD exacerbation includes both a change in symptoms and a treatment requirement. Inclusion of both components of the definition is likely to increase uniformity in the study, as therapy patterns are known to vary across geographic regions. The definition is essentially the same as the one used for the Spiriva Respimat program and in the Spiriva HandiHaler VA study (Protocol 205.266), with only a slight variation in wording. Advair is the only other medication that has a labeling claim (and indication) for reduction of COPD exacerbations so we now have a regulatory path established for this particular claim. No well-accepted definition of exacerbations exists, although in general the definition used in this study is acceptable.

The Applicant initially proposed to combine events with one day or fewer between events, and look at combination of 7 days between events as a sensitivity analysis. The applicant changed the SAP based on feedback from FDA. From a clinical perspective, recurrence of an event a few days after stopping therapy likely represents recurrence of an incompletely treated exacerbation rather than a new event. In previous Spiriva trials (including 205.266),

sensitivity analysis evaluating combining events with one versus 7 days between events did not make a significant difference in overall outcome.

The definition of COPD exacerbation was essentially the same for Protocol 205.266 as in the UPLIFT trial. A slight difference was that the list of symptoms did not include sputum purulence, although increased sputum was included.

6.2.3 Study Design

See Section 6.1.3.

6.2.4 COPD Exacerbation related Efficacy Findings

Key secondary endpoints

There were two key secondary endpoints for Protocol 205.235, time to first COPD exacerbation and time to first COPD exacerbation leading to hospitalization.

For COPD exacerbations, the Applicant reports that patients in the tio HH18 group had a significantly longer time to event than patients in the placebo group ($p<0.0001$, RR 0.86, 95% CI 0.81-0.91). The median time to first exacerbation was 12.5 months in the placebo group and 16.7 months in the tio HH18 group. A Kaplan-Meier estimate of the probability of no exacerbation as provided by the Applicant is presented in Figure 4.

Figure 4: Study 205.235 Kaplan-Meier estimates of the probability of no exacerbation

The Applicant also reports that patients in the tio HH18 group had a statistically significantly longer time to first hospitalization due to COPD exacerbation compared to placebo (p= 0.0024, RR 0.86, 95% CI 0.78, 0.95). The lower quartile for time to first exacerbation requiring hospitalization was 28.6 months in the placebo group and 35.9 months in the tio HH group. Since only 27% of the placebo group and 25% of the tio HH18 group experienced exacerbations leading to hospitalizations, the median time to first exacerbation was calculated based on the first 25% of patients with exacerbations. A Kaplan-Meier estimate of the probability of no exacerbation resulting in hospitalization as provided by the Applicant is presented in Figure 5.

Figure 5: Protocol 205.235 Kaplan-Meier estimates of the probability of no exacerbation leading to hospitalization

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Reviewer comment:

Significance was not achieved for the co-primary endpoints; however, the key secondary endpoints showed a significant difference from placebo with an unadjusted p-value of <0.0001. Strictly speaking, because the trial adjusted for multiplicity using a step-wise approach, i.e. allowing testing of secondary endpoints only if the primary endpoints were met, the trial could be considered "failed" for the secondary endpoints as well. Adjusting for multiplicity in a more-conventional way, a p<0.01 would be considered to show statistical significance. See Statistical Review by Dr. Joan Buenconsejo, NDA 21-395, S029.

Clinically, the exacerbation endpoints are clinically important, and the failure of the study to show an improvement in disease progression does not detract from the finding of improvement in exacerbations, which was also replicated in a second, independent study (Protocol 205.235). If the exacerbation finding had been less robust, adjustments for multiplicity would pose a greater concern. As a litmus test for evaluating impact of primary versus secondary endpoints, if the study had been designed differently, with COPD exacerbations as the primary endpoint and rate of decline in FEV1 as a secondary endpoint, the conduct of study and analyses would have been the same.

This same argument also applies to labeling claims regarding lung function, which from a statistical standpoint also represent secondary endpoints with a failed primary. In addition, it would be difficult to provide a description of the study in the label without discussing lung function. Regardless of efficacy, it is important to describe the UPLIFT in the product label due to the safety implications of such a large, long-term trial.

On November 19, 2009, the PADAC voted (11 yes, 1 no) that the UPLIFT and VA trials provide substantial and convincing evidence to support the claim that Spiriva HandiHaler reduces COPD exacerbations. The single negative vote was secondary to the lack of exact wording of the claim in the question and not because evidence of efficacy was lacking for a COPD exacerbation claim in general.

Other COPD exacerbation related endpoints

A number of additional endpoints related to COPD exacerbations were examined, including:

- number of COPD exacerbations
- time to first exacerbation treated with steroids
- time to first exacerbation treated with antibiotics
- number of patients with at least one COPD exacerbation
- number of exacerbations treated with steroids
- number of exacerbation days
- number of COPD exacerbations leading to hospitalization
- number of patients with at least one exacerbation leading to hospitalization
- number of days hospitalized due to exacerbation per patient year

The endpoints involving number of exacerbation events are calculated per person year, with a correction for overdispersion. Results as calculated by the applicant are presented in Table 8. All recorded COPD events were included in the analysis. The applicant reports that 98.8% of the recorded exacerbation events agreed with the protocol definition.

Table 8: Protocol 205.235 COPD related events endpoints

Endpoint	Placebo	Tio HH18	Rate Ratio	p-value
Exacerbations/pt year	0.85	0.73	0.86	<0.0001
Time to first exacerbation with steroids [median, month]	26.4	36.5	0.84[1]	<0.0001
Time to first exacerbation with antibiotics [median, month]	16.2	19.8	0.87[1]	<0.0001
Pts with exacerbations [%]	68	67	NC	0.3481
Exacerbations with steroids	0.52	0.44	0.84	<0.0001
Exacerbations with antibiotics	0.71	0.62	0.87	<0.0001
Exacerbation days [mean]	13.6	12.1	0.89	0.0011
Exacerbations with hospitalization	0.16	0.15	0.94	0.3413
Pts hospitalized due to exacerbation [%]	27	25	NC	0.1766
Days in hospital due to exacerbations [mean]	3.13	3.17	1.01	0.8624

All endpoints other than time to first event and percent of patients are reported as number of events per patient-year. Poisson regression analysis adjusted for overdispersion was used.
NC=not calculated; [1]Hazard Ratio

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Reviewer comment:

These exacerbation endpoints are generally in favor of tiotropium, supportive of a claim regarding reduction in COPD exacerbations. The number of exacerbations per patient year is consistent with that found in Study 205.266 (VA study, NDA 21-395, S-024), in which the number of exacerbations per patient year was 0.876 in the placebo group and 0.711 in the tio HH18 group, giving a risk ratio of 0.812. The percent of patients with exacerbations and hospitalized with exacerbations may be biased against tiotropium due to differential drop out from the placebo group.

This analysis correctly adjusts for overdispersion. The default Poisson regression technique assumes that all patients are homogenous with respect to their rate of exacerbation. The correction for overdispersion takes into account that for COPD, the majority of exacerbations occur in a small portion of patients while the rest of the population has no exacerbations.[4] The method of calculation of exacerbation rate and correction for overdispersion is critical as different statistical methodologies may give very different results.

COPD exacerbation subgroup analysis

Subgroup analyses were conducted for the time to first exacerbation, time to first exacerbation leading to hospitalization, and number of exacerbations per patient year. The following subgroup parameters were investigated:

- Age (<55, ≥55-<65, ≥65-<75, ≥75 years)
- Gender (male/female)
- Smoking status (active smoker/ex-smoker)
- Race (white/black/Asian)
- Baseline long-acting ß-agonist use (yes/no)
- Baseline inhaled corticosteroid use (yes/no)
- LABA and ICS combination use (yes/no)
- Baseline anticholinergic use (yes/no)
- GOLD stage (I or II/III/IV)
- Region (Asia/Eastern Europe/Latin America/USA/Western Europe)
- Reversibility (yes/no)
- Body mass index (<20/ ≥20-<25/ ≥25-<30/ ≥30)

There were no significant subgroup by treatment interactions. Patients with GOLD stage I/II disease overall had fewer exacerbations with a longer time to the first exacerbation, as would be expected for milder disease. For patients with GOLD stage IV disease, the time to first COPD exacerbation was not improved with Spiriva as it was in other subgroups. However, this may have been a statistical anomaly as the numbers were relatively small and the time to first COPD exacerbation requiring hospitalization and number of exacerbations per year were improved in this subgroup. All other subgroups were relatively homogeneous with respect to COPD exacerbation treatment effect. See Table 9 for the subgroup analysis of number of patients with exacerbations and median time to first exacerbation. See the statistical review by Dr. Joan Buenconsejo for the subgroup analyses of COPD exacerbations leading to hospitalization (number of patients and median time to first exacerbation for 25% of patients) and estimated rate of exacerbations per patient-year.

Table 9: Protocol 205.235 subgroup analysis of COPD exacerbation: number (%) of patients with an exacerbation and median time to first exacerbation (in months)

	Placebo	Tiotropium	Hazard Ratio 95% CI	p-value*
Overall	2049/3006 (68%) 13 months	2001/2986 (67%) 17 months	0.86 (0.81, 0.91)	
Sex: Female	539/784 (69%) 10 months	496/735 (68%) 15 months	0.83 (0.74, 0.94)	
Male	1510/2222 (68%) 13 months	1505/2251 (67%) 17 months	0.87 (0.81, 0.93)	0.5632
Gold Stage: I/II	883/1356 (65%) 17 months	824/1386 (60%) 23 months	0.82 (0.75, 0.90)	
III	942/1331 (71%) 10 months	944 /1304 (72%) 13 months	0.87 (0.79, 0.95)	
IV	188/271 (69%) 9 months	200/250 (80%) 10 months	0.99 (0.81, 1.21)	0.2341
Baseline Smoking Status: Ex-Smoker	1458/2108 (69%) 12 months	1437/2112 (68%) 16 months	0.86 (0.80, 0.93)	
Smoker	591/898 (66%) 14 months	564/874 (65%) 18 months	0.85 (0.76, 0.95)	0.8680
Reversibility: Yes	1036/1513 (69%) 13 months	1021/1520 (67%) 17 months	0.86 (0.79, 0.94)	
No	946/1393 (68%) 12 months	913/1357 (67%) 16 months	0.86 (0.79, 0.94)	0.9854
Baseline ICS: Yes	1338/1860 (72%) 10 months	1302/1840 (71%) 13 months	0.85 (0.79, 0.92)	
No	711/1146 (62%) 18 months	699/1146 (61%) 23 months	0.86 (0.78, 0.96)	0.8068
Baseline LABA: Yes	1302/1808 (72%) 11 months	1275/1796 (71%) 13 months	0.85 (0.79, 0.92)	
No	747/1198 (62%) 17 months	726/1190 (61%) 22 months	0.87 (0.78, 0.96)	0.7171
Baseline ICS/LABA: Yes	1066/1462 (73%) 10 months	1052/1464 (72%) 12 months	0.86 (0.79, 0.93)	
No	983/1544 (64%) 17 months	949/1522 (62%) 21 months	0.86 (0.78, 0.94)	0.9146

	Placebo	Tiotropium	Hazard Ratio 95% CI	p-value*
Overall	2049/3006 (68%) 13 months	2001/2986 (67%) 17 months	0.86 (0.81, 0.91)	
Race: White	1845/2697 (68%) 12 months	1817/2691 (68%) 16 months	0.87 (0.81, 0.92)	
Black	36/53 (68%) 18 months	19/38 (50%) 41 months	0.48 (0.28, 0.85)	
Asian	118/185 (64%) 13 months	119/192 (62%) 18 months	0.81 (0.63, 1.05)	0.2310
Region: Asia	114/178 (64%) 13 months	113/184 (61%) 18 months	0.81 (0.62, 1.05)	
E. Europe	402/597 (67%) 20 months	367/590 (62%) 21 months	0.88 (0.76, 1.01)	
Latin America	163/207 (79%) 9 months	142/198 (72%) 15 months	0.78 (0.63, 0.98)	
USA	489/767 (64%) 12 months	477/767 (62%) 18 months	0.80 (0.71, 0.91)	
W. Europe	881/1257 (70%) 11 months	902/1247 (72%) 13 months	0.90 (0.82, 0.99)	0.5122
Age: <55	254/382 (67%) 12 months	248/384 (65%) 18 months	0.83 (0.70, 0.99)	
55 –<65	716/1055 (68%) 14 months	714/1054 (68%) 17 months	0.90 (0.81, 0.99)	
65 –<75	825/1198 (69%) 13 months	810/1208 (67%) 17 months	0.86 (0.78, 0.95)	
≥ 75	254/371 (69%) 9 months	229/340 (67%) 13 months	0.76 (0.64, 0.91)	0.4440
BMI: <20	263/352 (75%) 10 months	216/297 (73%) 13 months	0.76 (0.64, 0.91)	
20 –<25	673/1024 (66%) 12 months	709/1074 (66%) 16 months	0.86 (0.78, 0.96)	
25 –<30	704/1033 (68%) 14 months	705/1039 (68%) 17 months	0.91 (0.82, 1.01)	
≥ 30	407/597 (68%) 13 months	371/576 (64%) 19 months	0.82 (0.71, 0.94)	0.4118
Baseline Anticholinergic: Yes	922/1350 (68%) 11 months	950/1366 (70%) 14 months	0.87 (0.79, 0.95)	
No	1127/1656 (68%) 15 months	1051/1620 (65%) 18 months	0.85 (0.78, 0.92)	0.7960

*Hazard ratio based on Cox model with treatment, baseline covariate and baseline covariate by treatment interaction; p-value was obtained using the test for interaction.

6.2.5 Clinical Microbiology

No clinical microbiology data is applicable to this NDA.

6.2.6 COPD Exacerbation Efficacy Conclusions

For the key secondary endpoints of time to first COPD exacerbation and time to first COPD exacerbation leading to hospitalization, tiotropium showed significant difference compared to placebo. For COPD exacerbations, the Applicant reports that patients in the tio HH18 group had a significantly longer time to event than patients in the placebo group ($p<0.0001$, RR 0.86, 95% CI 0.81-0.91). The median time to first exacerbation was 12.5 months in the placebo group and 16.7 months in the tio HH18 group. Patients in the tio HH18 group also had a statistically significantly longer time to first hospitalization due to COPD exacerbation compared to placebo ($p= 0.0024$, RR 0.86, 95% CI 0.78, 0.95). The lower quartile to time to first exacerbation requiring hospitalization was 28.6 months in the placebo group and 35.9 months in the tio HH group. The UPLIFT trial adjusted for multiplicity using a step-wise approach, i.e. allowing testing of secondary endpoints only if the primary endpoints were met. From a statistical viewpoint, the trial could be considered "failed" for the exacerbation endpoints. This issue of multiplicity was discussed at the PADAC meeting on November 19, 2009.

A significant improvement in most of the additional COPD exacerbation-related endpoints was also observed. These included the number of COPD exacerbations, time to first exacerbation treated with steroids, time to first exacerbation treated with antibiotics, number of exacerbations treated with steroids, number of exacerbation days, number of COPD exacerbations leading to hospitalization, and number of days hospitalized due to exacerbation per patient year. In conjunction with primary evidence from Protocol 205.266 (VA study, submitted under NDA 21-395, S-024), these data are generally supportive of an exacerbation claim. The exact wording of the claim will need consideration as various aspects of exacerbation were measured in this trial.

On November 19, 2009, the PADAC voted (11 yes, 1 no) that the UPLIFT and VA trials provide substantial and convincing evidence to support the claim that Spiriva HandiHaler reduces COPD exacerbations. The single negative vote was secondary to the lack of exact wording of the claim in the question and not because evidence of efficacy was lacking for a COPD exacerbation claim in general.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Safety review included Protocol 205.235 (UPLIFT) as well as an analysis of pooled data from 30 clinical trials conducted with tiotropium (HandiHaler and Respimat). Safety endpoints for the UPLIFT trial included all adverse events, including serious adverse events,

all cause mortality, and respiratory mortality. The review of pooled data is provided in Section 7.2.2. All other data presented in the ISS are from the analysis of UPLIFT data.

7.1.1 Deaths

The UPLIFT Mortality Adjudication Committee adjudicated all the causes of death. Several terms were pre-specified on the worksheets used by the UPLIFT Mortality Adjudication Committee: stroke, COPD (with pneumonia, without pneumonia, or pneumonia not specified), pneumonia, pulmonary embolism, congestive heart failure, myocardial infarction, lung cancer, breast cancer, colorectal cancer, sudden cardiac death, sudden death, and death of unknown cause.

Vital status was collected on all patients who prematurely discontinued from the trial extending to 4 years post-randomization. The primary cause of each death was adjudicated by an independent committee. Time to death was defined as time to the end date of the fatal AE (date of death). The primary analysis evaluated deaths with a cut off date of 1440 days (4 years); however, evaluations with a cut off date of 1470 days (4 years plus 30 days) and no cut off date were also conducted. The applicant also presents fatal events in two ways: 1) deaths on treatment and 2) deaths including post-discontinuation vital status. The adjudicated cause of death is presented as the primary analysis, but investigator-reported cause of death is also presented. Both on-treatment deaths and deaths collected as vital status on discontinued patients were adjudicated as to cause.

Overall, the total number of deaths during treatment (including the last day of study drug plus 30 days) was 792; 411 (13.7%) in the placebo group and 381 (12.8%) in the tio HH18 group. The risk ratio for death from any cause (tiotropium/placebo) was 0.84 [95% CI (0.73, 0.97)]. The risk ratio for death remains significantly or nearly significantly different from placebo regardless of the cut off used or inclusion of vital status data. See Table 10.

Table 10: Protocol 205.235 fatal event summary

	Placebo N (%)	Tio HH18 N (%)	Rate difference	Risk Ratio	Risk Ratio Tio HH18 vs. Placebo 95% CI	p-value
On treatment (Day 1440)	400 (13.3)	361 (12.1)	1.2%	0.83	0.72, 0.95	0.010
On treatment (Day 1470)	402 (13.4)	374 (12.5)	0.9%	0.85	0.74, 0.98	0.024
On treatment (all)	411 (13.7)	381 (12.8)	0.9%	0.84	0.73, 0.97	0.016
Vital status (Day 1440)	491 (16.3)	430 (14.4)	1.9%	0.87	0.76, 0.99	0.034
Vital status (Day 1470)	495 (16.5)	446 (14.9)	1.6%	0.89	0.79, 1.02	0.086
Vital status (all)	514 (17.1)	467 (15.6)	1.5%	0.89	0.78, 1.00	0.058

On-treatment mortality

A Kaplan-Meier estimate of the probability of no death on treatment as presented by the applicant is given in Figure 6. The curves show separation after 12 months out to 48 months.

Figure 6: Protocol 205.235 Kaplan-Meier estimates of probability of no all cause mortality [adjudicated on treatment deaths censored at Day 1470]

Reviewer comment:

The sudden drop off in the tio HH18 group at 48 months is due to the small number of patients left at risk at this time point (103 in the tio HH18 group), i.e. only a few patients remained in the trial past the protocol-specified study end date.

The most common causes (adjudicated) of death on-treatment were COPD exacerbation, lung cancer, and death of unknown cause. See Table 11: Protocol 205.235 on-treatment adjudicated cause of death occurring in ≥ 10 patients in either treatment group. There were 271 patients who died of lower respiratory causes by Day 1470, 140 (4.7%) in the placebo group and 131 (4.4%) in the tio HH18 group [RR=0.85, 95% CI (0.67, 1.08)]. Forty-nine patients died of cardiac causes, 25 (0.8%) in the placebo group and 24 (0.8%) in the tio HH18 group [RR=0.88, 95% CI (0.50, 1.55)]. The preferred terms of sudden death, sudden cardiac death, and death of unknown cause are coded by MedDRA under the General Disorders System Organ Class; however, these terms are often considered cardiac events. Combining these three preferred terms, 127 patients died with sudden or unknown causes of death. Of these, 70 (2.3%) were in the placebo group and 57 (1.9%) were in the tio HH18 group [RR=0.75, 95% CI (0.53, 1.06)].

Table 11: Protocol 205.235 on-treatment adjudicated cause of death occurring in ≥ 10 patients in either treatment group

Cause of death	Placebo N (%) [n=3006]	Tio HH18 N (%) [n=2986]	Risk Ratio	p-value (95% CI)
COPD exacerbation	121 (4.0)	103 (3.4)	0.79	0.07 (0.60, 1.02)
Lung cancer	66 (2.2)	73 (2.4)	1.02	0.89 (0.73,1.43)
Death (unknown cause)	36 (1.2)	29 (1.0)	0.74	0.23 (0.46, 1.21)
Sudden cardiac death	23 (0.8)	15 (0.5)	0.60	0.13 (0.31, 1.15)
Pneumonia	18 (0.6)	27 (0.9)	1.39	0.28 (0.76, 2.52)
Congestive heart failure	14 (0.5)	15 (0.5)	0.99	0.98 (0.48, 2.05)
Sudden death	12 (0.4)	14 (0.5)	1.08	0.85 (0.50, 2.33)
Cerebrovascular accident	13 (0.4)	12 (0.4)	0.85	0.69 (0.39, 1.87)

Reviewer comment:

Evaluating the mortality benefit by cause of death, nearly 40% of the benefit observed with tiotropium is driven by a reduction in fatal COPD exacerbations. This is consistent with the mechanism of action of the drug as a bronchodilator improving pulmonary function, as well as the efficacy benefit of reduction in COPD exacerbations seen in Protocols 205.235 and 205.266. Approximately one third of the benefit was attributable to a reduction in death of unknown cause and sudden cardiac death. Although mortality falling into these categories is generally considered to be related to cardiovascular disease, in a population with moderate to severe COPD, one could postulate that some of these deaths may actually be attributed to hypoxia or respiratory failure precipitating death of unknown cause or a cardiac event.

The small increase in deaths attributed to pneumonia is not expected in a drug of the anticholinergic class. A subgroup analysis of concomitant medication use in patients who died of pneumonia demonstrated that the increase was only found in patients who were taking ICS, LABAs or both at baseline. This finding suggests that the difference in pneumonia deaths may be confounded by ICS/LABA use, although the numbers are too small to draw any definitive conclusions. Of note, most patients taking one of these concomitant medications were taking a combination drug, with relatively few using LABAs alone. See Table 12 and Joan Buenconsejo, PhD, Statistical Review NDA 21-395, S029.

Table 12: Protocol 205.235 subgroup analysis of pneumonia deaths

	Placebo N (Pt-Year at risk)	N (%)	Tio HH18 N (Pt-Year at risk)	N (%)	Risk Ratio (95% CI)
Overall	3006 (8740)	18 (0.2)	2986 (9453)	27 (0.3)	1.39 (0.76, 2.52)
Baseline ICS	1860 (5335)	10 (0.2)	1840 (5797)	19 (0.3)	1.75 (0.81, 3.76)
No ICS	1146 (3411)	8 (0.2)	1146 (3663)	8 (0.2)	0.93 (0.35, 2.48)
Baseline LABA	1808 (5214)	8 (0.2)	1796 (5695)	17 (0.3)	1.95 (0.84, 4.51)
No LABA	1198 (3532)	10 (0.3)	1190 (3765)	10 (0.3)	0.94 (0.39, 2.25)
Baseline ICS/LABA	1462 (4197)	7 (0.2)	1464 (4610)	15 (0.3)	1.95 (0.80, 4.78)
No ICS/LABA	1544 (4549)	11 (0.2)	1522 (4850)	12 (0.2)	1.02 (0.45, 2.32)

Deaths were counted as on treatment (all), adjudicated.

Vital status mortality

Vital status information was known for 98% of tiotropium treated patients and 97% of placebo treated patients out to at least 45 months post-randomization. There were a total of 921 deaths, including vital status, for the full 4 year protocol defined study period (1440 days). There were 941 deaths for the period of 4 years plus 30 days (1470 days). See Table 47. Compared to the on-treatment mortality, an additional 149 deaths were collected for patients who discontinued.

The cause of death for deaths determined via collection of vital status were also adjudicated by an independent committee. Similar to on-treatment causes of death, the most frequent causes of death in the group including vital status were COPD exacerbation, lung cancer, and death of unknown cause.

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Number needed to treat

As calculated by Dr. Joan Buenconsejo, FDA statistical reviewer, the number of patients that need to be treated with tiotropium over a four year period to prevent one death varies between 63 and 111 depending on what mortality grouping (on treatment versus vital status and cut-off day) an method of calculation is used. See Table 13. This number compares favorably with other treatments that have known mortality benefits. For example, statins are associated with a NNT of 33-167 for all cause mortality depending on the drug and the patient population in which they are used.[5]

Table 13: Protocol 205.235 number needed to treat for mortality

	Placebo N=3006	Tiotropium N=2986	Risk Difference	NNT
FATAL AE				
On-Treatment (all)	411 (13.7)	381 (12.8)	0.009	111
Vital Status (1470 cut-off)	495 (16.5)	446 (14.9)	0.016	63

NNT=number needed to treat

Subgroup analysis of mortality

The Applicant conducted subgroup analyses for time to all cause death and on-treatment death. The following subgroup parameters were investigated:

- Age (<55, ≥55-<65, ≥65-<75, ≥75 years)
- Gender (male/female)
- Smoking status (active smoker/ex-smoker)
- Race (white/black/Asian)
- Baseline long-acting ß-agonist use (yes/no)
- Baseline inhaled corticosteroid use (yes/no)
- Baseline LABA and ICS combination use (yes/no)
- GOLD stage (I or II/III/IV)
- Region (Asia/Eastern Europe/Latin America/USA/Western Europe)
- Reversibility (yes/no)
- Body mass index (<20/ ≥20-<25/ ≥25-<30/ ≥30)

For time to all cause death, there were two significant subgroup by treatment interactions, smoking status (p=0.0472) and body mass index (BMI) (p=0.0130). These same two subgroup interactions were also borderline significant for on treatment death, with p values of 0.0613 and 0.0782 respectively. For smoking status, ex-smokers obtained greater mortality benefit than current smokers. This seems plausible, as any potential drug effect could be overwhelmed by the detrimental effects of smoking. For BMI, the greatest mortality benefit was observed in the ≥25-<30 subgroup. Again, this seems medically plausible, as cachexia is generally a marker for worse disease in COPD patients, and obese patients have alternative mechanisms of respiratory mortality, such as obesity-hypoventilation. No treatment by subgroup interaction was observed for region; however, it is notable that the mortality benefit was driven by patients in Latin America, Asia, and Western Europe, with no benefit observed in the United States. This may be due to regional differences in standard of care and treatment for COPD or due to other confounders such as smoking status.

As with any subgroup analysis, the results must be interpreted cautiously, as the study was not powered to support such analyses. See Table 14 and Figure 7. The results presented are those of the sponsor. Dr. Joan Buenconsejo (statistical reviewer) verified these results.

Table 14: Protocol 205.235 subgroup analysis of on-treatment deaths (all)

	Placebo N (# of deaths)	Tiotropium N (# of deaths)	Subgroup interaction p-value	Risk Ratio (95% CI)	p-value*
Overall	3006 (411)	2764 (381)		0.84 (0.73, 0.97)	0.016
Gender: Male	2222 (335)	2251 (310)	0.8610	0.84 (0.72, 0.98)	0.0253
Female	784 (76)	735 (71)		0.84 (0.61, 1.16)	0.2946
Gold Stage: I/II	1356 (134)	1386 (119)	0.8363	0.83 (0.65, 1.07)	0.1525
III	1331 (204)	1304 (200)		0.86 (0.71, 1.05)	0.1333
IV	271 (66)	250 (57)		0.76 (0.53, 1.09)	0.1325
Smoking Status: Ex-Smoker	2108 (299)	2112 (256)	0.0613	0.77 (0.65, 0.91)	0.0024
Smoker	898 (112)	874 (125)		1.04 (0.80, 1.34)	0.7847
Reversibility: No	1393 (227)	1357 (210)	0.9145	0.84 (0.70, 1.01)	0.0666
Yes	1513 (171)	1520 (157)		0.84 (0.68, 1.05)	0.1270
Baseline ICS: No	1146 (169)	1146 (158)	0.7180	0.87 (0.70, 1.08)	0.2151
Yes	1860 (242)	1840 (223)		0.83 (0.69, 0.99)	0.0399
Baseline LABA: No	1198 (178)	1190 (168)	0.7252	0.87 (0.70, 1.08)	0.2003
Yes	1808 (233)	1796 (213)		0.82 (0.68, 0.99)	0.0403

	Placebo N (# of deaths)	Tiotropium N (# of deaths)	Subgroup interaction p-value	Risk Ratio (95% CI)	p-value*
Overall	3006 (411)	2764 (381)		0.84 (0.73, 0.97)	0.016
Baseline ICS/LABA:			0.9098		
No	1544 (233)	1522 (211)		0.84 (0.70, 1.01)	0.0640
Yes	1462 (178)	1464 (170)		0.85 (0.69, 1.05)	0.1323
Race[†]: White	2697 (353)	2691 (339)	0.3248	0.87 (0.75, 1.01)	0.0686
Black	53 (5)	38 (2)		0.42 (0.08, 2.19)	0.3068
Asian	185 (42)	192 (30)		0.63 (0.40, 1.01)	0.0545
Region: Asia	178 (39)	184 (29)	0.3975	0.66 (0.41, 1.07)	0.0950
E. Europe	597 (86)	590 (86)		0.96 (0.71, 1.30)	0.7872
Latin Amer.	207 (52)	198 (35)		0.66 (0.43, 1.02)	0.0594
USA	767 (86)	767 (93)		0.97 (0.72, 1.30)	0.8264
W. Europe	1257 (148)	1247 (138)		0.83 (0.65, 1.04)	0.1060
Age: <55	382 (26)	384 (24)	0.3348	0.82 (0.47, 1.43)	0.4873
55 –<65	1055 (108)	1054 (96)		0.79 (0.60, 1.04)	0.0966
65 –<75	1198 (191)	1208 (194)		0.95 (0.78, 1.17)	0.6507
≥ 75	371 (86)	340 (67)		0.69 (0.50, 0.95)	0.0237
BMI: <20	352 (72)	297 (75)	0.0782	1.06 (0.77, 1.47)	0.7111
20 –<25	1024 (131)	1074 (140)		0.90 (0.71, 1.14)	0.3714
25 –<30	1033 (145)	1039 (103)		0.65 (0.51, 0.84)	0.0009
≥ 30	597 (63)	576 (63)		0.95 (0.67, 1.35)	0.7866

	Placebo N (# of deaths)	Tiotropium N (# of deaths)	Subgroup interaction p-value	Risk Ratio (95% CI)	p-value*
Overall	3006 (411)	2764 (381)		0.84 (0.73, 0.97)	0.016
Baseline Anticholinergic:			0.6153		
No	1656 (221)	1620 (199)		0.87 (0.72, 1.05)	0.0348
Yes	1350 (190)	1366 (182)		0.80 (0.65, 0.98)	0.1465

*Hazard ratio based on Cox model with treatment, baseline covariate and baseline covariate by treatment interaction; p-value was obtained using log-rank test. †Numbers do not add up to total due to missing data.

Reviewer comment:

As was noted in the efficacy review, the subgroup analysis notes baseline anticholinergic use in 45% of the study population. This should not be construed to mean that these patients remained on anticholinergics, which were prohibited during the trial. The rate of protocol violations for anticholinergic use was approximately 3.8%.

Figure 7: Protocol 205.235 mortality subgroup analysis Forest plot

Reviewer comment:

The applicant is requesting a claim for mortality. BI proposes the following language for the clinical studies section of the label: "In the 4-year multicenter trial, there was a 16% reduction in the risk of death while on treatment with Spiriva HandiHaler compared to placebo. The incidence rate of death was 4.10 per 100 patient years in the tiotropium group vs. 4.78 per 100 patient years in the placebo group [Hazard Ratio (tiotropium/placebo) = 0.84, 95% CI = 0.73, 0.97]."

Since UPLIFT is a major study that doubles the size of the safety database for tio HH18, it is reasonable to describe major findings such as reduction in mortality in the product label. The persistence of the effect across many different analyses strengthens the evidence for a mortality benefit as does a plausible mechanism. However, a number of factors come into consideration for this claim:

- *Mortality is a major claim which requires a substantive body of evidence. To support a labeling claim, the Agency typically requires replication of findings in two or more*

clinical trials. However, according to the Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biologic Products, reliance on a single study is possible in situations in which a trial has demonstrated a clinically meaningful effect on mortality or irreversible morbidity. In addition, the single study would typically be large multicenter center, such as UPLIFT, with consistency across study subsets and statistically very persuasive findings.

- *A small numerical imbalance in mortality in favor of the placebo group was observed in 3 one-year Phase 3 studies of Spiriva Respimat.. Although Spiriva Respimat is a different drug product from an efficacy perspective, it contains the same drug substance as Spiriva HandiHaler, thus the two products would be expected to have a similar systemic safety profile. These data, complicate approval of a mortality claim.*
- *A recent meta-analysis by Singh, et al.[1] concludes that anticholinergic medications including tiotropium increase long-term cardiovascular mortality. Dr. Simone Pinheiro of the Office of Surveillance and Epidemiology reviewed the relevant literature, including this meta-analysis. Dr. Pinheiro concluded that the currently available data implicating tiotropium and ipratropium in increasing risk of cardiovascular death, myocardial infarction, and stroke is not compelling. Refer to the Office of Surveillance and Epidemiology review document for details.*
- *The Pulmonary and Allergy Drugs Advisory Committee (PADAC), in their meeting on November 19, 2009, concluded that UPLIFT was a compelling and important study, demonstrating generally beneficial effects on mortality. Although the Respimat results were felt to be somewhat concerning and additional data are needed, the Respimat results do not necessarily convey to the HandiHaler. Because of the Respimat data, any mortality information included in the Spiriva HandiHaler label will require careful consideration.*

7.1.2 Other Serious Adverse Events

Serious adverse events (SAEs) occurred in 50.9% of the overall study population, including 51.6% of the tio HH18 group and 50.2% of the placebo group. The most common SAEs were COPD exacerbation, pneumonia, and respiratory failure. SAEs occurring in more than 1% in either treatment group are given in Table 15. SAEs were generally balanced between treatment groups.

Table 15: Protocol 205.235 serious adverse events occurring in ≥ 1% of patients in either treatment group (as reported by applicant)

MedDRA System Organ Class MedDRA Preferred Term	Placebo N (%)	Tio HH18 N (%)	Total N (%)
Total Treated N (%)	3006 (100)	2986 (100)	5992 (100)
Total with serious adverse events	1509 (50.2)	1540 (51.6)	3049 (50.9)
Cardiac disorders	350 (11.6)	322 (10.8)	672 (11.2)
Angina#	31 (1.0)	48 (1.6)	79 (1.3)
Atrial fibrillation#	67 (2.2)	69 (2.3)	136 (2.3)
Cardiac failure	42 (1.4)	57 (1.9)	99 (1.7)
Cardiac failure congestive	42 (1.4)	27 (0.9)	69 (1.2)
Coronary artery disease	32 (1.1)	20 (0.7)	52 (0.9)
Myocardial infarction#	84 (2.8)	65 (2.2)	149 (2.5)
Neoplasms	170 (5.7)	197 (6.6)	367 (6.1)
Prostate cancer	22 (0.7)	31 (1.0)	53 (0.9)
Respiratory system disorders* (Lower)	985 (32.8)	911 (30.5)	1896 (31.6)
Acute respiratory failure	31 (1.0)	29 (1.0)	60 (1.0)
Bronchitis#	27 (0.9)	35 (1.2)	62 (1.0)
COPD exacerbation#	742 (24.7)	688 (23.0)	1430 (23.9)
Dyspnea#	54 (1.8)	36 (1.2)	90 (1.5)
Pneumonia#	290 (9.6)	296 (9.9)	586 (9.8)
Respiratory failure	113 (3.8)	85 (2.8)	198 (3.3)
Respiratory system disorders* (Other)	156 (5.2)	170 (5.7)	326 (5.4)
Lung neoplasm malignant	34 (1.1)	40 (1.3)	74 (1.2)
Pulmonary embolism	29 (1.0)	25 (0.8)	54 (0.9)

BI Collapsed Preferred Terms include multiple MedDRA Preferred Terms.

*All system organ classes are defined by MedDRA with the exception of respiratory, thoracic and mediastinal disorders which have been divided into 3 separate classes of respiratory system disorders lower, upper, and other.

<u>Reviewer comment:</u>

Based on the SAE data, the applicant is requesting a claim for reduction in respiratory failure. BI proposes the following language for the clinical studies section of the label: "In the 4-year multicenter trial….Treatment with tiotropium reduced the risk of respiratory failure by 19% (2.09 vs. 1.68 cases per 100 patient years [relative risk (tiotropium/placebo) = 0.81, 95% CI 0.65, 1.00]."

While the incidence of SAEs of respiratory failure is reduced in the tio HH18 group, the difference is marginally significant and there are multiple related preferred terms that have been analyzed separately. Unlike mortality, which is a hard endpoint and was pre-specified in the protocol as an event of interest (including vital status collection and an independent adjudication committee), the term "respiratory failure" is undefined and subject to investigator interpretation. In addition, multiplicity is a concern since many adverse event variables were evaluated in the safety analysis and the effect is only marginally significant. Inclusion of the term respiratory failure may be appropriate as part of adverse event

reporting for the study; however, there is insufficient evidence to justify a specific claim that Spiriva HandiHaler reduces respiratory failure.

7.1.3 Dropouts and Other Significant Adverse Events

Adverse events leading to discontinuation

There were 618 (20.7%) patients in the tio HH18 group and 735 (24.5%) patients in the placebo group who discontinued prematurely due to an adverse event. The most frequent AEs leading to discontinuation were all lower respiratory events—COPD exacerbation, dyspnea, pneumonia, and respiratory failure. Fewer patients in the tio HH18 group discontinued due to a lower respiratory AE compared to patients in the placebo group [291 (9.7%) versus 412 (13.7%), respectively]. This was driven by a reduced number of patients in the tio HH18 group with COPD exacerbations and dyspnea. See Table 16.

Table 16: Protocol 205.235 adverse events leading to discontinuation occurring in ≥ 10 patients overall

MedDRA System Organ Class MedDRA Preferred Term	Placebo N (%)	Tio HH18 N (%)	Total N (%)
Total Treated N (%)	3006 (100)	2986 (100)	5992 (100)
Total with AEs leading to discontinuation	735 (24.5)	618 (20.7)	1353 (22.6)
Cardiac disorders	81 (2.7)	70 (2.3)	151 (2.5)
Atrial fibrillation#	7 (0.2)	7 (0.2)	14 (0.2)
Cardiac failure	7 (0.2)	13 (0.4)	20 (0.3)
Cardiac failure congestive	6 (0.2)	5 (0.2)	11 (0.2)
Myocardial infarction#	21 (0.7)	15 (0.5)	36 (0.6)
Gastrointestinal disorders	32 (1.1)	29 (1.0)	61 (1.0)
Dry mouth#	4 (0.1)	9 (0.3)	13 (0.2)
General disorders	38 (1.3)	47 (1.6)	85 (1.4)
Death	12 (0.4)	19 (0.6)	31 (0.5)
Sudden death	11 (0.4)	9 (0.3)	20 (0.3)
Nervous system disorders	38 (1.3)	39 (1.3)	77 (1.3)
Cerebrovascular accident	8 (0.3)	11 (0.4)	19 (0.3)
Respiratory system disorders* (Lower)	412 (13.7)	291 (9.7)	703 (11.7)
Acute respiratory failure	10 (0.3)	8 (0.3)	18 (0.3)
COPD exacerbation#	209 (7.0)	152 (5.1)	361 (6.0)
Dyspnea#	118 (3.9)	54 (1.8)	172 (2.9)
Pneumonia#	51 (1.7)	48 (1.6)	99 (1.7)
Respiratory failure	31 (1.0)	21 (0.7)	52 (0.9)
Respiratory system disorders* (Other)	82 (2.7)	89 (3.0)	171 (2.9)
Bronchial carcinoma	5 (0.2)	11 (0.4)	16 (0.3)
Lung neoplasm	5 (0.2)	8 (0.3)	13 (0.2)
Lung neoplasm malignant	19 (0.6)	21 (0.7)	40 (0.7)
Non-small cell lung cancer	7 (0.2)	5 (0.2)	12 (0.2)
Non-small cell lung cancer, malignant	4 (0.1)	6 (0.2)	10 (0.2)
Pulmonary embolism	9 (0.3)	5 (0.2)	14 (0.2)
Small cell lung cancer, stage unspecified	3 (0.1)	7 (0.2)	10 (0.2)

BI Collapsed Preferred Terms include multiple MedDRA Preferred Terms.

*All system organ classes are defined by MedDRA with the exception of respiratory, thoracic and mediastinal disorders which have been divided into 3 separate classes of respiratory system disorders lower, upper, and other.

[m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/0202-0235-01-15-study-report-body.pdf/page 142]

Adverse events of stroke

Stroke is an adverse event of interest based on a potential safety signal observed in an analysis of combined tiotropium HandiHaler and Respimat trials. The results of UPLIFT (Protocol 205.235) show that stroke-related adverse events, SAEs, and fatal stroke events were not significantly increased in the tiotropium group compared to placebo. See Table 17. There were no specific treatment by subgroup interactions for stroke adverse events other than as related to small numbers. However, the overall incidence of stroke events in both

treatment groups did increase with age, as would be expected. See Section 7.1.5.2 and Table 18 for the definition of the combined term of "stroke."

Table 17: Protocol 205.235 stroke adverse events

	Tio HH18 N=2986		Placebo N=3006		
	N	Rate/100 pt yrs	N	Rate/100 pt yrs	Risk Ratio (95% CI)
AE	82	0.88	80	0.93	0.95 (0.70, 1.29)
SAE	66	0.70	63	0.73	0.97 (0.69, 1.37)
Fatal (on treatment)	12	0.13	13	0.15	0.85 (0.39, 1.87)
Fatal (vital status, D1470)	14	0.13	17	0.15	0.82 (0.40, 1.66)

[m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/0202-0235-01-15-study-report-body.pdf/pages 141-142]

Reviewer comment:

In recently completed pooled analyses of tiotropium clinical trial data, the Applicant identified stroke as occurring at higher rates in patients receiving tiotropium compared with patients receiving placebo (RR 1.37, 95% CI 0.73-1.56). This data was submitted to FDA in November 2007 and an Early Communication was issued by FDA for Spiriva HandiHaler on March 18, 2008. This pooled trial population presented information on 13,344 patients from 29 clinical trials, contributing 4,572 person-years of exposure to tiotropium and 3,065 person-years of exposure to placebo. This population included 25 trials from the Spiriva HandiHaler program and 4 trials from the Spiriva Respimat program (205.251, 205.252, 205.254, and 205.255). The analysis also investigated a large number of other adverse events without correction for multiplicity. The pooled trials in the Respimat program did not demonstrate a significantly increased risk (RR 0.87, 95% CI 0.30-2.56).

Likewise, the UPLIFT trial does not show a specific signal for stroke events, The UPLIFT trial does not show a specific signal for stroke events. The Risk Ratio for adverse events of stroke is less than one, and the upper bound of the confidence interval is less than 1.3, suggesting that if there is any adverse drug effect, it is minimal. Because stroke was a pre-specified term for the adjudication of cause of death, readers can have confidence that fatal strokes were appropriately classified and are not "hiding" under some other preferred term. Serious adverse events and fatal adverse events of stroke are subgroups and as expected, have slightly wider confidence intervals, although the conclusions are the same.

On November 19, 2009, the PADAC voted (11 yes, 1 no) that the UPLIFT trial adequately addressed the potential stroke signal raised by the pooled Spiriva analysis. The single negative vote was secondary to the fact that by virtue of required exclusion criteria for MI and baseline cardiovascular disease, the clinical trial population from UPLIFT does not

exactly match that of the population using marketed Spiriva HandiHaler, and a small increase in risk cannot be ruled out (upper bound of the confidence interval >1).

Major adverse cardiac events

In UPLIFT, there were pre-specified definitions of MI and sudden cardiac death utilized the adjudication committee. Sudden cardiac death was defined as unexplained death occurring within one hour of an abrupt change of a person's clinical state without other obvious cause. Sudden death was defined as death occurring more than one and less than 24 hours of last being observed alive and without evidence of a deteriorating medical condition. There was no increase in deaths due to cardiac disorders, sudden cardiac death, sudden death, or death due to unknown cause, although confidence intervals were wide. See Table 11.

There was no increase in adverse events of myocardial infarction in the tiotropium group compared to placebo (see Table 15), with a Risk Ratio of 0.71, 95% CI (0.52, 0.99). Overall, there was a borderline significant decrease in AEs in the cardiac SOC [RR 0.84, 95% CI (0.73, 0.98)], driven by a decrease in congestive heart failure and MI.

There were no treatment by subgroup interactions for cardiovascular adverse events. Combined cardiac ischemic events (angina/ischemia/MI) for both treatment groups were increased in current smokers compared to non-smokers and were also mildly increased in patients with ICS use. This result was not seen in combined ICS/LABA use, so the increase in cardiac ischemic events with ICS use likely represents a spurious result due to multiple comparisons and low numbers. Adverse events of congestive heart failure were increased in both treatment groups with age and with increasing GOLD stage, both of which could be plausible medically.

A post-hoc analysis evaluated the combined term of cardiovascular death, which included all serious events with an outcome of death in the cardiac and vascular SOCs in addition to the terms sudden death and sudden cardiac death. Cardiovascular death was not increased in the UPLIFT trial, with a Risk Ratio of 0.73 (95% CI, 0.56, 0.96).

Reviewer's Comment:

Because myocardial infarction and sudden cardiac death were pre-specified terms for the adjudication of cause of death, readers can have confidence that these events were appropriately classified and are not "hiding" under some other preferred term.

On November 19, 2009, the PADAC voted (11 yes, 1 abstain) that the UPLIFT trial adequately addressed the potential stroke signal raised by the pooled Spiriva analysis.

7.1.4 Other Search Strategies

No adverse events leading to dose reduction were reported in this Application. COPD exacerbations were defined by the study protocol (205.235) as an efficacy endpoint and are discussed under Section 6 (Integrated Summary of Efficacy) and in Section 10.1.2.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

All adverse events, serious and non-serious, were collected in an ongoing fashion throughout the trial (Protocol 205.235) until the end of the double-blind treatment period. At each study visit, all AEs regardless of causality were recorded after review of the Patient Daily Record and discussion with the patient. In addition, all serious adverse events that occurred within 30 days of the last dose of study drug were reported. Adverse events were followed until resolution, until follow up was agreed adequate by the monitor and investigator, or until a patient was lost to follow up. Elective procedures planned prior to signing informed consent were not considered adverse events. Adverse events were monitored by an independent Data Safety Monitoring Board (DSMB).

[m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/0202-0235-01-15-study-report-body.pdf/pages 74-75]

Protocol Amendment 2 allowed for long-term assessment of outcome for patients prematurely discontinued from UPLIFT. Vital status, including cause of death, if known, was collected every 6 months beginning November 15, 2005 for each discontinued patient until completion of the planned observation period (4 years). Vital status was recorded on a separate CRF that captured the following variables: 1) patient's vital status (alive, deceased, or unknown), 2) date of death, 3) cause of death, 4) source of information, 5) additional information regarding the circumstances, 6) if the patient's status was unknown, the date the patient was last known to be alive, and 7) the investigator's signature and date. At the time the amendment was instituted, approximately 1,500 of the 6,000 patients enrolled in the UPLIFT trial had prematurely discontinued from participation.

[m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/0202-0235-01-15-study-report-body.pdf/pages 46-50 and 76-77]

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were classified according to the MedDRA version 11.0. Since the development program focused on respiratory outcomes, the Applicant further divided the MedDRA system organ class (SOC) of "respiratory, thoracic, and mediastinal disorders" into three categories: respiratory (lower), respiratory (upper), and respiratory (other). The Applicant classified pneumonia into the "respiratory (lower)" SOC, which in theory groups all pneumonias into a single category. MedDRA also permits classification of pneumonias by organism in the "infections and infestations" SOC. In addition, the Applicant classified neoplasms of the respiratory system into the SOC of "respiratory (other)" rather than under the "neoplasms" SOC.

In order to see combined occurrence rates of medically similar adverse events, the Applicant collapsed multiple MedDRA preferred terms into Spiriva-specific preferred terms. The

Applicant also provided a full set of adverse event tables without collapsing of events for comparative purposes. These combined terms are designated in adverse event tables in this review with the symbol "#." Spiriva defined combined terms include: angina, atrial fibrillation, myocardial infarction, tachycardia, glaucoma, abdominal pain, dry mouth, vomiting, edema, oropharyngeal candidiasis, urinary tract infection, asthma, bronchitis, cystic fibrosis, dyspnea, pneumonia, pharyngitis, sinusitis, upper respiratory tract infection

Stroke is an adverse event of interest in the Spiriva HandiHaler program due to a potential increase in adverse events of stroke noted in a pooled analysis of 29 placebo-controlled studies. See Section 7.1.3. MedDRA permits classification of terms related to stroke under either the "nervous system disorders" SOC or the "vascular disorders" SOC. In Protocol 205.235, the Applicant classified all stroke preferred terms under nervous system disorders.

While they are broken out separately in the adverse event tables, BI includes a number of terms in the analysis of "stroke" adverse events. Preferred terms were chosen from the Standardized MedDRA Queries (SMQ) for central nervous system hemorrhage and cerebrovascular accident (MedDRA version 11), which is collapsed into a single SMQ of central nervous system hemorrhages and cerebrovascular conditions in MedDRA version 12.0. Because the SMQs for stroke are very broad and include terms that are not true strokes, inclusion of all terms in the SMQ could generate noise and dilute out any potential signal. For example, BI did not include the preferred terms of "angiogram cerebral abnormal" and "cerebral aneurysm ruptured syphilitic" in the collapsed term of stroke. Overall, the list of preferred terms classified as stroke by BI is a conservative and appropriate choice. See Table 18.

Table 18: Protocol 205.235 combined stroke definition

Preferred terms	Broad SMQ Stroke†	BI Custom Stroke
Amaurosis fugax	X	X
Angiogram cerebral abnormal	X	
Aphasia	X	
Balint's syndrome	X	
Basal ganglia hemorrhage	X	X
Basal ganglia infarction	X	
Basilar artery occlusion	X	X
Basilar artery stenosis	X	
Basilar artery thrombosis	X	X
Brain stem hemorrhage	X	X
Brain stem infarction	X	X
Brain stem ischemia	X	X
Brain stem stroke	X	
Brain stem thrombosis	X	X
Capsular warning syndrome	X	
Carotid aneurysm rupture	X	X
Carotid arterial embolus	X	X
Carotid arteriosclerosis	X	
Carotid artery aneurysm	X	
Carotid artery bypass	X	
Carotid artery disease	X	

Preferred terms	Broad SMQ Stroke†	BI Custom Stroke
Carotid artery dissection	X	
Carotid artery insufficiency	X	
Carotid artery occlusion	X	X
Carotid artery stenosis	X	X
Carotid artery stent insertion	X	
Carotid artery thrombosis	X	X
Carotid endarterectomy	X	
Central pain syndrome	X	
Cerebellar artery occlusion	X	X
Cerebellar artery thrombosis	X	X
Cerebellar embolism	X	X
Cerebellar hematoma	X	X
Cerebellar hemorrhage	X	X
Cerebellar infarction	X	X
Cerebellar ischemia	X	
Cerebral aneurysm ruptured syphilitic	X	
Cerebral arteriosclerosis	X	
Cerebral arteriovenous malformation hemorrhagic	X	X
Cerebral artery embolism	X	X
Cerebral artery occlusion	X	X
Cerebral artery stenosis	X	
Cerebral artery thrombosis	X	X
Cerebral hematoma	X	X
Cerebral hemorrhage	X	X
Cerebral hemorrhage fetal	X	X
Cerebral hemorrhage neonatal	X	X
Cerebral infarction	X	X
Cerebral infarction fetal	X	X
Cerebral ischemia	X	X
Cerebral revascularization synangiosis	X	
Cerebral thrombosis	X	X
Cerebral vasoconstriction	X	
Cerebral venous thrombosis	X	
Cerebrovascular accident	X	X
Cerebrovascular accident prophylaxis	X	
Cerebrovascular disorder	X	
Cerebrovascular insufficiency	X	
Cerebrovascular spasm	X	
Cerebrovascular stenosis	X	
Charcot-Bouchard microaneurysms	X	
Diplegia	X	
Dysarthria	X	
Embolic cerebral infarction	X	X
Embolic stroke	X	X
Fetal cerebrovascular disorder	X	
Hematomyelia	X	
Hemiparesis	X	
Hemiplegia	X	
Hemorrhage intracranial	X	X
Hemorrhagic cerebral infarction	X	X

Preferred terms	Broad SMQ Stroke†	BI Custom Stroke
Hemorrhagic stroke	X	X
Hemorrhagic transformation stroke	X	X
Intracerebral aneurysm operation	X	
Intracerebral hematoma evacuation	X	
Intracranial aneurysm	X	
Intracranial hematoma	X	X
Intracranial tumor hemorrhage		X
Intraoperative cerebral artery occlusion		X
Intraventricular hemorrhage	X	X
Intraventricular hemorrhage neonatal	X	X
Ischemic cerebral infarction	X	X
Ischemic stroke	X	X
Lacunar infarction	X	X
Lateral medullary syndrome	X	X
Meningorrhagia	X	
Millard-Gubler syndrome	X	
Monoparesis	X	
Monoplegia	X	
Moyamoya disease	X	
Paralysis	X	
Paralysis flaccid	X	
Paraparesis	X	
Paraplegia	X	
Paresis	X	
Pituitary hemorrhage		X
Pituitary infarction		X
Postprocedural stroke	X	X
Precerebral artery occlusion	X	X
Putamen hemorrhage	X	X
Quadriparesis	X	
Quadriplegia	X	
Red blood cells CSF positive	X	
Reversible ischemic neurologic deficit	X	X
Ruptured cerebral aneurysm	X	X
Spastic paralysis	X	
Spastic paraplegia	X	
Spinal artery embolism	X	
Spinal cord hemorrhage	X	
Spinal epidural hemorrhage	X	
Spinal hematoma	X	
Stroke in evolution	X	X
Subarachnoid hemorrhage	X	X
Subarachnoid hemorrhage neonatal	X	X
Subdural hemorrhage	X	
Subdural hemorrhage neonatal	X	
Thalamic infarction	X	X
Thalamus hemorrhage	X	X
Thrombotic cerebral infarction	X	X
Thrombotic stroke	X	X
Transient ischemic attack	X	X

Preferred terms	Broad SMQ Stroke†	BI Custom Stroke
Vascular encephalopathy	X	
Vertebral artery occlusion	X	X
Vertebral artery stenosis	X	
Vertebral artery thrombosis	X	X
Vertebrobasilar insufficiency	X	
Visual midline shift syndrome	X	
Wallenberg syndrome	X	

†Taken from MedDRA version 12.0, SMQ term "Central nervous systems hemorrhages and cerebrovascular conditions"

For the purposes of adjudication of cause of death, the UPLIFT Mortality Adjudication Charter specifies that all stroke-related events will be classified as "stroke," through the use of mortality adjudication worksheets. Therefore, this term in the adjudicated cause of death was pre-specified and grouped as considered appropriate by the adjudicators. Other terms pre-specified on the worksheets used by the Adjudication Committee include COPD (with pneumonia, without pneumonia, or pneumonia not specified), pneumonia, pulmonary embolism, congestive heart failure, myocardial infarction, lung cancer, breast cancer, colorectal cancer, sudden cardiac death, sudden death, and death of unknown cause. In the UPLIFT Mortality Adjudication Charter, sudden cardiac death was defined as unexplained death occurring within one hour of an abrupt change of a person's clinical state without other obvious cause. Sudden death was defined as death occurring more than one and less than 24 hours of last being observed alive and without evidence of a deteriorating medical condition.

In the pooled analysis of Spiriva HandiHaler and Spiriva Respimat blinded, placebo-controlled trial data (see Section 7.2.2.1), BI uses the combined terms of "cardiovascular death" and "cardiovascular endpoint." These terms were defined as follows.

The term "cardiovascular death" includes deaths due to:

- cardiac disorders SOC
- vascular disorders SOC
- BI expanded MI term
- BI stroke term (see Table 18)
- sudden death
- cardiac death
- sudden cardiac death

The term "cardiovascular endpoint" includes AEs of:

- fatal AEs in the cardiac disorders SOC
- fatal AEs in the vascular disorders SOC

- BI expanded MI term (fatal and non-fatal)
- BI expanded stroke term (fatal and non-fatal, see Table 18)
- sudden death
- cardiac death
- sudden cardiac death

Reviewer comment:

The Applicant's division of the respiratory category into upper, lower, and other is appropriate for a COPD study. It is also very useful for analysis to have all pneumonias grouped together. In addition, the grouping of terms, including classification of stroke terms, is appropriate and helpful to the review. Because stroke and myocardial infarction were pre-specified terms for the adjudication of cause of death, readers can have confidence that fatal strokes and myocardial infarctions were appropriately classified and are not "hiding" under some other preferred term. The other terms and grouping used in the analysis appear reasonable.

7.1.5.3 Incidence of common adverse events

Non serious adverse events were reported in almost all patients in both groups (92.3% of placebo patients and 92.6% of tio HH18 patients), an expected finding given the length of the study and the severity of disease in this patient population. In order to account for differential drop out, the applicant also reported AEs as exposure adjusted rates (number of patients experiencing an event divided by the person-years at risk).

The most frequently reported AEs were COPD exacerbation, pneumonia, dyspnea, nasopharyngitis, and upper respiratory tract infection. If evaluated by exposure adjusted rates, COPD exacerbation, dyspnea, and respiratory failure occurred significantly less frequently in the tio HH18 group compared to placebo. In contrast, dry mouth and insomnia occurred significantly more frequently in the tio HH18 group. Dry mouth is a known anticholinergic side effect of tiotropium. Other known anticholinergic side effects also occurred with greater frequency in the tiotropium group although not significantly so. These included constipation, benign prostatic hypertrophy, dizziness, sinusitis, nasopharyngitis, cough, and urinary tract infection. See Table 19.

[m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/0202-0235-01-15-study-report-body.pdf/pages 130-133]

Table 19: Protocol 205.235 frequency and incidence rates (per 100 patient years) of patients with AEs occurring in >3% of either treatment group

	Placebo N=3006		Tio HH18 N=2986		Tio HH18/ placebo
	N (%)	Incidence Rate	N (%)	Incidence Rate	Rate Ratio (95% CI)
Total with AE	**2774 (92.3)**		**2764 (92.6)**		
COPD exacerbation#	1986 (66.1)	45.5	1934 (64.8)	38.1	0.84 (0.79, 0.89)
Pneumonia#	418 (13.9)	5.14	433 (14.5)	4.94	0.96 (0.84, 1.10)
Dyspnea#	443 (14.7)	5.49	364 (12.2)	4.09	0.75 (0.65, 0.86)
Nasopharyngitis	324 (10.8)	4.06	373 (12.5)	4.33	1.07 (0.92, 1.24)
Upper respiratory tract infection#	290 (9.6)	3.57	298 (10.0)	3.38	0.95 (0.81, 1.11)
Hypertension	284 (9.4)	3.45	275 (9.2)	3.08	0.89 (0.75, 1.05)
Bronchitis#	233 (7.8)	2.82	232 (7.8)	2.57	0.91 (0.76, 1.10)
Cough	213 (7.1)	2.57	238 (8.0)	2.64	1.03 (0.86, 1.24)
Back pain	188 (6.3)	2.25	198 (6.6)	2.18	0.97 (0.79, 1.18)
Urinary tract infection#	169 (5.6)	2.00	190 (6.4)	2.08	1.04 (0.85, 1.28)
Sinusitis#	160 (5.3)	1.90	194 (6.5)	2.14	1.12 (0.91, 1.39)
Influenza	158 (5.3)	1.87	158 (5.3)	1.73	0.92 (0.74, 1.15)
Headache	136 (4.5)	1.61	171 (5.7)	1.88	1.17 (0.94, 1.47)
Edema#	130 (4.3)	1.52	145 (4.9)	1.57	1.03 (0.82, 1.31)
Constipation	111 (3.7)	1.29	151 (5.1)	1.63	1.26 (0.99, 1.61)
Diarrhea	122 (4.1)	1.43	138 (4.6)	1.5	1.04 (0.82, 1.33)
Cataract	123 (4.1)	1.45	120 (4.0)	1.3	0.90 (0.70, 1.15)
Atrial fibrillation#	113 (3.8)	1.32	119 (4.0)	1.28	0.97 (0.75, 1.26)
Dry mouth#	80 (2.7)	0.93	152 (5.1)	1.68	1.80 (1.37, 2.36)
Depression	98 (3.3)	1.14	131 (4.4)	1.42	1.25 (0.96, 1.62)
Insomnia	91 (3.0)	1.06	131 (4.4)	1.42	1.34 (1.02, 1.75)
Arthralgia	94 (3.1)	1.10	125 (4.2)	1.36	1.24 (0.95, 1.62)
Benign prostatic hyperplasia	96 (3.2)	1.12	122 (4.1)	1.32	1.18 (0.90, 1.54)
Rhinitis	112 (3.7)	1.32	101 (3.4)	1.09	0.83 (0.63, 1.08)
Abdominal pain#	96 (3.2)	1.12	113 (3.8)	1.22	1.09 (0.83, 1.43)
Respiratory failure	120 (4.0)	1.39	88 (2.9)	0.94	0.67 (0.51, 0.89)
Hypercholesterolemia	97 (3.2)	1.13	104 (3.5)	1.12	0.99 (0.75, 1.31)
Nausea	94 (3.1)	1.09	93 (3.1)	1.00	0.91 (0.69, 1.22)
Dizziness	81 (2.7)	0.94	103 (3.4)	1.11	1.18 (0.88, 1.58)

BI Collapsed Preferred Terms include multiple MedDRA Preferred Terms.
*All system organ classes are defined by MedDRA with the exception of respiratory, thoracic and mediastinal disorders which have been divided into 3 separate classes of respiratory system disorders lower, upper, and other.

Reviewer comment:

The adverse events observed in the UPLIFT trial are consistent with the known adverse event profile of Spiriva HandiHaler. The findings of significant reductions in COPD exacerbation, dyspnea, and respiratory failure are supportive of the efficacy findings in the trial. Intestinal obstruction has not been mentioned previously in the Spiriva HandiHaler label, but could be consistent with the known anticholinergic side effect of constipation. No particular cardiac signals were identified.

7.1.6 Less Common Adverse Events

All AEs with a risk ratio ≥3 in the tio HH18 group compared to placebo are presented in Table 20. Analysis of these events reveals that while the risk ratio may be high, the number of patients with each event is very low and in most cases there is no biologic plausibility for a causal relationship. The risk ratio reached statistical significance for only one event, intestinal obstruction. Events that could be secondary to anticholinergic effects include atrial tachycardia, tachyarrhythmia, intestinal obstruction, and prostate infection. Supraventricular tachyarrhythmic events in general did not appear to be increased overall in the tio HH18 group, with atrial fibrillation occurring in 113 (3.8%) patients in the placebo group and 119 (4.0%) patients in the tio HH18 group [RR 0.97, 95% CI (0.75, 1.26)] and tachycardia occurring in 43 (1.4%) patients in the placebo group and 40 (1.3%) patients in the tio HH18 group [RR 0.86, 95%CI (0.56, 1.32)].

Table 20: Protocol 205.235 frequency and incidence rates (per 100 patient years) of patients with AEs with a risk ratio of ≥3

	Placebo N=3006		Tio HH18 N=2986		Tio HH18/ placebo
	N (%)	Incidence Rate	N (%)	Incidence Rate	Rate Ratio (95% CI)
Total with AE	2774 (92.3)		2764 (92.6)		
Atrial tachycardia	1 (0.0)	0.01	8 (0.3)	0.08	7.39 (0.92, 59.1)
Tachyarrhythmia	2 (0.1)	0.02	8 (0.3)	0.08	3.70 (0.79, 17.4)
Tricuspid valve incompetence	1 (0.0)	0.01	6 (0.2)	0.06	5.54 (0.67, 46.1)
Epigastric discomfort	1 (0.0)	0.01	5 (0.2)	0.05	4.62 (0.54, 39.6)
Intestinal obstruction*	2 (0.1)	0.02	12 (0.4)	0.13	5.55 (1.24, 24.8)
Large intestinal perforation	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Peritonitis	1 (0.0)	0.01	5 (0.2)	0.05	4.62 (0.54, 39.6)
Tongue disorder	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Ulcer	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Bile duct stone	2 (0.1)	0.02	8 (0.3)	0.08	3.70 (0.79, 17.4)
Abscess	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Appendicitis	2 (0.1)	0.02	9 (0.3)	0.10	4.16 (0.90, 19.3)
Osteomyelitis	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Prostate infection	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Foreign body trauma	1 (0.0)	0.01	5 (0.2)	0.05	4.62 (0.54, 39.6)
Tendon rupture	2 (0.1)	0.02	9 (0.3)	0.10	4.16 (0.90, 19.3)
Ulna fracture	1 (0.0)	0.01	5 (0.2)	0.05	4.62 (0.54, 39.6)
INR increased	1 (0.0)	0.01	5 (0.2)	0.05	4.62 (0.54, 39.6)
Vitamin B12 deficiency	2 (0.1)	0.02	7 (0.2)	0.07	3.24 (0.67, 15.6)
Costochondritis	2 (0.1)	0.02	9 (0.3)	0.10	4.16 (0.90, 19.3)
Lumbar spinal stenosis	2 (0.1)	0.02	7 (0.2)	0.07	3.24 (0.67, 15.6)
Musculoskeletal discomfort	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Intercostal myalgia	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Non-Hodgkin's lymphoma	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Esophageal carcinoma	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Neurosis	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Restlessness	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Urethral stenosis	2 (0.1)	0.02	7 (0.2)	0.07	3.24 (0.67, 15.6)
Metastases to lung	2 (0.1)	0.02	7 (0.2)	0.07	3.24 (0.67, 15.6)
Small cell lung cancer, metastatic	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Rash generalized	1 (0.0)	0.01	6 (0.2)	0.06	5.55 (0.67, 46.1)
Skin disorder	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)

*p=0.02

Reviewer comment:

Intestinal obstruction is included in the postmarketing section of the Spiriva HandiHaler label and could be consistent with the known anticholinergic side effect of constipation.

7.1.7 Laboratory Findings

There were no laboratory evaluations performed in Protocol 205.235 aside from pregnancy testing conducted at screening for women of childbearing potential.

7.1.8 Vital Signs

Vital signs were performed as part of the complete physical examination at the start and end of each patient's participation in the trial. Any new or clinically relevant worsening of baseline conditions detected at the follow up physical examination were reported as adverse events. The applicant did not conduct additional analyses of vital sign or physical examination data.

7.1.9 Electrocardiograms (ECGs)

There were no ECGs performed in Protocol 205.235.

7.1.10 Immunogenicity

Since tiotropium is a small molecule, immunogenicity is not a concern. No evaluation of immunogenicity was performed for this supplement.

7.1.11 Human Carcinogenicity

Inhalational carcinogenicity studies in animals did not suggest carcinogenic potential for tiotropium. In Protocol 205.235, a total of 464 patients overall had SAEs of neoplasm including benign, malignant, and unspecified as well as cysts and polyps. Events excluded neoplasms of the respiratory system, which were categorized under the respiratory SOC. These included 245 patients (8.2%) in the tio HH18 group, and 219 (7.3%) patients in the placebo group. Accounting for discontinuations, the Relative Risk per 100 patient years was 1.04 [95% CI 0.86, 1.25] for tio HH18 versus placebo. The most common neoplasms reported overall were prostate cancer, basal cell carcinoma, colon cancer, bladder cancer, and metastases to the liver, all of which were balanced between treatment groups. There were 37 fatal cancers in the tio HH18 group and 45 in the placebo group (adjudicated, on-treatment population). Given the older male population enrolled in these studies, the neoplasms observed are not unexpected.

In addition to the neoplasm system organ class, tumors of the lung were categorized under the SOC of "respiratory, other." When the reviewer combined preferred terms into a single

"lung cancer" category, there were 263 patients with AEs of lung cancer, 140 (4.7%) in the tio HH18 group and 123 (4.1%) in the placebo group, making lung cancer the single most prevalent neoplasm reported in Protocol 205.235. Due to differential discontinuations, the AE numbers are comparable between groups. There were 79 fatal respiratory neoplasms in the tio HH18 group and 68 in the placebo group (adjudicated, on-treatment population). These included laryngeal cancer, lung cancer, mediastinum neoplasm, pharyngeal cancer, and pleural mesothelioma. The majority were classified by the Mortality Adjudication Committee as lung cancer, with 73 tio HH18 group and 66 in the placebo group [RR 1.02 (95% CI 0.73, 1.43)]. Given the heavy smoking history of the patient population enrolled in these studies, the neoplasms observed are not unexpected.

Reviewer comment:

The reviewer added AEs of lung cancer related preferred terms in the respiratory (other) category to determine total lung cancer events. Addition of events in this fashion may result in overestimation of effect if a single patient experienced more than one lung-cancer AE in this category. The preferred terms that were combined into the reviewer-specified "lung cancer" category are: large cell carcinoma of the respiratory track stage unspecified, lung adenocarcinoma, lung adenocarcinoma metastatic, lung adenocarcinoma recurrent, lung cancer metastatic, lung carcinoma cell type unspecified recurrent, lung carcinoma cell type unspecified Stage 0, lung carcinoma cell type unspecified Stage III, lung neoplasm, lung neoplasm malignant, lung squamous cell carcinoma Stage III, lung squamous cell carcinoma Stage IV, lung squamous cell carcinoma metastatic, non-small cell lung cancer, non-small cell lung cancer metastatic, small cell lung cancer extensive stage, small cell lung cancer limited stage, small cell lung cancer metastatic, and small cell lung cancer stage unspecified.

7.1.12 Special Safety Studies

No special safety studies were conducted as part of this application.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Spiriva HandiHaler is not a controlled substance and has no known abuse potential. Withdrawal was not assessed in Protocol 205.235, but has not been otherwise demonstrated with Spiriva HandiHaler.

7.1.14 Human Reproduction and Pregnancy Data

In Protocol 205.235, the majority of the population was males with an average age of 64.5 years; therefore, this study did not provide any new data with regards to human reproduction and pregnancy. No clinical data are available for pregnancies exposed to tiotropium or for nursing females. Because COPD is a disease that generally occurs only in older patients with a significant smoking history, clinical trials for tiotropium in COPD patients only

enrolled patients greater than 40 years of age. Studies in animals have shown evidence of reproductive toxicity.

7.1.15 Assessment of Effect on Growth

COPD is a disease that occurs only in the adult population. No data are available regarding the use of tiotropium in the pediatric population. Therefore, an assessment of effect on growth does not apply to this application. A pediatric waiver was granted for this application.

7.1.16 Overdose Experience

In the Spiriva HandiHaler development program submitted in the original NDA, there were no systemic anticholinergic adverse effects following a single inhaled dose of up to 340 mcg in healthy volunteers. In a dose ranging study of tiotropium bromide administered via nebulizer to healthy volunteers once daily for 14 days, doses of 10, 20, and 40 mcg were evaluated. A dose dependent increase in mild-moderate dry nose and dry mouth was observed in addition to a pronounced reduction in salivary flow from day 7 on in the 40 mcg dose group (Protocol 205.112).

The Applicant does not propose changes to the overdose section of the label.

7.1.17 Postmarketing Experience

The Applicant did not provide post-marketing experience data as part of this supplement (S029). According to the Periodic Adverse Drug Experience Report submitted to NDA 21-395 on January 30, 2009, during the reporting period of December 2007 through November 2008, IMS Health Prescription Data indicated that there were (b) (4) prescriptions for Spiriva HandiHaler written in the United States. During the reporting period, there were 433 initial 15-day expedited adverse event reports and 457 follow up reports submitted to the FDA. Of these, 94 cases had a fatal outcome. However, 34 of these contained no information other than that the patient died and the cause was not reported. Overall, no particular adverse event signals were associated with these reports.

One adverse event of interest that was specifically captured for the first time in the 2008 reporting period was accidental oral ingestion of Spiriva HandiHaler capsules. During the reporting period, there were 1560 reported oral ingestions of Spiriva capsules, for an incidence rate of approximately 0.20 accidental ingestions per 1000 prescriptions written. Of these reported oral ingestions, only 7 reported associated SAEs. These events included coronary blockage, infection in the feet secondary to diabetes, pneumonia (pre-existing), CPK increased and muscle rigidity, overdose (patient was hospitalized because she swallowed two capsules), and one report of ingestion of Spiriva capsule as the SAE. There were also 25 non-serious associated AEs, many of which were reported as “drug

ineffective." Because tiotropium has very poor oral absorption, adverse events other than "drug ineffective" are not anticipated.

FDA issued a Public Health Advisory on February 29, 2009 regarding correct use of Spiriva HandiHaler and swallowing of capsules. In addition, labeling changes to address this issue were approved in 2009.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Only one study was reviewed as part of this supplement, Protocol 205.235.

7.2.1.2 Demographics

The mean age of the patients in Protocol 205.235 was 64.5 years (range 40-88 years). The majority of the trial population (74.6%) was male and 89.9% were white. The mean duration of COPD was 9.8 years. All patients were current (29.6%) or ex-smokers (70.4%), with a mean smoking history of 48.7 pack years. The mean pre-bronchodilator FEV_1 was 1.096L with a mean percent predicted of 39.4%. The mean pre-bronchodilator FEV_1/FVC was 42.3%. The overall demographic profile was generally balanced across the treatment groups. Pulmonary function data at baseline were generally comparable. Demographic and disease characteristics are provided in Table 21, and baseline PFT variables are provided in Table 22.

[m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/0202-0235-01-15-study-report-body.pdf/pages 100-102, Table 15.1.4.1, pages 177-180]

Table 21: Protocol 205.235 patient demographic and disease characteristics

	Placebo	Tio HH18	Total
Number of patients[1]	3006	2986	5992
Gender [N (%)]			
Male	2222 (73.9)	2251 (75.4)	4473 (74.6)
Female	784 (26.1)	735 (24.6)	1519 (25.4)
Race [N (%)]			
White	2697 (89.7)	2691 (90.1)	5388 (89.9)
Black	53 (1.8)	38 (1.3)	91 (1.5)
Asian	185 (6.2)	192 (6.4)	377 (6.3)
Missing	71 (2.4)	64 (2.2)	136 (2.3)
Age [years]			
Mean	64.5	64.5	64.5
SD	8.5	8.4	8.5
Min	40.0	40.0	40.0
Max	88.0	88.0	88.0
Smoking history [N (%)]			
Ex smoker	2108 (70.1)	2112 (70.7)	4220 (70.4)
Smoker	898 (29.9)	874 (29.3)	1772 (29.6)
Smoking history [pack years]			
Mean	48.4	49	48.7
SD	27.9	28.0	27.9
Min	10.0	10.0	10.0
Max	285.0	225.0	285.0
Duration of COPD [years]			
Mean	9.7	9.9	9.8
SD	7.4	7.6	7.5
Min	0.0	0.08	0.0
Max	53.0	55.0	55.0
Gold stage [N (%)]			
Stage I	1 (0.0)	2 (0.1)	3 (0.1)
Stage II	1355 (45.1)	1384 (46.3)	2739 (45.7)
Stage III	1331 (44.3)	1304 (43.7)	2635 (44.0)
Stage IV	271 (9.0)	250 (8.4)	521 (8.7)
missing	48 (1.6)	46 (1.5)	94 (1.6)

Table 22: Protocol 205.235 baseline PFT data

	Tio HH18	Placebo	Total
Number of patients	3006	2986	5992
Pre-bronchodilator FEV_1 [L]			
Mean	1.092	1.101	1.096
SD	0.40	0.40	0.40
Min	0.29	0.28	0.28
Max	2.71	2.64	2.71
Pre-bronchodilator % predicted normal FEV_1			
Mean	39.3	39.5	39.4
SD	11.9	12.0	12.0
Min	9.0	11.0	9.0
Max	76.0	73.0	76.0
Pre-bronchodilator FVC [L]			
Mean	2.63	2.63	2.63
SD	0.83	0.81	0.82
Min	0.64	0.67	0.64
Max	6.70	6.13	6.70
Pre-bronchodilator FEV_1 / FVC [%]			
Mean	42.1	42.4	42.3
SD	10.5	10.5	10.5
Min	15.0	14.0	14.0
Max	76.0	75.0	76.0

Data were Obtained from Visit 2, Randomization Visit.

Reviewer comment:

The demographics in this study are highly consistent with those across the Phase 3 programs for both Spiriva HandiHaler and Spiriva Respimat. For example, the pre-bronchodilator baseline FEV_1 observed in the 1-year Spiriva Respimat Phase 3 studies (205.254 and 205.255) had a mean of 1.09L and median of 1.03L.

7.2.1.3 Extent of exposure (dose/duration)

A total of 5992 COPD patients were randomized and received at least one dose of study drug. The planned exposure for each patient was 1440 days (approximately 48 months). One eligible patient withdrew at the randomization visit, prior to receiving study drug. One additional patient was randomized twice in error (once to each treatment group).

Mean exposure to study drug for all patients was 1080 days. Significantly fewer ($p<0.0001$) patients in the tio HH18 group prematurely discontinued than in the placebo group [1080 (36.2%) versus 1341(44.6%)]. The highest percentage of discontinuations occurred in the first year of treatment. A summary of patient exposure is provided in Table 23.

Table 23: Protocol 205.235 summary of treatment exposure

	Placebo N=3006 n (%)	Tio HH18 N=2986 n (%)	Total N=5992 n (%)
Total treated Exposure (months)			
≥ 1	2867 (95.4)	2915 (97.6)	5782 (96.5)
≥ 3	2740 (91.2)	2816 (94.3)	5556 (92.7)
≥ 6	2618 (87.1)	2726 (91.3)	5344 (89.2)
≥ 9	2513 (83.6)	2634 (88.2)	5147 (85.9)
≥ 12	2418 (80.4)	2565 (85.9)	4983 (83.2)
≥ 15	2344 (78.0)	2496 (83.6)	4840 (80.8)
≥ 18	2249 (74.8)	2432 (81.4)	4681 (78.1)
≥ 21	2161 (71.9)	2363 (79.1)	4524 (75.5)
≥ 24	2090 (69.5)	2293 (76.8)	4383 (73.1)
≥ 27	2013 (67.0)	2236 (74.9)	4249 (70.9)
≥ 30	1947 (64.8)	2177 (72.9)	4124 (68.8)
≥ 33	1891 (62.9)	2117 (70.9)	4008 (66.9)
≥ 36	1831 (60.9)	2060 (69.0)	3891 (64.9)
≥ 39	1779 (59.2)	2001 (67.0)	3780 (63.1)
≥ 42	1723 (57.3)	1970 (66.0)	3693 (61.6)
≥ 45	1665 (55.4)	1904 (63.8)	3569 (59.6)
Treatment Exposure (days)			
Mean	1032.7	1128.1	1080.3
Min	1	1	1
Max	1550	1655	1655

[m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/0202-0235-01-15-study-report-body.pdf/pages 125-128]

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

As part of this NDA, Boehringer Ingelheim submitted pooled analyses of adverse event data from 30 clinical trials. These trials consisted of 26 Spiriva HandiHaler trials and 4 Spiriva Respimat trials. The criteria used for selection of these trials are as follows:

- Randomized, placebo controlled, parallel group design
- COPD patient population
- Duration of at least 4 weeks of treatment intervention
- Spiriva HandiHaler 18 mcg or Spiriva Respimat 5 or 10 mcg

A variety of different analyses were performed, including the following combination of trials:

- UPLIFT alone
- HandiHaler trials excluding UPLIFT (25 trials)
- Respimat trials (4 trials)
- UPLIFT + HandiHaler trials
- UPLIFT + HandiHaler + Respimat
- 4 Respimat trials, 5 versus 10 mcg Respimat

The following subgroups were analyzed for the 30 combined trials:

- Age (<60, 60 - <70, ≥70)
- Gender
- GOLD Stage (I/II, III, IV)
- Cardiac disorders flag
- Coronary artery disease flag
- Renal disorder flag
- Atherosclerotic disease flag
- Anticholinergics use flag
- LABA use flag
- ICS use flag
- Other steroids use flag
- Statins use flag (defined by ATC-4 code HMG CoA Reductase Inhibitors)

Dr. Banu Karimi-Shah (Clinical Review IND 46,687, S-275 dated August 26, 2008) and Dr. Sally Seymour (Clinical Review IND 46,678, S-275 dated February 14, 2008) previously reviewed the pooled analysis of 29 clinical trials (excluding UPLIFT). In this analysis, a numerical increased risk of stroke events with tiotropium, specifically Spiriva HandiHaler, was observed [Risk Ratio 1.36, 95% CI (0.73, 1.56)].

Based on patient-years of exposure in patients with COPD participating in placebo-controlled trials, the UPLIFT study more than quadruples (4.37 times larger) the safety database for Spiriva HandiHaler, and more than triples (3.35 times larger) the safety database for tiotropium as a whole. See Table 24 for patient years of exposure.

Table 24: Patient-years of exposure across the tiotropium program

Database	Placebo	Tiotropium
HandiHaler trials (25)	2079	2736
Respimat trials (4)	517	1188
UPLIFT	8499	9222
UPLIFT + HandiHaler trials	10578	11958
All 30 trials	11095	13146

As might be expected for a pooled analysis when including a trial of large size, the UPLIFT data dominate the pooled analysis. Combining UPLIFT with the HandiHaler studies or with the 29 studies eliminates the potential stroke signal previously observed. In addition, no cardiovascular signals were observed. See Table 25.

Table 25: Pooled analysis results for major adverse cardiac events

	MI		Stroke		Cardiovascular death	
	Risk Ratio	95% CI	Risk Ratio	95% CI	Risk Ratio	95% CI
HandiHaler trials	1.251	0.682, 2.296	1.607	0.825, 3.132	NP	NP
Respimat trials	0.376	0.117, 1.213	0.873	0.298, 2.555	NP	NP
HandiHaler + Respimat trials	NP	NP	NP	NP	0.973	0.542, 1.747
UPLIFT	0.726	0.527, 1.000	0.946	0.695, 1.287	0.730	0.560, 0.951
UPLIFT + HandiHaler trials	0.820	0.619, 1.086	1.045	0.791, 1.380	NP	NP
All 30 trials	0.788	0.600, 1.035	1.033	0.789, 1.353	0.767	0.603, 0.976

MI=myocardial infarction, NP=not provided in this supplement

The subgroup analysis was systematically reviewed for interactions with MI and stroke. No treatment by subgroup interactions were observed for either of these events. In both treatment groups, however, the incidence of MI and stroke were increased with a history of cardiac disorder, history of coronary artery disease, history of atherosclerotic disease, and history of statin use. These are all expected correlations. Presumably, statin use is serving as

a marker for hypercholesterolemia, which was not measured in these studies, rather than statins causing MI and stroke. Incidentally, lower respiratory infections and pneumonia were increased in both treatment groups in patients using inhaled corticosteroids and other steroids.

Reviewer comment:

Because UPLIFT is such a large study, the pooled analysis does not add significantly to the understanding of adverse events for tiotropium.

7.2.2.2 Postmarketing experience

Postmarketing experience is discussed under Section 7.1.17 Postmarketing Experience.

7.2.2.3 Literature

In September 2008, JAMA published a meta-analysis by Singh, et al. entitled "Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis."[1] This article has received wide press.

The Singh, et al. meta-analysis identified trials from the literature that had the following inclusion criteria: 1) randomized controlled trial with more than 30 days of follow up, 2) trial participants with a diagnosis of COPD of any severity, 3) inhaled anticholinergic (short or long-acting) versus control (active or placebo), and 4) trial reported on the incidence of serious cardiovascular adverse events, including MI, stroke, or cardiovascular death. Of 703 potentially relevant trials, the analysis included only 17. Twelve of the trials included tiotropium (all Spiriva HandiHaler), and four included ipratropium. Of the tiotropium trials, two were replicate studies of others in the analysis, which resulted in double counting of over 1000 patients, and one included open-label tiotropium. The primary endpoint of the meta-analysis was pre-specified as a composite of nonfatal MI, nonfatal stroke (including transient ischemic attack), and cardiovascular death (including sudden death). The authors note that cardiovascular events were determined from the SAE reporting in the trial and were not uniformly defined across the studies, nor were patient-level data evaluated to further define events in the meta-analysis.

Initial results were reported in September 2008,[1] and revised results were published in March 2009.[6] These results demonstrated a significant increase in the risk of myocardial infarction (MI) and cardiovascular death. Stroke and all cause mortality were not significantly increased. See Table 26. The increase in MI and cardiovascular death was primarily found in long-term trials (>6 months), and was driven by the Lung Health Study.[2] The Lung Health Study was a large NIH-sponsored multicenter clinical trial of smoking intervention and inhaled bronchodilator (ipratropium) use in middle-aged smokers with mild-moderate COPD. With 5-years of follow up, a small increase in cardiovascular mortality was reported in the ipratropium group compared to placebo. On further analysis, this increase was attributed to a statistical anomaly due to non-compliance.[7]

Table 26: Singh, et al. anticholinergic meta-analysis results

Outcome	No of RCTs	Inhaled anticholinergic n/N	Controls n/N	RR (95% CI)	p-value
As reported September 2008					
CV death	12	57/6156	31/6220	1.80 (1.17-2.77)	0.008
MI	11	68/5430	43/5168	1.53 (1.05-2.23)	0.03
Stroke	7	25/4548	18/4703	1.46 (0.81-2.62)	0.20
All cause mortality	17	149/7472	115/7311	1.26 (0.99-1.61)	0.06
As reported March 2009					
CV death	12	56/5668	28/5615	1.92 (1.23-3.00)	0.004
MI	13	68/5430	43/5123	1.52 (1.04-2.22)	0.03
Stroke	9	25/4548	18/4703	1.46 (0.81-2.62)	0.20
All cause mortality	17	146/6984	108/6661	1.29 (1.00-1.65)	0.05

RCT=randomized controlled trials, RR=risk ratio, CV=cardiovascular, MI=myocardial infarction

A number of methodological issues exist with the Singh meta-analysis, including double counting of trials, use of open-label data, and results driven by a single large trial (Lung Health Study). These are examined in detail in a review of published literature of meta-analyses and cohort studies by Dr. Simone Pinheiro of the Office of Safety and Epidemiology. (See OSE Review, Simone Pinheiro, PhD, NDA 21-395, S029). In brief, other issues include:

- Study selection: Only trials reporting AEs were included. Sixty-nine trials were excluded from the analysis because cardiovascular AEs were not reported in the publication. This is particularly important as none of the trials were originally designed to evaluate risk of cardiovascular adverse events. Studies with an imbalance in the number of adverse events may be both more likely to provide information on adverse events and to be included in the meta-analysis. This could have resulted in a biased selection of studies which could explain, at least in part, the associations observed in Singh et al.

- Meta-analysis combined data from both ipratropium and tiotropium: While these two compounds belong to the same class and may share many of the same side effects, the short-versus long-acting nature of the drugs could have significant implications for systemic effects such as cardiovascular events.

- Meta-analysis combined data from placebo and active controlled trials: The nature and design of these two types of trials are fundamentally different, and the active controls may have side effects of their own.
- Meta-analysis did not account for differential discontinuation rates: As there are generally more patients who discontinue from placebo than from active treatment, this may bias against the drug as patients who tolerate placebo tend to be healthier than those who discontinue, particularly in long-term follow up.
- No patient-level data were utilized: The fact that randomized studies were included in the meta-analysis does not mean that comparisons between trials are randomized comparisons. Therefore, risk factors such as smoking status, BMI, COPD severity, and LABA use could confound the analyses if they differ across trials and are associated with the outcomes of interest.

Reviewer comment:

While the Singh, et al. article raises issues with regards to cardiovascular mortality and MI with tiotropium, these issues are addressed with randomized, placebo-controlled data from the UPLIFT trial. According to Dr. Pinheiro, other studies in the literature also do not support cardiovascular, stroke, or mortality safety signals for tiotropium. In addition, the numerous methodological issues with the Singh analysis call the results into question.

7.2.3 Adequacy of Overall Clinical Experience

The UPLIFT trial (Protocol 205.235) enrolled nearly 6000 patients with moderate to severe COPD who were followed for four years. This study doubles the size of the safety database for Spiriva HandiHaler and provides adequate data to evaluate the potential safety signals of stroke and cardiovascular mortality that were raised for this compound.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No special animal or in vitro testing was submitted as part of this application.

7.2.5 Adequacy of Routine Clinical Testing

Protocol 205.266 included minimal clinical testing. Because an extensive safety database exists for Spiriva HandiHaler, additional laboratory data is unlikely to add substantively to the understanding of risk for this compound.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

No additional data regarding metabolism or clearance was provided in this supplement. The clinical trial submitted in this application (205.235) included patients on chronic oxygen

therapy as well as patients on long-acting beta agonists, both of which were excluded from other tiotropium pivotal trials. The efficacy results of this trial suggest that there is no interaction with these commonly prescribed COPD therapies.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

See Section 7.2.3 Adequacy of Overall Clinical Experience.

7.2.8 Assessment of Quality and Completeness of Data

Because of the size and scope of the UPLIFT trial, DSI audits were requested for a number of sites. See Section 4.4.1 Division of Scientific Investigation audits. Based on these audits, the UPLIFT data was determined to be of reliable quality.

Protocol violations

There were a total of 440 patients with protocol violations in this study; 7.5% (223 patients) of the tioHH18 group and 7.2% (217 patients) of the placebo group. The most common protocol violations were due to use of anticholinergics on at least 2 consecutive visits (112 patients in the tiotropium group and 115 in the placebo group. Of the 60 patients with post-bronchodilator FEV1 >70% of predicted or post-bronchodilator FEV1>70% of FVC at either Visit 1 or 2, the majority had post-bronchodilator FEV1% of predicted or post-bronchodilator FEV1% of FVC values ranging from 71-75%. See Table 27.

Table 27: Protocol 205.235 protocol violations

Protocol violation	Tio HH18 N=3006 n (%)	Placebo N=2986 n (%)	Total N=5992 n (%)
Total with protocol violation	217 (7.2)	223 (7.5)	440 (7.3)
Entrance criteria not met			
Known active tuberculosis	0	1 (0.0)	1 (0.0)
History of excluded pulmonary disease	10 (0.3)	7 (0.2)	17 (0.3)
History of thoracotomy with resection	1 (0.0)	4 (0.1)	5 (0.1)
Respiratory infection/COPD exacerbation	26 (0.9)	29 (1.0)	55 (0.9)
Unstable respiratory medication use	7 (0.2)	10 (0.3)	17 (0.3)
Known narrow angle glaucoma	1 (0.0)	3 (0.1)	4 (0.1)
Symptomatic prostatic hyperplasia	0	1 (0.0)	1 (0.0)
Malignancy in last 5 years	5 (0.2)	2 (0.1)	7 (0.1)
Anticholinergic drug hypersensitivity	0	1 (0.0)	1 (0.0)
Involved in other trials	0	1 (0.0)	1 (0.0)
FEV1>70% or FEV1/FVC>70%	28 (0.9)	32 (1.1)	60 (1.0)
Informed consent signed late	2 (0.1)	2 (0.1)	4 (0.1)
Improper medication wash out	39 (1.3)	43 (1.4)	82 (1.4)
Incorrect trial medication taken	1 (0.0)	0	1 (0.0
Anticholinergic use for ≥2 consecutive visits	115 (3.8)	112 (3.8)	227 (3.8)

Reviewer comment:

Protocol violations were generally balanced between the treatment groups. The rate of protocol violations is consistent with those seen across the Spiriva Phase 3 programs. The persistent use of anticholinergics was noted in only a small percentage of patients, which was similar between treatment groups. This is unlikely to affect the results of the study.

Treatment compliance

Medication compliance was determined by counting returned capsules of study medication. Compliance was defined as the percentage of capsules taken over the planned total. As a patient should take one capsule per day, compliance of the patient was calculated as number of capsules used divided by the number of days that the patient was on treatment. More

patients in the tio HH18 group than in the placebo group had compliance of >80%. See Table 28.

[m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/0202-0235-01-15-study-report-body.pdf/page 104]

Table 28: Protocol 205.235 treatment compliance

Compliance	Placebo N=3006 N (%)	Tio HH18 N=2986 N (%)	Total N=5992 N (%)
0 - < 50%	212 (7.1)	138 (4.6)	350 (5.8)
50% - <80%	425 (14.1)	347 (11.6)	772 (12.9)
80% - <120%	2331 (77.5)	2467 (82.6)	4798 (80.1)
≥ 120%	8 (0.3)	7 (0.2)	15 (0.3)
incomplete	5 (0.2)	6 (0.2)	11 (0.2)
missing	25 (0.8)	21 (0.7)	46 (0.8)

Reviewer comment:

Compliance for this study overall was good, although lower than in the Phase 3 Spiriva programs. In comparison, overall reported compliance for the 1-year Phase 3 Spiriva Respimat studies was 95.4-96.1% for the tiotropium groups and 95.7% for the placebo groups. This is to be expected, because the UPLIFT protocol had a duration of 4 years, during which compliance might be expected to decrease. It is also relevant that patients in the Spiriva group had improved compliance compared to the placebo group, suggesting that patients may have felt benefit from the drug.

7.2.9 Additional Submissions, Including Safety Update

BI did not submit a safety update report for this efficacy supplement, which is acceptable. The complete response to NDA 21-395, S024 referred to this submission.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

With regards to potential safety signals under investigation for tiotropium, the UPLIFT trial did not show a clinically significant increase in mortality, stroke, or cardiovascular events in the tio HH18 group relative to placebo.

Overall, the total number of deaths during treatment (including the last day of study drug plus 30 days) was 792; 411 (13.7%) in the placebo group and 381 (12.8%) in the tiotropium group. Vital status information was known for 98% of tio HH18 treated patients and 97% of placebo treated patients including discontinued patients out to at least 45 months post-randomization. Compared to the on-treatment mortality, an additional 149 deaths were collected for patients who discontinued. The risk ratio for death from any cause

(tiotropium/placebo) on treatment was 0.84 [95% CI (0.73, 0.97)]. The risk ratio for death remains significantly or nearly significantly different from placebo regardless of the cut off used or inclusion of vital status data.

The primary cause of each death in the UPLIFT trial was adjudicated by an independent committee. The most common causes (adjudicated) of death both on-treatment and including vital status were COPD exacerbation, lung cancer, and death of unknown cause. Combining the preferred terms of sudden death, sudden cardiac death, and death of unknown cause, 127 patients died with sudden or unknown causes of death. Of these, 70 (2.3%) were in the placebo group and 57 (1.9%) were in the tio HH18 group [RR=0.75, 95% CI (0.53, 1.06)].

Overall, these data are supportive of a beneficial effect on mortality, as UPLIFT is a major study that doubles the size of the safety database, prespecified mortality endpoints and vital status collection were appropriately collected and adjudicated, and the salutary effect on mortality is robust across multiple different analyses. In addition, the mortality benefit was driven by a reduction in fatal COPD exacerbations, suggesting a plausible mechanism of action. However, outstanding issues with regards to mortality with Spiriva Respimat need to be considered. Also, the mortality benefit was observed in only a single, albeit very large, trial. The Pulmonary and Allergy Drugs Advisory Committee (PADAC), in their meeting on November 19, 2009, concluded that UPLIFT was a compelling and important study, demonstrating generally beneficial effects on mortality. Although the Respimat results were felt to be somewhat concerning and additional data are needed, the Respimat results do not necessarily convey to the HandiHaler. Because of the Respimat data, any mortality information included in the Spiriva HandiHaler label will require careful consideration.

Serious adverse events (SAEs) occurred in 50.9% of the overall study population, including 51.6% of the tio HH18 group and 50.2% of the placebo group. The most common SAEs were COPD exacerbation, pneumonia, and respiratory failure. SAEs were generally balanced between treatment groups, although COPD exacerbations were significantly reduced in the tio HH18 group compared to placebo [RR 0.86, 95% CI (0.76, 0.94), p=0.0014). While the incidence of SAEs of respiratory failure is reduced in the tio HH18 group, the difference is marginally significant and there are multiple related preferred terms that have been analyzed separately. Multiplicity is also an issue. Unlike mortality, which is a hard endpoint and was pre-specified in the protocol as an event of interest (including vital status collection and an independent adjudication committee), the term “respiratory failure” is undefined and subject to investigator interpretation. There is insufficient evidence to justify a specific claim that Spiriva HandiHaler reduces respiratory failure.

There were 618 (20.7%) patients in the tio HH18 group and 735 (24.5%) patients in the placebo group who discontinued prematurely due to an adverse event. The most frequent AEs leading to discontinuation were all lower respiratory events—COPD exacerbation, dyspnea, pneumonia, and respiratory failure. A reduced number of patients in the tio HH18 group discontinued due to COPD exacerbations and dyspnea compared to the placebo group.

The most frequently reported AEs were COPD exacerbation, pneumonia, dyspnea, nasopharyngitis, and upper respiratory tract infection. If evaluated by exposure adjusted rates, COPD exacerbation, dyspnea, and respiratory failure occurred significantly less frequently in the tio HH18 group compared to placebo. In contrast, dry mouth and insomnia occurred significantly more frequently in the tio HH18 group. Dry mouth is a known anticholinergic side effect of tiotropium. In addition, although the numbers were small, intestinal obstruction occurred significantly more frequently in the tio HH18 group and could represent an anticholinergic side effect related to constipation.

Stroke is an adverse event of interest based on a potential safety signal observed in an analysis of combined tiotropium HandiHaler and Respimat trials. Stroke-related adverse events (AEs, SAEs, or fatal events) were not significantly increased in the tio HH18 group relative to placebo (Risk Ratio of 0.95, 0.97, and 0.85, respectively). On November 19, 2009, the PADAC voted that the UPLIFT trial adequately addressed the potential stroke signal raised by the pooled Spiriva analysis.

Cardiovascular events are also adverse events of interest based on a potential safety signal observed in a meta-analysis literature report. There was no increase in adverse events of myocardial infarction in the tiotropium group compared to placebo, with a Risk Ratio of 0.71, 95% CI (0.52, 0.99). Overall, there was a borderline significant decrease in AEs in the cardiac SOC [RR 0.84, 95% CI (0.73, 0.98)], driven by a decrease in congestive heart failure and MI. Likewise, there was no increase in deaths due to cardiac disorders, sudden cardiac death, sudden death, or death due to unknown cause. The PADAC voted that the UPLIFT trial adequately addressed the potential cardiovascular signal raised in the literature.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

A pooled analysis of 30 placebo-controlled tiotropium studies (both Spiriva HandiHaler and Spiriva Respimat) was submitted in this supplement (S029). The review of this pooled analysis is found in Section 7.2.2.1 Other Studies.

7.4.2 Explorations for Predictive Factors

Subgroup analyses to explore for possible predictive factors were carried out for mortality, stroke, and cardiovascular events. The following subgroups were investigated:

- Age (<55, ≥55-<65, ≥65-<75, ≥75 years)
- Gender (male/female)
- Smoking status (active smoker/ex-smoker)

- Race (white/black/Asian)
- Baseline long-acting ß-agonist use (yes/no)
- Baseline inhaled corticosteroid use (yes/no)
- Baseline LABA and ICS combination use (yes/no)
- Anticholinergic use (yes/no)
- GOLD stage (I or II/III/IV)
- Region (Asia/Eastern Europe/Latin America/USA/Western Europe)
- Reversibility (yes/no)
- Body mass index (<20/ ≥20-<25/ ≥25-<30/ ≥30)

A discussion of these analyses may be found in the Section 7.1.1 Deaths and Section 7.1.3 Dropouts and Other Significant Adverse Events.

7.4.3 Causality Determination

SAEs were generally balanced between tio HH18 and placebo groups in Protocol 205.235. There were no increases in stroke or cardiovascular events, and an overall mortality benefit was demonstrated. No new safety signals attributable to tiotropium were identified.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The proposed dosing regimen for the new COPD indication is 18 mcg once daily. This is the currently approved dose of tiotropium HandiHaler.

8.2 Drug-Drug Interactions

No formal drug-drug interaction studies were submitted in this supplement. Patients in the primary trial submitted as part of this supplement (205.235) were permitted to be on regularly scheduled doses of inhaled corticosteroids, xanthenes, low and mid dose oral corticosteroids, antileukotrienes, long-acting beta-agonists, supplemental oxygen, and as needed albuterol. No interactions were observed between these drugs and tiotropium HandiHaler with regards to efficacy, except that tio HH18 showed a potential benefit on disease progression for patients not receiving ICS or LABAs. See Section 10.1.2.

8.3 Special Populations

There are no proposed changes to the special populations sections of the label.

8.4 Pediatrics

COPD is a disease which occurs only in adults; as such, this condition qualifies for a PREA waiver because studies in children would be impossible or highly impractical.

8.5 Advisory Committee Meeting

FDA convened a meeting of the Pulmonary-Allergy Drugs Advisory Committee (PADAC) on November 19, 2009 to discuss the COPD exacerbation claim for NDA 21-395as well as potential safety issues related to stroke, cardiovascular events, and all cause mortality for Spiriva HandiHaler. Members from the Drug Safety and Risk Management Advisory Committee were also present.

The following questions were addressed at the meeting:

1. Please comment on the mortality data from Spiriva HandiHaler trial 205.235 (UPLIFT). [non-voting question]
2. Please comment on the mortality data form the Spiriva Respimat Phase 3 trials (205.254, 205.255, and 205.372). [non-voting question]
3. Do the data from trials 205.235 (UPLIFT) and 205.266 (VA study) provide substantial and convincing evidence to support the claim that Spiriva HandiHaler reduced COPD exacerbations? [voting question]
    a. If not, what additional data are needed?
4. Do the data from trial 205.235 (UPLIFT) adequately address the potential safety signal of stroke events? [voting question]
    a. If not, what additional data are needed?
5. Do the data from trial 205.235 (UPLIFT) adequately address the potential safety signal of adverse cardiovascular outcomes? [voting question]
    a. If not, what additional data re needed?

The PADAC concluded that UPLIFT was a compelling and important study, demonstrating generally beneficial effects on mortality. However, the Respimat results were felt to be somewhat concerning and additional data are needed.

The PADAC voted (11 yes, 1 no) that the UPLIFT and VA trials provide substantial and convincing evidence to support the claim that Spiriva HandiHaler reduces COPD exacerbations. The single negative vote was secondary to the lack of exact wording of the claim in the question and not because evidence of efficacy was lacking for a COPD exacerbation claim in general.

Regarding the potential safety signals, the PADAC voted (11 yes, 1 no) that the data from the UPLIFT trial adequately address the potential stroke signal raised by the pooled Spiriva analysis. The single negative vote was secondary to the fact that by virtue of required exclusion criteria for MI and baseline cardiovascular disease, the clinical trial population from UPLIFT does not exactly match that of the population using marketed Spiriva HandiHaler, and a small increase in risk cannot be ruled out (upper bound of the confidence interval >1). The PADAC also voted (11 yes, 1 abstain) that the data from the UPLIFT trial adequately address the potential stroke signal raised by the pooled Spiriva analysis.

8.6 Literature Review

See Section 7.2.2.3 Literature.

8.7 Postmarketing Risk Management Plan

The Applicant did not submit a post-marketing risk management plan.

8.8 Other Relevant Materials

No other relevant materials were used in this review.

9 OVERALL ASSESSMENT

9.1 Conclusions

Protocol 205.235 was a multicenter, randomized, double-blind, placebo-controlled, parallel group trial to determine the effect of tiotropium 18 mcg capsule dry powder inhaler (tio HH18) on disease progression over 4 years in 5992 patients with COPD. The two co-primary endpoints were the yearly rate of decline in trough FEV1 from day 30 until completion of double blind treatment and the yearly rate of decline in FEV1 90 minutes after study drug and bronchodilator administration from day 30 until completion of double blind treatment. A number of secondary endpoints included other spirometry endpoints, COPD exacerbation-related endpoints, and the St. George Respiratory Questionnaire (SGRQ). For the purposes of the UPLIFT trial, a COPD exacerbation was defined as “an increase or new onset of more than one respiratory symptoms (cough, sputum, sputum purulence, wheezing, dyspnea) with a duration of three days or more requiring treatment with antibiotics and/or systemic (oral, intramuscular, or intravenous) steroids.” Although there is no well-accepted definition of COPD exacerbation, the definition used in this clinical program is reasonable as it includes both symptoms and treatment and is consistent with definitions in the literature.

The UPLIFT trial showed no significant difference between treatment groups in the primary endpoints of rate of decline in pre- and post-bronchodilator FEV1. There was a loss of 30 ml per year of pre-bronchodilator FEV1 in both the placebo and tio HH18 groups and a loss of 42 (placebo) versus 40 ml (tio HH18) per year in post-bronchodilator FEV1. In a subgroup analysis, patients who were sustained quitters from smoking did experience a significant decrease in rate of decline in FEV1 compared to sustained smokers. This effect was observed across both treatment groups and provides internal validation for the trial.

For the key secondary endpoints of time to first COPD exacerbation and time to first COPD exacerbation leading to hospitalization, tiotropium showed a significant difference compared to placebo. For COPD exacerbations, patients in the tio HH18 group had a significantly longer time to event than patients in the placebo group ($p<0.0001$, RR 0.86, 95% CI 0.81-0.91). The median time to first exacerbation was 12.5 months in the placebo group and 16.7 months in the tio HH18 group. Patients in the tio HH18 group also had a statistically significantly longer time to first hospitalization due to COPD exacerbation compared to placebo ($p= 0.0024$, RR 0.86, 95% CI 0.78, 0.95). The lower quartile for time to first exacerbation requiring hospitalization was 28.6 months in the placebo group and 35.9 months in the tio HH group. The UPLIFT trial adjusted for multiplicity using a step-wise approach, i.e. allowing testing of secondary endpoints only if the primary endpoints were met. From a statistical viewpoint, the trial could be considered “failed” for the exacerbation endpoints. This issue of multiplicity was discussed at the PADAC meeting on November 19, 2009.

A significant improvement in most of the additional COPD exacerbation-related endpoints was also observed. These included the number of COPD exacerbations, time to first exacerbation treated with steroids, time to first exacerbation treated with antibiotics, number of exacerbations treated with steroids, number of exacerbation days, number of COPD exacerbations leading to hospitalization, and number of days hospitalized due to exacerbation per patient year.

Spirometry endpoints included trough FEV1, FVC, and SVC response and 90 minute FEV1, FVC, and SVC response. Endpoints were measured every six months throughout the four-year treatment period. Consistent with the known bronchodilator properties of the drug, the tio HH18 group generally demonstrated a significant improvement ($p<0.0001$) over placebo for all endpoints and time points tested. These data are supportive of the description of spirometry outcomes for the trial the Applicant proposes for the label. Based upon review of the pulmonary function data, the Applicant’s proposed claim regarding lung function is generally supported. It is reasonable to describe UPLIFT in the product label and note that the primary endpoints were not significantly different. Regarding the sustained improvement in trough FEV1, this is consistent with the current indication and efficacy data in the product label and would also be reasonable to include in the description of the outcomes of UPLIFT in the product label.

SGRQ endpoints included rate of SGRQ deterioration, as well as total and component SGRQ scores. There were no differences in rate of decline in SGRQ scores from month 6 until completion of treatment for the activity component, impact component, or total scores.

The mean SGRQ scores showed a statistically significant but not clinically important decrease across all domains and timepoints for the tio HH18 group compared to placebo, with a treatment difference ranging from -2.30 to -3.35 ($p<0.0001$) for the total SGRQ score.

Protocol 205.266 (VA trial, submitted under NDA 21-395, S-024) was a multicenter, 6-month, randomized double-blind, placebo controlled trial of tio HH18 mcg in COPD patients in a Veteran's Affairs setting. The enrollment criteria were similar to UPLIFT. There were two co-primary endpoints: 1) the proportion of patients who experienced a COPD exacerbation and 2) the proportions of patients with a hospitalization associated with a COPD exacerbation during the 6 month period. The definition of COPD exacerbation used in this clinical trial is also reasonable as it includes both symptoms and treatment and is consistent with definitions in the literature.

The results of the VA study demonstrated that fewer patients in the tio HH18 group compared to placebo (27.9% versus 32.3%, $p=0.037$) experienced a COPD exacerbation over the 6 months of the trial. In addition, there were significantly fewer exacerbations per patient year. This evidence from Protocol 205.266, in conjunction with data from the UPLIFT trial, are supportive of an exacerbation claim. The exact wording of the claim will need consideration as various aspects of exacerbation were measured in this trial.

On November 19, 2009, the PADAC voted that the UPLIFT and VA trials provide substantial and convincing evidence to support the claim that Spiriva HandiHaler reduces COPD exacerbations.

The safety discussion for this application is complex because there are several potential safety signals that have recently been indentified for Spiriva HandiHaler. These potential safety signals include stroke, myocardial infarction, and cardiovascular death. Because of its size, duration, and randomized, placebo-controlled design, the UPLIFT trial (Protocol 205.235) is particularly useful to address these potential safety signals.

Mortality is an important outcome to address. The Applicant made protocol amendments to UPLIFT to provide more robust mortality data. Mortality was collected both on-treatment and for discontinued patients out to the time of their scheduled exit date from the study (vital status). Cause of death was adjudicated in a blinded fashion by an independent committee. While the Applicant has withdrawn their initial proposal for a mortality benefit claim, a detailed discussion of mortality is still warranted. In addition, when considering the mortality data from UPLIFT, it is of interest to briefly discuss an issue with the mortality data from a tiotropium product under development, Spiriva Respimat. Spiriva Respimat is a completely new inhalation solution formulation of tiotropium. The Applicant has conducted 3 one year clinical trials with Spiriva Respimat in patients with COPD that show a numerical imbalance in mortality, favoring placebo. There is no consistent cause of death. A review of the mortality data from the Spiriva Respimat program is available under NDA 21-936 and IND (b) (4)

In UPLIFT (Protocol 205.235), the total number of deaths during treatment (including the last day of study drug plus 30 days) was 792; 411 (13.7%) in the placebo group and 381

(12.8%) in the tiotropium group. Vital status information was known for 98% of tio HH18 treated patients and 97% of placebo treated patients including discontinued patients out to at least 45 months post-randomization. Compared to the on-treatment mortality, an additional 149 deaths were collected for patients who discontinued. The risk ratio for death from any cause (tiotropium/placebo) on treatment was 0.84 [95% CI (0.73, 0.97)]. The risk ratio for death remains significantly or nearly significantly different from placebo regardless of the cut off used or inclusion of vital status data.

The primary cause of each death in the UPLIFT trial was adjudicated by an independent committee. The most common causes (adjudicated) of death both on-treatment and including vital status were COPD exacerbation, lung cancer, and death of unknown cause. Combining the preferred terms of sudden death, sudden cardiac death, and death of unknown cause, 127 patients died with sudden or unknown causes of death. Of these, 70 (2.3%) were in the placebo group and 57 (1.9%) were in the tio HH18 group [RR=0.75, 95% CI (0.53, 1.06)].

Overall, these data are supportive of a mortality claim, as UPLIFT is a major study that doubles the size of the safety database, prespecified mortality endpoints and vital status collection were appropriately collected and adjudicated, and the salutary effect on mortality is robust across multiple different analyses. In addition, the mortality benefit was driven by a reduction in fatal COPD exacerbations, suggesting a plausible mechanism of action. However, outstanding issues with regards to mortality with Spiriva Respimat temper such a claim. Also, the mortality benefit was observed in only a single, albeit very large, trial. The Pulmonary and Allergy Drugs Advisory Committee (PADAC), in their meeting on November 19, 2009, concluded that UPLIFT was a compelling and important study, demonstrating generally beneficial effects on mortality. However, the Respimat results were felt to be somewhat concerning and additional data are needed.

Serious adverse events (SAEs) occurred in 50.9% of the overall study population, including 51.6% of the tio HH18 group and 50.2% of the placebo group. The most common SAEs were COPD exacerbation, pneumonia, and respiratory failure. SAEs were generally balanced between treatment groups, although COPD exacerbations were significantly reduced in the tio HH18 group compared to placebo [RR 0.86, 95% CI (0.76, 0.94), p=0.0014). While the incidence of SAEs of respiratory failure is reduced in the tio HH18 group, the difference is marginally significant and there are multiple related preferred terms that have been analyzed separately. Multiplicity is also an issue. Unlike mortality, which is a hard endpoint and was pre-specified in the protocol as an event of interest (including vital status collection and an independent adjudication committee), the term “respiratory failure” is undefined and subject to investigator interpretation. There is insufficient evidence to justify a specific claim that Spiriva HandiHaler reduces respiratory failure.

There were 618 (20.7%) patients in the tio HH18 group and 735 (24.5%) patients in the placebo group who discontinued prematurely due to an adverse event. The most frequent AEs leading to discontinuation were all lower respiratory events—COPD exacerbation, dyspnea, pneumonia, and respiratory failure. A reduced number of patients in the tio HH18 group discontinued due to COPD exacerbations and dyspnea compared to the placebo group.

The most frequently reported AEs were COPD exacerbation, pneumonia, dyspnea, nasopharyngitis, and upper respiratory tract infection. If evaluated by exposure adjusted rates, COPD exacerbation, dyspnea, and respiratory failure occurred significantly less frequently in the tio HH18 group compared to placebo. In contrast, dry mouth and insomnia occurred significantly more frequently in the tio HH18 group. Dry mouth is a known anticholinergic side effect of tiotropium. In addition, although the numbers were small, intestinal obstruction occurred significantly more frequently in the tio HH18 group and could represent an anticholinergic side effect related to constipation.

Stroke is an adverse event of interest based on a potential safety signal observed in an analysis of combined tiotropium HandiHaler and Respimat trials. Stroke-related adverse events (AEs, SAEs, or fatal events) were not increased in the tio HH18 group relative to placebo (Risk Ratio of 0.95, 0.97, and 0.85, respectively).

Cardiovascular events are also adverse events of interest based on a potential safety signal observed in a meta-analysis literature report. There was no increase in adverse events of myocardial infarction in the tiotropium group compared to placebo, with a Risk Ratio of 0.71, 95% CI (0.52, 0.99). Overall, there was a borderline significant decrease in AEs in the cardiac SOC [RR 0.84, 95% CI (0.73, 0.98)], driven by a decrease in congestive heart failure and MI. Likewise, there was no increase in deaths due to cardiac disorders, sudden cardiac death, sudden death, or death due to unknown cause.

The PADAC voted that the UPLIFT trial adequately addressed potential safety signals of stroke and cardiovascular events for Spiriva HandiHaler.

9.2 Recommendation on Regulatory Action

Tiotropium bromide dry powder inhaler (HandiHaler inhalation device, 18 mcg tiotropium) was approved on January 30, 2004 (NDA 21-395) for the long-term, once-daily maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. Tiotropium is a specific antagonist at muscarinic acetylcholine receptors, often called anticholinergic. The Applicant, Boehringer Ingelheim Pharmaceuticals, Inc., now seeks additional efficacy claims for the HandiHaler with an additional 3 years of marketing exclusivity. Requested efficacy claims included in the clinical trials section of the label are: 1) description of the long-term effects on lung function, 2) reduction in exacerbations, 3) reduction in mortality, and 4) reduction in respiratory failure.

To support this application, BI submitted a 4-year, placebo-controlled, parallel group trial enrolling nearly 6000 patients with moderate-severe COPD. The short title of this trial is UPLIFT: Understanding Potential Long-term Impacts on Function with Tiotropium (Protocol 205.235). In addition, BI referenced trial 205.266 (submitted under S024) to support the COPD exacerbation claim. On July 22, 2009, BI withdrew the mortality claim. According to BI, there were no new Spiriva HandiHaler data contributing to this decision. From an efficacy perspective, the applicant has provided sufficient data to support two of the proposed claims: lung-term effects on lung function and reduction in exacerbations.

Reduction in respiratory failure is not supported because the improvement is marginally significant and is not predefined.

From a safety perspective, there have been potential safety signals of stroke and cardiovascular events associated with Spiriva HandiHaler in the public domain recently. The UPLIFT trial did not show an increase in mortality, stroke, or cardiovascular events in the tiotropium group relative to placebo, although the upper bound of the confidence interval for stroke was greater than one. However, concerns regarding a numeric increase in mortality relative to placebo with another formulation of tiotropium (Spiriva Respimat) that is currently under investigation complicate the mortality evaluation for Spiriva HandiHaler. Potential safety signals of stroke and cardiovascular events previously identified as part of pooled analyses and meta-analyses were also discussed at the meeting. The committee voted in favor of support of the exacerbation claim and that the UPLIFT trial adequately addressed potential safety signals of stroke and cardiovascular events.

The clinical recommendation for this application is that the lung function and reduction of exacerbation claims are adequately supported. The respiratory failure claim is not adequately supported. The clinical recommendation is approval pending agreed upon labeling.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Risk Management activity is not recommended for this application.

9.3.2 Required Phase 4 Commitments

There are no required Phase 4 commitments for this application.

9.3.3 Other Phase 4 Requests

There are no other Phase 4 requests for this application.

9.4 Labeling Review

9.4.1 PLR format

In addition to the proposed exacerbation claim language, Boehringer Ingelheim proposes changing the Spiriva HandiHaler label into the new PLR format. The following clinical comments were provided to the Applicant on November 5, 2009 in addition to a number of small edits directly to the text of the label.

General Labeling Comments

1. We have not included comments regarding your proposed language for the UPLIFT trial (Protocol 205.235). We will provide comments regarding the UPLIFT trial after the Pulmonary Allergy Drugs Advisory Committee meeting to be held on November 19, 2009.

Highlights of Prescribing Information

2. The Adverse Reactions section of HIGHLIGHTS should contain a list of adverse reactions that are included in Table 1. Inclusion of adverse reactions from the Spiriva HandiHaler placebo controlled trials is acceptable.

Full Prescribing Information

3. In Section 4, Contraindications, include hypersensitivity to tiotropium or any ingredients in Spiriva HandiHaler. Include descriptions of hypersensitivity reactions that have occurred in patients receiving Spiriva HandiHaler from clinical trials and post-marketing. For example, "In clinical trials and post-marketing experience with Spiriva HandiHaler, cases of X, X, X have been reported."
4. In Section 5.2, Warnings and Precautions, Immediate Hypersensitivity Reactions, include a brief list of hypersensitivity reactions that have occurred in clinical trials or post-marketing with Spiriva HandiHaler or refer back to Section 4 for the list.
5. Delete Section 5.4 and create two separate sections (5.4 and 5.5) to highlight the potential eye and urinary issues with Spiriva HandiHaler. For example:

   5.4 Worsening of Narrow-Angle Glaucoma

   5.5 Urinary Retention.
6. In the two distinct sections noted in Comment #5 above, include relevant information from clinical trials or post-marketing regarding these potential effects. Include information for prescribers and patients, e.g. "Prescribers and patients should be alert for be signs of acute narrow-angle glaucoma, e.g. eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema. Instruct patients to consult a physician immediately should any of these signs and symptoms develop."
7. In Section 6, Adverse Reactions, revise the 3rd bullet regarding anticholinergic effects to be consistent with the revised sections 5.4 and 5.5.
8. We note that you have [redacted] (b) (4) Replace these data in Table 1 and the sentence immediately after Table 1 as per the currently approved label. The purpose of inclusion of these data is to provide a more complete picture of the Spiriva HandiHaler adverse reaction profile. While we generally do not include active controlled clinical trial information in product labels, inclusion of active

controlled clinical trial information can be useful in certain situations, e.g. transitioning from a short acting to long acting product, such as Spiriva HandiHaler.

9. Include a brief description of demographic data from your trials in Section 6.1, Adverse Reactions, Clinical Trial Experience. Include a description of the overall clinical trial database from which adverse reaction data have been drawn, including a discussion of overall exposure (number of patients, dose schedule, duration) and demographics of the exposed population.
10. The multiple different presentations of adverse reaction data in Section 6, Adverse Reactions, seem disjointed, i.e. Table 1, ≥3% but <1% greater than placebo, 1-3%, <1% and Additional Adverse Reactions. Consider combining some of the information to improve the readability of the section.
11. We have revised Section 12.2, Clinical Pharmacology, Pharmacodynamics, to include QT study language that was approved for Supplement S-027 on November 13, 2008.

Patient's Instructions for Use

12. Revise the Patient Instructions for Use (PIU) to include language that was approved for Supplement S-014 on March 3, 2009. Also include figures in the PIU you submitted as an amendment to S-029 on July 28, 2009.

9.4.2. New language

Numerous comments regarding labeling can be found throughout this review, and the proposed language from the Applicant has changed over the course of the review period. General comments regarding new language in the label include the following:

- Reduction in COPD exacerbations is considered a new label indication. List reduction in COPD exacerbations in the indications section in addition to a description in the clinical trials section.
- Efficacy data from Spiriva Respimat do not apply to Spiriva HandiHaler because the two locally acting formulations are considered different drug products. As such, remove all reference to Spiriva Respimat.
- The VA study is the primary trial supporting efficacy for COPD exacerbations and should be described in the label.
- The claim for a reduction in respiratory failure is not supported, thus should be removed from the label.

9.5 Comments to the Applicant

Since the recommended action is approval, there are no comments to the Applicant.

10 APPENDICES

10.1 Review of Individual Study Reports: 205.235

10.1.1 Protocol

Study title

UPLIFT: Understanding Potential Long-term Impacts on Function with Tiotropium

A randomized, double-blind, placebo-controlled, parallel group trial assessing the rate of decline of lung function with tiotropium 18 mcg inhalation capsule once daily in patients with chronic obstructive pulmonary disease (COPD)

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Design

This was a 4-year, multicenter, multinational, randomized, double-blind, placebo-controlled, parallel group study comparing the rate of decline in forced expiratory volume in one second (FEV1) in patients with COPD receiving tiotropium HandiHaler 18 mcg (tio HH18) to those receiving placebo in addition to their usual care for COPD. Usual care included short- and long-acting inhaled beta-agonists, steroids, and theophyllines but excluded inhaled anticholinergics. Following an initial screening period of 14-30 days, qualifying patients were randomized to tiotropium or placebo. Patients were seen after 1 month of treatment, at 3 months, and then every 3 months until study drug termination at 4 years. At study drug termination, patients received open-label ipratropium for 30 days. The final visit occurred approximately 30 days post-treatment.

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Duration

The duration of active treatment was 4 years. Patients attended a screening visit 2-4 weeks prior to randomization. There was no run-in period. A post-treatment scheduled follow up period of 30 days was conducted for all patients completing 4-years of therapy. The study was performed during the period of January 9, 2003 to February 22, 2008. The final study report is dated October 28, 2008.

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Investigators and centers

Patients were enrolled from 490 investigative centers and were randomized from 487 investigative centers in 37 countries: 95 in the United States; 36 in Spain; 31 in Italy; 30 in Denmark; 27 in Belgium; 26 in Czechia; 20 in Hungary; 17 in France; 14 each in Brazil, Germany, and the United Kingdom; 13 in The Netherlands; 12 each in Japan and Turkey; 11 in South Africa; 10 each in Argentina and Greece; 9 in Poland; 8 in Australia; 7 in Switzerland; 6 in Mexico; 5 each in Austria, Finland, Philippines, Portugal, Russia, Slovakia, Slovenia, and Thailand; 4 each in Hong Kong and Norway; 3 each in Ireland, Lithuania, Malaysia, Singapore, and Taiwan; and 2 in New Zealand.

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Materials

The study treatments were:

- tio HH18: tiotropium HandiHaler 18 mcg (1 capsule dry powder inhalation) once daily in the morning
- placebo: identical to HandiHaler capsule dry powder inhalation once daily in the morning

Patients received different batches of tiotropium and placebo over the 4 years of treatment. Open label ipratropium was supplied for use during the 30-days follow up period. Spacer (Aerochamber) devices were allowed to be used with the metered-dose inhaler (MDI) medication during the 30 day follow up period.

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Objectives

The primary objective of this trial was to determine whether tio HH18 reduces the rate of decline of FEV1 over time in patients with COPD.

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Population

A total of 8,020 male and female patients with moderate to severe COPD ($FEV_1 \leq 70\%$ predicted) were screened. Of these, 5993 were randomized; 2987 in the tio HH18 group, and 3006 in the placebo group. A total of 2457 (41%) of randomized patients prematurely discontinued study medication. Fewer patients in the tio HH18 group (1,099 patients, 36.8%) prematurely discontinued trial medication than in the placebo group (1,358 patients, 45.2%).

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Inclusion criteria

Notable inclusion criteria included:

- Diagnosis of COPD and with the following spirometric criteria:
  - post-bronchodilator $FEV_1 \leq 70\%$ of predicted normal and $FEV_1 \leq 70\%$ of FVC
- Male or female patients 40 years of age or older
- Current or ex-smokers with a smoking history of more than 10 pack-years
- Maintained on stable respiratory medications for 6 weeks prior to Visit 2
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Exclusion criteria

Notable exclusion criteria included:

- Significant diseases other than COPD which, in the opinion of the investigator, may either have put the patient at risk because of participation in the study or a disease which may have influenced the results of the study or the patient's ability to participate in the study
- Recent history (6 months or less) of myocardial infarction
- Unstable or life-threatening cardiac arrhythmia or cardiac arrhythmia that required intervention or a change in drug therapy within the year prior to enrollment
- Hospitalization for heart failure (NYHA Class III or IV) within the year prior to enrollment
- Known active tuberculosis
- History of asthma, cystic fibrosis, bronchiectasis, interstitial lung disease, or pulmonary thromboembolic disease.
- History of thoracotomy with pulmonary resection.
- Patients who planned to undergo lung transplantation or lung volume reduction surgery.
- Malignancy for which the patient had undergone resection, radiation therapy, or chemotherapy within the last 5 years. Patients with treated basal cell carcinoma were allowed.
- Respiratory infection or exacerbation of COPD in the 4 weeks prior to the screening visit (Visit 1) or during the baseline period (between Visits 1 and 2).
- Known moderate to severe renal impairment.
- Known narrow angle glaucoma.

- Significant symptomatic prostatic hyperplasia or bladder-neck obstruction. Patients whose symptoms were controlled on treatment were allowed to be included.
- Oral corticosteroids in unstable daily dose or > 10 mg prednisone/day
- Significant alcohol or drug abuse within the year prior to enrollment.
- Use of supplemental oxygen therapy or >12 hours per day.

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Reviewer comment:
Of note, bronchodilatory reversibility was not an inclusion criterion. The population was not enriched for patients with a history of COPD exacerbation. In comparison with Phase 3 tiotropium HandiHaler trials, exclusion criteria were liberalized to include a broader population of patients with COPD. These included shortened time periods from previous myocardial infarction and congestive heart failure episodes, inclusion of patients with stable arrhythmias, inclusion of patients with malignancy (not during active treatment), a higher permitted dose of oral corticosteroids, and unrestricted use of oxygen. In addition, patients were permitted to be on all baseline medications except for anticholinergics.

Procedures

During the initial 14-30 day screening period, demographic data, baseline history and medications, a physical examination, and post-bronchodilator pulmonary function tests (PFTs) were collected. If a patient had a respiratory infection or COPD exacerbation during the screening period, Visit 2 could be postponed once in order for the patient to be stable for 6 weeks prior to randomization at Visit 2. Smoking patients were encouraged to stop. All patients were required to pass qualifying PFTs at both Visits 1 and 2 in order to be randomized into the study.

Following the initial screening period, patients were randomized into the 4-year, double-blind treatment period in which they received tio HH18 or placebo in a 1:1 ratio. The drugs were administered using the HandiHaler as one capsule taken once daily in the morning. All patients were instructed to take rescue medication (albuterol) as needed. Patients also received a patient record book to record any hospitalizations or exacerbations. Visit 3 was scheduled one month after randomization. All subsequent visits were at 3 month intervals.

At each visit, study personnel collected used and unused study drug capsules, reviewed washout compliance for PFTs, exacerbation information, concomitant therapies, smoking status, and adverse events since the previous visit. Pulmonary function testing and the St. George's Hospital Respiratory Questionnaire (SGRQ) were completed at baseline and every 6 months until the end of the trial (Visits 5, 7, 9, 11, 13, 15, 17, and 19). A new record book was provided at the end of each visit.

At the end of Visit 19, patients who completed the 4-year treatment period received open-label ipratropium with instructions to take 2 inhalations four times a day for 30 days. Pulmonary function testing pre- and post-bronchodilator and a complete physical examination was conducted 30 days later at the final study visit. In addition, patients who

terminated study drug early were asked to follow up 30 days after their last dose of study drug.

[m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/0202-0235-0101-protocol-or-amendment.pdf/pages 29-32]

The Applicant states that the study was conducted in compliance with the protocol, the principles lain down in the Declaration of Helsinki (1996 version), in accordance with the ICH Tripartite Guideline for Good Clinical Practice (GCP), and in accordance with applicable regulatory requirements and BI Standard Operating Procedures (SOPs). The sponsor held 4 investigator meetings worldwide (Miami, United States; Phuket, Thailand; Coolum, Australia; and Helsinki, Finland) prior to the start of the study. The sponsor also held yearly world-wide investigator meetings, and annual international clinical monitor meetings throughout the course of the study.

[m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/0202-0235-01-15-study-report-body.pdf/page 59-60]

The study flow chart as revised by protocol Amendment 1 is presented in Table 29.

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Table 29: Protocol 205.235 study flow chart

Trial Periods	**Screening (Baseline)**	**Treatment (4 years)**					**Follow up (30 days post treatment)**
Visit Number	1	2	3	4	5-18[2]	19[3]	End of Trial
Months	N/A	0	1	3	Q3	48	49
Day	-30 to -14[1]	1 ± 3 days	30 ± 3 days	90 ± 7 days	Q90 ± 7 days	1440 ± 7 days	1470 ± 7 days
Informed Consent	X						
Demographics	X						
Medical History	X						
Inclusion/Exclusion Criteria	X	X					
Physical Examination/ Vital Signs	X						X
Randomization		X					
Dispense Study Drug		X	X	X	X		
Train/Dispense HandiHaler®		X			X[4]		
Patient Record		X	X	X	X	X	
Dispense Open-Label Ipratropium						X	
Collect Medication			X	X	X	X	X
Drug Accountability			X	X	X	X	X
Smoking Cessation Program and Patient Education Material[5]	X	X	X	X	X	X	
Medication Washout Compliance		X	X		X	X	X
PFTs (SVC/FEV_1/FVC)[6]	X[7]	X[8]	X[9]		X[9]	X[9]	X[8]
SGRQ[10]		X			X	X	
EQ-5D[11]		X					
Smoking Status Assessment		X	X	X	X	X	X
Exacerbation Information	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X
Concomitant Therapy	X	X	X	X	X	X	X
Termination of Trial Medication						X	
Trial completion							X

[1] In the event of an exacerbation, the time between Visit 1 and 2 could be extended once.

[2] Visit 5-19 were separated by 3 months each and continued until the patient completed the protocol.

[3] Visit 19 represents the final treatment visit occurring approximately 4 years from randomization.

[4] New HandiHaler® dispensed each year after starting study medication.

[5] A 4-week smoking cessation program was offered beginning at Visit 1 and completed at time of randomization. Additional materials were provided throughout the trial at the discretion of the investigator.

[6] Pulmonary function testing (PFT) performed at the screening visit, Day 1, Day 30 and then every 6 months (Visits 5, 7, 9, 11, 13, 15, 17 and 19) until the end of treatment. A final PFT was done at the end of trial visit.

[7] Post-bronchodilator spirometry (administer 4 inhalations ipratropium [80 mcg], wait 1 hour; then administer 4 inhalations salbutamol [400 mcg], wait 30 minutes; then perform PFT [no washout required prior to PFT]).

[8] Spirometry pre- and post-bronchodilator (administer 4 inhalations ipratropium [80 mcg], wait 1 hour; then administer 4 inhalations salbutamol [400 mcg], wait 30 minute; then perform PFT [washout required prior to PFT]).

[9] Two spirometry measurements were taken as follows (washout required prior to PFT): pre-study drug PFT; then administer study drug; then administer 4 inhalations of ipratropium (80 mcg), wait 1 hour; then administer 4 inhalations of salbutamol (400 mcg), wait 30 minutes; then conduct second PFT.

[10] SGRQ is completed Day 1and then every 6 months until end of treatment (Visits 5, 7, 9, 11, 13, 15, 17 and 19).

[11] EQ-5D was completed Day 1 (in a limited number of countries).

Protocol amendments

During the course of the trial, the protocol was amended on three occasions: Amendment 1 (dated 16 May 2003) to include a validated generic quality of life instrument, the EQ-5D questionnaire; Amendment 2 (dated 15 November 2005) to include the monitoring of long-term outcomes for patients prematurely discontinued from the study, and Amendment 3 (dated 25 April 07) to establish an external committee to independently assess the primary cause of deaths for all fatal cases.

Because Amendment 1 was initiated during the enrollment period, only the last 1235 patients from 13 countries with significant enrollment remaining (Australia, Belgium, Czechia, Denmark, France, Germany, Hungary, Italy, Netherlands, Poland, Russia, Spain, and the United States) completed the EQ-5D. The results of this questionnaire are not included in this supplement (S-029).

[m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/0202-0235-01-15-study-report-body.pdf/pages 90-91]

Reviewer comment:

Amendments 2 and 3 occurred in response to data from the Spiriva Respimat Phase 3 program, which showed a mortality imbalance favoring placebo between the treatment groups. Monitoring of long-term outcomes (vital status) of patients prematurely discontinued from the trial permits determination if an imbalance in premature discontinuations between treatment groups may lead to a "healthy survivor" effect. This approach was recommended by the Drug Safety Oversight Board on June 15, 2006, which reviewed the Spiriva Respimat data. In addition, an independent committee to adjudicate cause of death is important to provide consistency in nomenclature across study sites in this multinational trial, thus providing improved safety reporting. All amendments were instituted prior to end of the trial.

Efficacy endpoints

Primary

- The yearly rate of decline in trough FEV1 from day 30 (steady state) until completion of double blind treatment. Trough FEV1 is the pre-dose value measured approximately 24 hours after the previous dose of study drug
- The yearly rate of decline in FEV1 90 minutes after study drug and ipratropium administration (including 30 minutes post albuterol) from day 30 (steady state) until completion of double blind treatment

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Pulmonary function testing

Trough FEV_1 was defined as the FEV_1 measured at the -5 minute time point at the end of the dosing interval 24 hours post drug administration. Trough FEV_1 response was defined as the change from baseline in trough FEV_1. Baseline FEV_1 was the pre-treatment FEV_1 value

measured at Visit 2 in the morning 5 minutes prior to administration of the first dose of study medication.

FEV1, FVC, and SVC measurements were obtained through pulmonary function testing at screening (Visit 1), baseline (Visit 2), after 30 days (Visit 3) and every 6 months thereafter until the end of the double-blind treatment period (Visits 5, 7, 9, 11, 13, 15, 17, and 19). PFTs were also performed at the final visit after being off study drug (on open-label ipratropium) for 30 days. PFTs were performed using standardized spirometry equipment provided by the applicant and calibrated by study staff on all test days. A calibration log was maintained for the spirometry equipment. Equipment and techniques conformed to American Thoracic Society (ATS) criteria.

Patients were instructed to arrive at the clinic approximately 1 hour prior to the time they were scheduled to take study drug having abstained from medications as specified in the protocol. Spirometric measurements commenced at approximately the same time at all visits. If a patient arrived for a visit without adequate washout, the visit was postponed (once).

The following medications were appropriately restricted prior to PFT testing:

- inhaled corticosteroids (withhold morning dose)
- short-acting theophylline (at least 24 hour washout)
- long-acting theophylline (at least 48 hour washout)
- short-acting beta-adrenergic bronchodilators (at least 8 hour washout)
- long-acting beta-adrenergics (LABA) or combination LABA/inhaled steroid products (at least 24 hour washout)
- study medications (not to be taken prior to test-day pre-dose PFTs)
- ipratropium (at least 8-hour washout prior to the final visit)

In addition, patients were to refrain from strenuous exercise, smoking, caffeinated or ice-cold beverages, cold temperatures, dust, and environmental smoke the morning prior to spirometry.

If an oral corticosteroid burst occurred prior to PFT days, the visit was postponed for at least one, but no more than 2 weeks after the last increased or additional dose was given. The use of antibiotics was not restricted. Antibiotics were used as medically necessary for exacerbations and other infections. If antibiotics were prescribed for a respiratory illness prior to pulmonary function testing days, the visit was postponed for at least one, but no more than 2 weeks after the last dose was given. If an increase in or addition of theophylline dose occurred prior to PFT days, the visit was postponed for at least one, but no more than 2 weeks after the last increased dose was given.

PFTs were performed with the patient in a seated position. Slow vital capacity (SVC) by slow exhalation maneuver was the first spirometric maneuver performed. The forced

maneuvers, FEV_1 and forced vital capacity (FVC) were done in triplicate after obtaining the SVC. The best of three efforts was recorded in the case report form (CRF). The best of three efforts was defined as the highest FEV_1 and the highest FVC each obtained on any of three blows (even if not from the same curve) meeting the ATS criteria (with a maximum of five attempts).

At screening (Visit 1), spirometry was performed at the 90-minute post-bronchodilator timepoint (after administration of 4 inhalations of ipratropium [80 mcg] and 4 inhalations of albuterol [400 mcg]). For this visit, washout of respiratory medications was not required. At the randomization visit (Visit 2) and the end of trial visit (30 days after completion of study medication), washout of restricted medications was required and spirometry was performed pre-bronchodilator and at the 90 minute post-bronchodilator timepoint (after administration of 4 inhalations of ipratropium [80 mcg] and 4 inhalations of albuterol [400 mcg]). For visits at Day 30 (Visit 3) and then every 6 months until the end of treatment (Visits 5, 7, 9, 11, 13, 15, 17, and 19), washout of restricted medications was required and spirometry was performed pre-bronchodilator and at the 90 minute post-bronchodilator timepoint (after administration of study drug, 4 inhalations of ipratropium [80 mcg], and 4 inhalations of albuterol [400 mcg]).

nSpire Health Inc. centrally managed spirometry including providing spirometry equipment and training, and ensuring uniformity of the spirometry testing across all participating sites. All staff performing PFTs were required to have at least 6 months of experience performing spirometry and to have performed at least 120 PFTs over the last 6 months. All individuals performing spirometry tests were required to complete training including practice tests. Training on spirometry systems was provided at each investigator meeting. All spirometry technicians during the 4 years were required to demonstrate competency with the spirometer through completing a training checklist and submitting practice maneuvers for approval prior to study maneuvers being performed. The practice spirometry tests were reviewed for overall quality, protocol compliance, and integrity.

Standardized spirometry testing was completed via identical spirometers with secure access features (username and password). Custom software for use by the sites was designed and validated specifically for the study. This software incorporated both ATS criteria for acceptability, and criteria for calculating predicted values as specified by the Standardized Lung Function Testing of the European Community of Coal and Steel (ECCS).

Sites were expected to transmit spirometry data on each day of testing. Centralized quality review and data collection were performed by nSpire Health Inc. Spirograms were reviewed by nSpire Health Inc. technical staff for overall quality, morphology, and artifacts in accordance with the ATS criteria for acceptability, vendor quality assurance review standards, and protocol-specific quality review standard guidelines. Spirograms not meeting quality review standards were queried within 3 business days of receipt. The investigator signed copies of all spirometric reports to approve the data.

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Secondary

- Time to first COPD exacerbation
- Time to first COPD exacerbation leading to hospitalization
- Yearly rate of decline in trough FVC and slow vital capacity (SVC)
- Yearly rate of decline in trough FVC and slow vital capacity (SVC) from day 30 until completion of double-blind treatment. Trough FVC and SVC are the pre dose values measured approximately 24 hours after the previous dose of study drug.
- Yearly rate of decline in FVC and SVC measured 90 minutes after inhalation of study drug and ipratropium (and 30 minutes after albuterol) from day 30 until completion of double-blind treatment.
- Yearly rate of decline in FEV_1, FVC, and SVC prior to ipratropium and albuterol inhalation from day 1 until completion of the trial (30 days post study drug treatment).
- Yearly rate of decline in FEV_1, FVC, and SVC measured 90 minutes after inhalation of ipratropium (and 30 minutes after inhalation of albuterol) from day 1 until completion of the trial (30 days post study drug treatment).
- Estimated mean pre- and post-bronchodilator FEV_1, FVC, and SVC from day 30 until completion of double-blind treatment.
- Yearly rate of decline in St. George's Respiratory Questionnaire (SGRQ) total, impact, symptom, and activity scores from 6 months until completion of double-blind treatment.
- Estimated mean SGRQ total, impact, symptom, and activity scores from 6 months until completion of double-blind treatment.
- Additional endpoints for COPD exacerbations and associated hospitalizations
    - Number of COPD exacerbations
    - Number of patients with at least one COPD exacerbation
    - Number of COPD exacerbation days
    - Time to first COPD exacerbation treated with steroids*
    - Number of COPD exacerbations treated with steroids*
    - Time to first COPD exacerbation treated with antibiotics*
    - Number of COPD exacerbations treated with antibiotics*
    - Number of COPD exacerbations leading to hospitalizations per patient year
    - Number of patients with at least one COPD exacerbation leading to hospitalization
    - Number of days hospitalized due to COPD exacerbations

Endpoints designated with a * were added by the applicant in the Statistical Analysis Plan prior to unblinding.

Reviewer comment:

The time to first COPD exacerbation and the time to first COPD exacerbation leading to hospitalization were designated as key secondary endpoints and tested following the co-primary endpoints with a procedure used to address multiplicity. The Statistical Analysis Plan for this protocol was reviewed by FDA prior to unblinding the protocol.

The number of days between exacerbations was defined as a secondary endpoint in the protocol but was not included in the analyses due to potential bias. This is appropriate because for the first and last exacerbation it is impossible to accurately estimate the number of days from the previous exacerbation to the first event during the trial and from the last exacerbation in the trial to the next post-trial event.

Two other endpoints, estimated mean pre- and post-bronchodilator FEV_1, FVC, and SVC from day 30 until completion of double-blind treatment and estimated mean SGRQ total, impact, symptom, and activity scores from 6 months until completion of double-blind treatment, were not specified in the protocol. Both of these endpoints were specified in the Statistical Analysis Plan prior to unblinding. As these endpoints make clinical sense to evaluate in the setting of looking at yearly rate of decline and do not add new measurements to the study, it is appropriate to evaluate them as secondary endpoints.

[m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/0202-0235-01-15-study-report-body.pdf/pages 55-56]

COPD exacerbations

COPD exacerbations were recorded on an ongoing basis throughout the study. As an aid to recall, patients were given a Patient Daily Record book that was reviewed at each visit.

For the purposes of this study, a COPD exacerbation was defined as “an increase or new onset of more than one respiratory symptom (cough, sputum, sputum purulence, wheezing, dyspnea) with a duration of three days or more requiring treatment with antibiotics and/or systemic (oral, intramuscular, or intravenous steroids.” The onset of the COPD exacerbation was defined by the onset of the first recorded symptom. The end of the COPD exacerbation was recorded as defined by the investigator.

Exacerbation events were derived based on the adverse event (AE) records on the exacerbation AE CRF page. All events included by the investigator on the exacerbation AE CRF were included in the efficacy analysis whether or not BI determined that they met all components of the protocol exacerbation definition. In addition to standard AE reporting, total days on antibiotics, total days on systemic steroid bursts, and number of hospitalized days (broken into regular ward and intensive care unit) were also collected for all COPD exacerbation events. Overlapping exacerbations were collapsed into one exacerbation. Two exacerbations were considered distinct events if there were at least 7 exacerbation-free days between the end of one event and the start of the next one.

Exacerbations were categorized as mild, moderate, and severe according to the following definitions:

- mild: treated at home without seeing a health care provider
- moderate: visit with a health care provider (e.g., home visit, visit to an outpatient facility or an emergency department) but not requiring admission to hospital
- severe: hospitalization (emergency room visits >24 hours were considered hospitalizations

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Reviewer comment:

The definition of COPD exacerbation includes both a change in symptoms and a treatment requirement. Inclusion of both components of the definition is likely to increase uniformity in the study, as therapy patterns are known to vary across geographic regions. The definition is essentially the same as the one used for the Spiriva Respimat program and in the Spiriva HandiHaler VA study (Protocol 205.266), with only a slight variation in wording. Advair is the only other medication that has a labeling claim (and indication) for reduction of COPD exacerbations so we now have a regulatory path established for this particular claim. No well-accepted definition of exacerbations exists, although in general the definition used in this study is acceptable.

The applicant initially proposed to combine events with one day or fewer between events, and look at combination of 7 days between events as a sensitivity analysis. The applicant changed the SAP based on feedback from FDA. From a clinical perspective, recurrence of an event a few days after stopping therapy likely represents recurrence of an incompletely treated exacerbation rather than a new event. In previous Spiriva trials (including 205.266), sensitivity analysis evaluating combining events with one versus 7 days between events did not make a significant difference in overall outcome.

St. George's Respiratory Questionnaire

Disease-specific health related quality of life was assessed using the SGRQ instrument. Each patient completed the SGRQ prior to PFTs on Day 1 and then every six months until completion of the double-blind treatment period.

The St. George's Respiratory Questionnaire (SGRQ)[8] is a self-administered health related quality of life measure divided into three components: symptoms, activity, and impacts. The symptoms component contains items concerned with the level of symptomatology, including frequency of cough, sputum production, wheeze, breathlessness, and the duration and frequency of breathlessness or wheeze. The activity component is concerned with

physical activities that either cause or are limited by breathlessness. The impacts component covers such factors as employment, being in control of health, panic, stigmatization, the need for medication and its side effects, expectations for health and disturbance of daily life. Scores ranging from 0 to 100 are calculated for each component, as well as a total score which summarizes the responses to all items. A zero score indicates no impairment of quality of life. The questionnaire takes approximately 10 minutes to complete.

Safety endpoints

- all adverse events (including serious adverse events)
- all-cause mortality
- lower respiratory mortality

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Adverse events

All adverse events, serious and non-serious, were collected in an ongoing fashion throughout the study until the end of the double-blind treatment period. At each study visit, all AEs regardless of causality were recorded after review of the Patient Daily Record and discussion with the patient. In addition, all serious adverse events that occurred within 30 days of the last dose of study drug were reported. Adverse events were followed until resolution, until follow up was agreed adequate by the monitor and investigator, or until a patient was lost to follow up. Elective procedures planned prior to signing informed consent were not considered adverse events. Adverse events were monitored by an independent Data Safety Monitoring Board (DSMB). Stroke was defined as an adverse event of interest in the Statistical Analysis Plan (SAP) at the request of FDA.

[m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/0202-0235-01-15-study-report-body.pdf/pages 74-75]

Mortality

Protocol Amendment 2 allowed for long-term assessment of outcome for patients prematurely discontinued from UPLIFT. Vital status, including cause of death, if known, was collected every 6 months beginning November 15, 2005 for each discontinued patient until completion of the planned observation period (4 years). Vital status was recorded on a separate CRF that captured the following variables: 1) patient's vital status (alive, deceased, or unknown), 2) date of death, 3) cause of death, 4) source of information, 5) additional information regarding the circumstances, 6) if the patient's status was unknown, the date the patient was last known to be alive, and 7) the investigator's signature and date. At the time the amendment was instituted, approximately 1,500 of the 6,000 patients enrolled in the UPLIFT trial had prematurely discontinued from participation. The UPLIFT Joint Advisory Committee and DSMB both recommended collection of vital status. Analyses for mortality were performed with a variety of cut-off dates including and not including those deaths collected in patients after discontinuation from the study.

Protocol Amendment 3 added an independent assessment of the primary cause of death for all reported fatal cases in the UPLIFT trial as determined by an external committee. Beginning April 2007 (52 months following randomization of the first patient), a Mortality Adjudication Committee (MAC) centrally adjudicated all reported deaths in the study between the screening of the first patient and database lock. The MAC consisted of three members who were external to the sponsor and were not involved in the conduct of the study. Two members were experts in pulmonary/critical care medicine and one had expertise in cardiology; members were from Ireland, Canada, and the United States. Members of the MAC were not involved in the DSMB.

The committee received a CIOMS (Council for International Organizations of Medical Sciences) form for each death that contained a summary of the information available concerning the case. The narrative in the CIOMS form was written based on the information and reported cause of death provided by the investigator at the study center. If available, information from the death certificate, autopsy report, or witness description of the death was also included in the narrative. In addition to the CIOMS form, the medical history, baseline pre- and post-bronchodilator FEV1 values obtained at Visit 2, and all events reported in the SAE reports for each patient were provided to the committee. The committee was permitted to request additional information, when needed, to determine the primary cause of death. The committee was blinded to treatment group assignments.

Adjudication was a two-step process. First, the deaths were adjudicated independently by each member of the committee. Secondly, the committee members met to discuss the cases to arrive at a consensus cause. At the central adjudication meeting, all cases with unanimous agreement were recorded by the committee. Cases with disagreement were adjudicated by the following method:

1) All three members of MAC discussed the case in an effort to achieve consensus on the primary cause of death.
2) If one or more members of the committee believed that additional supporting information was required to determine the primary cause of death, the chairperson requested the sponsor to obtain the additional data and adjudication of the case was deferred to a future meeting. The sponsor made all reasonable efforts to obtain the requested information and include it in the package sent for one of the future adjudication meetings.
3) In situations where agreement by all members was not possible, the primary cause of death was determined by a majority vote.

All mortality adjudications were completed before database lock. Analyses were conducted for cause of death as determined by both the investigator and by the committee.

[m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/0202-0235-01-15-study-report-body.pdf/pages 46-50 and 76-77] [m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/0202-0235-016101-protocol-or-amendment.pdf/amendments pages 62-64]

Reviewer comment:

Handing of mortality with collection of vital status is consistent with recommendations by the FDA Drug Safety Oversight Board on June 15, 2006, which reviewed data on mortality for Spiriva. Further, adjudication of cause of death is very helpful in analysis of potential safety signals such as cardiovascular mortality and stroke.

Concomitant therapy

The following medications were permitted by the protocol:

- All pulmonary medications other than anticholinergic bronchodilators and combination drugs containing anticholinergic bronchodilators were permitted.
- The use of antibiotics was not restricted.
- The following medications were allowed to control acute exacerbations:
    - prn inhaled beta-agonists
    - increase or addition of theophylline
    - systemic steroids
    - antibiotics
- In the case of life-threatening exacerbations, any and all therapies (including ipratropium) and interventions deemed medically necessary by the treating physician were permitted.

The protocol included the following restrictions regarding concomitant therapy during the course of the study:

- All other investigational agents.
- Long-acting anticholinergics (tiotropium)
- Anticholinergic medications alone or in combination with other medications (e.g. Atrovent, oxitropium, Combivent, Berodual, Duovent).
- Intranasal anticholinergic formulations such as Atrovent nasal spray.
- Oxygen therapy of >12 hours per day

Medications were restricted on pulmonary function test days as described in the methods section on pulmonary function testing.

[m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/0202-0235-016101-protocol-or-amendment.pdf/pages 20-22]

Reviewer comment:

There were very few medication restrictions in the UPLIFT study, consistent with evaluation of the effects of tiotropium in a "real world" setting. This is helpful to determine what the risks and benefits are of the drug as it is currently used in the community. In addition, it would be highly impractical to expect that a large number of treatment restrictions could be followed over the prolonged length (4 years) of the study.

Statistical plan

There were two co-primary endpoints for this study, yearly rate of decline in trough (Pre-bronchodilator) FEV1 and the yearly rate of decline in peak (post-bronchodilator) FEV1 from Day 30 to the end of double-blind treatment. Time to first COPD exacerbation and time to first COPD exacerbation leading to hospitalization were key secondary endpoints.

Sample size

Based on data from previous long-term studies in patients with COPD, such as the Lung Health Studies, ISOLDE, and BRONCHUS, and data from the one-year and six-month studies of tiotropium, the standard deviation for the rate of decline in FEV_1 per year was assumed to be 90 mL. Therefore, to detect a difference of 15 mL in the rate of decline in FEV_1 between tiotropium and placebo at a 5% level of significance and 90% power, a sample of 758 patients per group was estimated to be needed. Assuming that 35% of patients would discontinue the study early, without adequate data, it was estimated that 1166 patients per treatment group would be required. To conduct subgroup analyses with adequate power (assuming 1166 patients were required per treatment group and 40% were current smokers as based on previous Phase 3 tio HH18 studies), the sample size needed for the study was determined to be 2916 per treatment group or 5832 total. Thus, a total of 6000 patients were planned.

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Statistical model and analysis

The random-effects model was used as the primary statistical model for the co-primary endpoints. The pre- and post-bronchodilator FEV_1 were assumed to follow linear trends over time. The primary analysis was conducted with center included as a random effect in the model. The primary endpoint was also analyzed for the subgroups (age, gender, smoking status, baseline concomitant medication use, COPD severity according to GOLD stages, race, region, reversibility, BMI) using a random-effects model. In addition, the primary analysis was carried out with adjusting for baseline covariates.

The two key secondary endpoints were compared between treatment groups using the log rank test. Additional analyses for the key secondary endpoints included an estimate of the hazard ratio between treatment groups using Cox regression with a single covariate of treatment and the Kaplan-Meier estimate of the probability of not having the event (first COPD exacerbation or first COPD exacerbation requiring hospitalization) for each treatment group.

Analyses for secondary efficacy endpoints included a repeated measures ANOVA model for PFT variables and SGRQ at each visit. The ANOVA model included treatment, visit, treatment by visit, and baseline by visit as covariates. Yearly rate of decline in SGRQ measures were analyzed using the regression slope from the random-effects model. Endpoints determining numbers of COPD exacerbations per patient year were estimated using Poisson regression adjusting for overdispersion with Pearson's method. Treatment exposure was adjusted as the offset of the model.

Descriptive statistics were used to report adverse events. Mortality events were analyzed for on treatment death (onset of the fatal AE was between first drug intake and last drug intake + 30 days) and all deaths including post-discontinuation visit vital status collection. Analyses were done for cause of death both as reported by the investigator and as adjudicated by the MAC. Analyses of time to death were performed using Kaplan-Meier estimates and Cox regression censoring based on the cut-off of Day 1470. Mortality endpoints included all cause, lower respiratory, cardiac disorders, stroke, and any fatal AE that occurred in more than 1% (or 60 cases) of the patients. Subgroup analyses were also carried out for all-cause, lower respiratory, and cardiac death.

Reviewer comment:

The Statistical Analysis Plan (SAP) for this study was reviewed by FDA and comments were provided to BI. All of FDA's comments were incorporated into the SAP prior to unblinding.

Multiplicity adjustments

The applicant took the following approaches to adjust for multiplicity in the UPLIFT trial:

- Hierarchical testing was performed for the co-primary endpoints. First, the rate of decline in pre-bronchodilator FEV_1 was compared between the tiotropium and the placebo groups at a significance level of 0.049. If significance was achieved in favor of tiotropium, the rate of decline in post-bronchodilator FEV_1 results was compared between groups at a significance level of 0.049.
- If statistical significance was achieved in favor of tiotropium for the co-primary endpoints, hierarchal testing of two key secondary endpoints, time to the first COPD exacerbation and time to the first COPD exacerbation leading to hospitalization, was performed using the log-rank test. First, the time to first exacerbation was tested at 0.049 level of significance. If significance was achieved, the time to the first COPD exacerbation leading to hospitalization was tested at 0.049 level of significance.
- In parallel with the testing of the co-primary endpoints, the number of COPD exacerbations leading to hospitalizations per patient year was compared between treatment groups at the significance level of 0.001.
- P-values for testing the co-primary endpoints, the number of COPD exacerbations leading to hospitalizations per patient year, and the two key secondary endpoints were adjusted for interim looks. For the other endpoints, p-values are reported at nominal p-values.

- As specified in the DSMB Charter, independent interim safety analyses were conducted and reviewed by the DSMB at approximately 12, 24, 36, 48, and 54 months after trial initiation. Also as specified in the DSMB Charter, independent interim efficacy analyses were conducted and reviewed by the DSMB at approximately 24 and 36 months after the trial initiation. For the final efficacy analyses, the p-values for the co-primary endpoint, number of exacerbations leading to hospitalization, and the two key secondary endpoints were adjusted for the DSMB efficacy data reviews.

[m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/0202-0235-01-15-study-report-body.pdf/pages 83-84]

Missing data

Missing data for PFTs and SGRQ were not imputed for the efficacy analysis. Missing data for exacerbation dates was first queried. Missing exacerbation dates that could not be resolved with data queries were imputed as follows:

- If the exacerbation was for a patient who died, the date of death was used for the exacerbation end date.
- The exacerbation end date for a patient who did not die was estimated using the exacerbation start date and the median length of an exacerbation based on all exacerbations with complete start and end dates starting during the treatment period.
- The exacerbation start date for a patient who did not die was estimated using the exacerbation start date and the median length of an exacerbation based on all exacerbations with complete start and end dates starting during the treatment period.
- No events occurred with that were missing both start and end dates.
- Missing values for antibiotic days, steroid days, and hospital days were not imputed.

Detailed rules regarding collapsing of exacerbation events with fewer than 7 days between events are provided in the statistical analysis plan for the study.

[m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235-16109f1-statistical-methods-interim-analysis-.pdf/pages 21-24]

Data sets

For the primary efficacy analysis, patients with at least 3 acceptable FEV1 measurements from Day 30 onward were included. As a sensitivity analysis, patients with at least 1 acceptable FEV1 measurement from Day 30 onward were included in the analysis. Analysis of change in SGRQ included patients in the treated set who had a least 2 SGRQ measurements from month 6 onward. A sensitivity analysis was performed for SGRQ total score in patients with at least one SGRQ measurement from month 6 onward.

For all other endpoints (including AEs, mortality, and COPD exacerbations), the treated set was considered to be all randomized patients who received study medication and were documented to have taken at least one dose.

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10.1.2 Results

Population characteristics

Disposition of patients

A total of 8,020 male and female patients with moderate to severe COPD ($FEV_1 \leq 70\%$ predicted) were screened. Of these, 5,993 patients were randomized; 2987 in the tio HH18 group and 3006 in the placebo group. A total of 3535 (59.0%) patients completed the study per protocol on study medication, 1887 (63.2%) in the tio HH18 group and 1648 (54.8%) in the placebo group. The highest percentage of discontinuations occurred in the first year of treatment (14% tio HH18 and 20% placebo). Patient disposition in the trial is provided in Table 30.

Table 30: Protocol 205.235 patient disposition

	Placebo N (%)	Tio HH18 N (%)	Total N (%)
Enrolled			**8016**
Not entered			2023
Entered	3006	2987	5993
Not treated	0	1[1]	1
Treated	3006 (100.0)	2986 (100.0)	5992 (100.0)
Not prematurely discontinued from trial medication	1648 (54.8)	1887 (63.2)	3535 (59.0)
Prematurely discontinued from trial medication	1358 (45.2)	1099 (36.8)	2457 (41.0)
Adverse events	746 (24.8)	627 (21.0)	1373 (22.9)
Worsening of disease under study	368 (12.2)	238 (8.0)	606 (10.1)
Worsening of other pre-existing disease	41 (1.4)	40 (1.3)	81 (1.4)
Other adverse event	337 (11.2)	349 (11.7)	686 (11.4)
Administrative	554 (18.4)	412 (13.8)	966 (16.1)
Non compliant with protocol	75 (2.5)	48 (1.6)	123 (2.1)
Lost to follow-up	76 (2.5)	64 (2.1)	140 (2.3)
Consent withdrawn	403 (13.4)	300 (10.0)	703 (11.7)
Other	58 (1.9)	60 (2.0)	118 (2.0)

[1]one patient was randomized twice in error

Reviewer comment:

A greater percentage of patients discontinued from the placebo group, primarily due to worsening of COPD and consent withdrawn. Because vital status was collected on all patients who discontinued from the trial, the mortality data is less likely to be biased by a "healthy survivor" effect.

The blind was broken for 22 patients in the trial, 9 in the tio HH18 group and 13 in the placebo group. In all cases, the unblinding occurred due to an adverse event. Of the 22 unblindings, 8 were related to COPD exacerbations, 2 in the tio HH18 group and 6 in the placebo group. Other events leading to unblinding in the tiotropium group were interstitial lung disease, pneumonia, ventricular fibrillation, acute myocardial infarction, atrial flutter, and hyperplasia of the prostrate/bladder neck obstruction. Two cases were unblinded due to sudden death, 1 in the tio HH18 group and 1 in the placebo group. A summary of AEs leading to unblinding is presented in Table 31.

Table 31: Protocol 205.235 unblinded patients

Country	Site number	Patient number	Treatment	Adverse event
Argentina	0107	10181	tio HH18	interstitial lung disease
Brazil	0514	10591	placebo	fecal impaction
Denmark	0801	17543	placebo	acute laryngitis
Germany	1110	18852	tio HH18	COPD exacerbation
Greece	1201	19016	placebo	dysphonia, pharyngeal disorder
Hungary	1304	16123	placebo	COPD exacerbation
Italy	1629	19800	tio HH18	pneumonia
Mexico	2002	10680	tio HH18	prostate hyperplasia, bladder neck obstruction
Netherlands	2109	20602	tio HH18	shortness of breath, COPD exacerbation
New Zealand	0212	23831	placebo	increased shortness of breath on exertion, wheeze, sub-acute exacerbation of COPD with asthmatic component
Singapore	1906	27043	placebo	COPD exacerbation
Spain	3027	21600	placebo	COPD exacerbation
Switzerland	3203	24308	tio HH18	ventricular fibrillation
Thailand	3404	26645	placebo	chest tightness, sudden death
Thailand	3404	26639	tio HH18	acute myocardial infarction
Turkey	3512	22812	placebo	COPD exacerbation
Turkey	3512	22815	placebo	type 2 respiratory failure, COPD exacerbation
United States	3787	13557	placebo	atrial flutter
United States	3788	13581	tio HH18	atrial flutter
United States	3789	13606	placebo	prolonged ileus
United States	3789	13615	tio HH18	sudden death, presumably arrhythmic
United States	3789	13685	placebo	atrial fibrillation

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Demographics and disease characteristics

The mean age of the patients was 64.5 years (range 40-88 years). The majority of the trial population (74.6%) was male and 89.9% were white. The mean duration of COPD was 9.8 years. All patients were current (29.6%) or ex-smokers (70.4%), with a mean smoking history of 48.7 pack years. The mean pre-bronchodilator FEV_1 was 1.096L with a mean percent predicted of 39.4%. The mean pre-bronchodilator FEV_1/FVC was 42.3%. The overall demographic profile was generally balanced across the treatment groups. Pulmonary function data at baseline were generally comparable. Demographic and disease characteristics are provided in Table 32, and baseline PFT variables are provided in Table 33.

[m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/0202-0235-01-15-study-report-body.pdf/pages 100-102, Table 15.1.4.1, pages 177-180]

Table 32: Protocol 205.235 patient demographic and disease characteristics

	Placebo	Tio HH18	Total
Number of patients[1]	3006	2986	5992
Gender [N (%)]			
Male	2222 (73.9)	2251 (75.4)	4473 (74.6)
Female	784 (26.1)	735 (24.6)	1519 (25.4)
Race [N (%)]			
White	2697 (89.7)	2691 (90.1)	5388 (89.9)
Black	53 (1.8)	38 (1.3)	91 (1.5)
Asian	185 (6.2)	192 (6.4)	377 (6.3)
Missing	71 (2.4)	64 (2.2)	136 (2.3)
Age [years]			
Mean	64.5	64.5	64.5
SD	8.5	8.4	8.5
Min	40.0	40.0	40.0
Max	88.0	88.0	88.0
Smoking history [N (%)]			
Ex smoker	2108 (70.1)	2112 (70.7)	4220 (70.4)
Smoker	898 (29.9)	874 (29.3)	1772 (29.6)
Smoking history [pack years]			
Mean	48.4	49	48.7
SD	27.9	28.0	27.9
Min	10.0	10.0	10.0
Max	285.0	225.0	285.0
Duration of COPD [years][3]			
Mean	9.7	9.9	9.8
SD	7.4	7.6	7.5
Min	0.0	0.08	0.0
Max	53.0	55.0	55.0
Gold stage [N (%)]			
Stage I	1 (0.0)	2 (0.1)	3 (0.1)
Stage II	1355 (45.1)	1384 (46.3)	2739 (45.7)
Stage III	1331 (44.3)	1304 (43.7)	2635 (44.0)
Stage IV	271 (9.0)	250 (8.4)	521 (8.7)
missing	48 (1.6)	46 (1.5)	94 (1.6)

Table 33: Protocol 205.235 baseline PFT data

	Tio HH18	Placebo	Total
Number of patients	3006	2986	5992
Pre-bronchodilator FEV_1 [L]			
Mean	1.092	1.101	1.096
SD	0.40	0.40	0.40
Min	0.29	0.28	0.28
Max	2.71	2.64	2.71
Pre-bronchodilator % predicted normal FEV_1			
Mean	39.3	39.5	39.4
SD	11.9	12.0	12.0
Min	9.0	11.0	9.0
Max	76.0	73.0	76.0
Pre-bronchodilator FVC [L]			
Mean	2.63	2.63	2.63
SD	0.83	0.81	0.82
Min	0.64	0.67	0.64
Max	6.70	6.13	6.70
Pre-bronchodilator FEV_1 / FVC [%]			
Mean	42.1	42.4	42.3
SD	10.5	10.5	10.5
Min	15.0	14.0	14.0
Max	76.0	75.0	76.0

1 Obtained from Visit 2, Randomization Visit

Reviewer comment:

The demographics in this study are highly consistent with those across the Phase 3 programs for both Spiriva HandiHaler and Spiriva Respimat. For example, the pre-bronchodilator baseline FEV_1 observed in the 1-year Spiriva Respimat Phase 3 studies (205.254 and 205.255) had a mean of 1.09L and median of 1.03L.

Protocol violations

There were a total of 440 patients with protocol violations in this study; 7.5% (223 patients) of the tioHH18 group and 7.2% (217 patients) of the placebo group. The most common protocol violations were due to use of anticholinergics on at least 2 consecutive visits (112 patients in the tiotropium group and 115 in the placebo group. Of the 60 patients with post-bronchodilator FEV1 >70% of predicted or post-bronchodilator FEV1>70% of FVC at either Visit 1 or 2, the majority had post-bronchodilator FEV1% of predicted or post-bronchodilator FEV1% of FVC values ranging from 71-75%. See Table 34.

Table 34: Protocol 205.235 protocol violations

Protocol violation	Tio HH18 N=3006 n (%)	Placebo N=2986 n (%)	Total N=5992 n (%)
Total with protocol violation	217 (7.2)	223 (7.5)	440 (7.3)
Entrance criteria not met			
Known active tuberculosis	0	1 (0.0)	1 (0.0)
History of excluded pulmonary disease	10 (0.3)	7 (0.2)	17 (0.3)
History of thoracotomy with resection	1 (0.0)	4 (0.1)	5 (0.1)
Respiratory infection/COPD exacerbation	26 (0.9)	29 (1.0)	55 (0.9)
Unstable respiratory medication use	7 (0.2)	10 (0.3)	17 (0.3)
Known narrow angle glaucoma	1 (0.0)	3 (0.1)	4 (0.1)
Symptomatic prostatic hyperplasia	0	1 (0.0)	1 (0.0)
Malignancy in last 5 years	5 (0.2)	2 (0.1)	7 (0.1)
Anticholinergic drug hypersensitivity	0	1 (0.0)	1 (0.0)
Involved in other trials	0	1 (0.0)	1 (0.0)
FEV1>70% or FEV1/FVC>70%	28 (0.9)	32 (1.1)	60 (1.0)
Informed consent signed late	2 (0.1)	2 (0.1)	4 (0.1)
Improper medication wash out	39 (1.3)	43 (1.4)	82 (1.4)
Incorrect trial medication taken	1 (0.0)	0	1 (0.0
Anticholinergic use for ≥2 consecutive visits	115 (3.8)	112 (3.8)	227 (3.8)

Reviewer comment:

Protocol violations were generally balanced between the treatment groups. The rate of protocol violations is consistent with those seen across the Spiriva Phase 3 programs. The persistent use of anticholinergics was noted in only a small percentage of patients, which was similar between treatment groups. This is unlikely to affect the results of the study.

Treatment compliance

Medication compliance was determined by counting returned capsules of study medication. Compliance was defined as the percentage of capsules taken over the planned total. As a patient should take one capsule per day, compliance of the patient was calculated as number of capsules used divided by the number of days that the patient was on treatment. More patients in the tio HH18 group than in the placebo group had compliance of >80%. See Table 35.

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Table 35: Protocol 205.235 treatment compliance

Compliance	Placebo N=3006 N (%)	Tio HH18 N=2986 N (%)	Total N=5992 N (%)
0 - < 50%	212 (7.1)	138 (4.6)	350 (5.8)
50% - <80%	425 (14.1)	347 (11.6)	772 (12.9)
80% - <120%	2331 (77.5)	2467 (82.6)	4798 (80.1)
≥ 120%	8 (0.3)	7 (0.2)	15 (0.3)
incomplete	5 (0.2)	6 (0.2)	11 (0.2)
missing	25 (0.8)	21 (0.7)	46 (0.8)

Reviewer comment:

Compliance for this study overall was good, although lower than in the Phase 3 Spiriva programs. In comparison, overall reported compliance for the 1-year Phase 3 Spiriva Respimat studies was 95.4-96.1% for the tiotropium groups and 95.7% for the placebo groups. This is to be expected, because the UPLIFT protocol had a duration of 4 years, during which compliance might be expected to decrease. It is also relevant that patients in the Spiriva group had improved compliance compared to the placebo group, suggesting that patients may have felt benefit from the drug.

Concomitant respiratory medications

As specified in the protocol, patients were allowed to take any pulmonary medication with the exception of anticholinergic bronchodilators. There was extensive use of maintenance medications, particularly LABAs and ICS in both treatment groups. Approximately 17% of patients used short-acting anticholinergics at least once during the trial, which likely reflects use during exacerbations. In contrast, only 3.8% of patients had protocol violations due to anticholinergic use. Anticholinergic use was counted as a protocol violation only if use persisted on 2 or more consecutive visits, which makes sense in light of the duration of the study. See Table 36.

[m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/0202-0235-01-15-study-report-body.pdf/pages 105-106]

Table 36: Protocol 205.235 concomitant pulmonary medications used at least once during the study

	Placebo N=3006 N (%)	Tio HH18 N=2986 N (%)	Total N=5992 N (%)
Taking any pulmonary medication	2819 (93.8)	2861 (95.8)	5680 (94.8)
Anticholinergic (long-acting)	66 (2.2)	71 (2.4)	137 (2.3)
Anticholinergic (short-acting)	520 (17.3)	501 (16.8)	1021 (17.0)
LABA	2166 (72.1)	2141 (71.7)	4309 (71.9)
Beta agonist (short acting or oral)	2371 (78.9)	2403 (80.5)	4775 (79.7)
LTRA	141 (4.7)	141 (4.7)	282 (4.7)
Mucolytics	804 (26.7)	817 (27.4)	1621 (27.1)
Oxygen	368 (12.2)	359 (12.0)	727 (12.1)
Steroids (inhaled)	2221 (73.9)	2210 (74.0)	4431 (73.9)
Steroids (other)	1654 (55.0)	1590 (53.2)	3244 (54.1)
Xanthines	1059 (35.2)	1035 (34.7)	2094 (34.9)
Xanthines/beta-agonist combination	7 (0.2)	5 (0.2)	12 (0.2)

Reviewer comment:

Almost all of the patients in this study were on concomitant medications. This study differs from most long-term COPD trials, including the one-year studies in the Spiriva program because long-acting beta-agonists (LABAs) were permitted as were inhaled corticosteroids. Note that these numbers differ from those used in subgroup analyses for the trial, which were based on baseline medication use. Presumably most of the anticholinergic use was in association with severe exacerbations, during which patients were permitted to use any medication, and use did not persist for more than one visit (a protocol violation).

Pharmacokinetic outcomes

No pharmacokinetic data were collected in this study.

Efficacy outcomes

Efficacy analyses for COPD exacerbations were performed on the treated set, which consisted of all randomized patients who took at least one capsule of the study drug.

For the analysis of rate of decline of FEV1, FVC, or SVC, treated patients with at least three corresponding acceptable PFT measurements after (including) Day 30 (Visit 2) until the completion of the double-blind treatment (Visit 19) were included. As a sensitivity analysis,

the analysis of rate of decline was also conducted for patients with at least one acceptable PFT measurement between Day 30 and completion of double-blind treatment.

For the analysis of rate of decline of SGRQ scores, patients with at least 2 measurements between (including) months 6 (Visit 5) and the completion of double-blind treatment (Visit 19) were included. As a sensitivity analysis, rate of decline for the SGRQ endpoints was estimated for patients with at least one measurement between Visits 5 and 19. Turkish patients (N=128 or 2% of the treated set) were not included in the analysis of SGRQ endpoints due to a missing question in the Turkish version of the questionnaire.

See Table 37 for a summary of numbers of patients included in the analyses.

Table 37: Protocol 205.235 patients included in the analysis of rate of decline of PFT and SGRQ

	Placebo N = 3006 n (%)	Tio HH18 N = 2986 n (%)	Total N = 5992 n (%)
PFT endpoints			
Post-bronchodilator FEV1	2410 (80.2)	2554 (85.5)	4964 (82.8)
Post-bronchodilator FVC	2410 (80.2)	2554 (85.5)	4964 (82.8)
Post-bronchodilator SVC	2383 (79.3)	2527 (84.6)	4910 (81.9)
Pre-bronchodilator FEV1	2413 (80.3)	2557 (85.6)	4970 (82.9)
Pre-bronchodilator FVC	2413 (80.3)	2557 (85.6)	4970 (82.9)
Pre-bronchodilator SVC	2374 (79.0)	2531 (84.8)	4905 (81.9)
SGRQ endpoints			
Activity score	2362 (78.6)	2505 (83.9)	4867 (81.2)
Impact score	2362 (78.6)	2505 (83.9)	4867 (81.2)
Symptom score	2364 (78.6)	2512 (84.1)	4876 (81.4)
Total score	2362 (78.6)	2505 (83.9)	4867 (81.2)

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Primary

There were two co-primary endpoints for this study, rate of decline of pre- and post-bronchodilator FEV1 from Day 30 (steady state) until completion of double-blind treatment. The endpoints did not achieve statistical significance, thus the applicant reported p-values as unadjusted for multiple comparisons.

There was no significant difference between treatment groups for rate of decline in either pre- or post-bronchodilator FEV1. The sponsor reports that sensitivity analyses including patients with at least one measurement and including center as a random effect also showed no significant treatment difference. Likewise, adjusting for baseline covariates of post-bronchodilator FEV1, age, sex, height and smoking status did not change significance. Pre-specified subgroups of age, gender, smoking status, baseline ICS use, baseline ICS/LABA

combination use, baseline anticholinergic use, GOLD stage, race, region, reversibility, and BMI were evaluated. No significant treatment by subgroup interaction was detected. See Table 38 and Figure 8.

Table 38: Protocol 205.235 rate of decline in FEV1 (random effects model)

	Placebo		Tio HH18		Difference		
	N	Mean (SE) ml/yr	N	Mean (SE) ml/yr	Mean (SE) ml/yr	95%CI	p-value
Pre-BD	2413	30 (1)	2557	30 (1)	0 (2)	(-4, 4)	0.9524
Post-BD	2410	42 (1)	2554	40 (1)	2 (2)	(-6, 2)	0.2074

Figure 8: Protocol 205.235 mean pre-bronchodilator FEV1

Treated set with at least 3 measurements after and including Day 30. Estimated based on repeated measure ANOVA model. Model adjusted for baseline measurement. Day 1 (baseline) value is overall mean, not estimated from the mixed model.

An evaluation of the association between smoking status and rate of decline in FEV1 demonstrated that in both treatment groups, sustained smokers had the highest mean rate of decline in FEV1, sustained ex-smokers had the lowest rate, and intermittent smokers were in between. Smokers were distributed evenly between the groups, and rate of decline was comparable between treatment groups for all smoker subgroups. See Table 39.

Table 39: Protocol 205.235 rate of decline in FEV1 by smoking status

	Placebo		Tio HH18			Difference	
	N	Mean (SE) ml/yr	N	Mean (SE) ml/yr	Subgroup treatment interaction p-value	Mean (SE) ml/yr	p-value
Pre-BD					0.8889		
Sustained ex-smoker	1438	23 (2)	1486	23 (2)		0 (2)	0.8465
Sustained smoker	303	51 (4)	313	51 (4)		0 (5)	0.9865
Intermittent smoker	672	36 (2)	758	35 (2)		2 (3)	0.6493
Post-BD					0.8424		
Sustained ex-smoker	1432	36 (2)	1484	36 (2)		3 (2)	0.1909
Sustained smoker	305	59 (4)	312	59 (4)		0 (5)	0.9807
Intermittent smoker	673	48 (3)	754	46 (2)		2 (3)	0.5731

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Reviewer comment:

This study failed on the primary endpoint, rate of decline of FEV1. However, it is important to note that the difference between treatment groups is maintained throughout the study, suggesting that tiotropium does not lose bronchodilator efficacy with prolonged use (see subsequent discussion of FEV1 at each timepoint). It is well-accepted in the COPD literature that sustained smoking causes a more rapid decline of lung function compared to patients who are able to quit smoking, in whom the rate of decline returns to similar slope as that of never smokers.[2, 3] The UPLIFT trial demonstrates this fact nicely, providing internal validation for the FEV1 measurements in the study.

The applicant conducted post-hoc analyses to evaluate the effect of LABA or ICS use as a potential confounder as well as the effect of differential discontinuation on rate of decline in FEV1. In the UPLIFT trial, 72% and 74% of patients used LABA and ICS, respectively, on at least one visit during the trial. The effect of these concomitant medications was evaluated in two ways: 1) modeling assuming two rates of decline in FEV1 for each patient (one during LABA or ICS use and one without LABA or ICS use), and 2) a subgroup analysis according to baseline LABA or ICS use. Results demonstrated that tio HH18 may reduce rate of decline in FEV1 for patients not on a LABA or ICS. See Table 40 and Table 41. Comparison of the rate of decline of FEV1 between patients who completed at least 45 months of the trial and non-completers demonstrated a higher rate of decline in non-completers (pre-bronchodilator loss of 29-30 ml/year in completers versus 37-40 ml/year in non-completers). Because 45% of placebo-treated patients discontinued prematurely

compared to only 36% of tio HH18 treated patients, differential drop-outs may have biased against tio HH18.

Table 40: Protocol 205.235 rate of decline in FEV1 modeled for different slopes during ICS/LABA use and non-use

	Placebo Mean (SE) ml/yr	Tio HH18 Mean (SE) ml/yr	Difference Mean (SE) ml/yr	95%CI	p-value
Pre-BD					
On LABA/ICS	28 (2)	29 (1)	-1 (2)	(-6, 3)	0.5244
Off LABA/ICS	39 (3)	33 (3)	6 (4)	(-2, 13)	0.1258
Post-BD					
On LABA/ICS	40 (2)	40 (2)	0 (2)	(-4, 5)	0.9285
Off LABA/ICS	49 (3)	39 (3)	10 (4)	(3, 18)	0.0082

Table 41: Protocol 205.235 rate of decline in FEV1 by baseline LABA or ICS use

	Placebo		Tio HH18		Difference		
	N	Mean (SE) ml/yr	N	Mean (SE) ml/yr	Subgroup treatment interaction p-value	Mean (SE) ml/yr	p-value
Pre-BD					0.0409		
No LABA/ICS	767	39 (3)	789	33 (2)		6 (3)	0.0846
LABA/ICS use	2096	26 (2)	2117	28 (1)		-2 (2)	0.2715
Post-BD					0.1070		
No LABA/ICS	764	47 (3)	787	40 (3)		7 (4)	0.0464
LABA/ICS use	2087	39 (2)	2117	39 (2)		0 (2)	0.8719

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Reviewer comment:

The applicant offers two plausible explanations for the failure of the UPLIFT trial to demonstrate a difference in long-term rate of decline in FEV1, confounding by concomitant disease-modifying therapy and differential discontinuation biasing against tiotropium. While these effects may be real, the UPLIFT design overall was significantly strengthened by its "real world" approach to inclusion of multiple concomitant medications, similar to the situation encountered in the COPD population in the United States. Thus, one can conclude that in the setting of high-quality COPD care, the addition of tiotropium is unlikely to significantly impact the natural history of disease.

Key secondary

There were two key secondary endpoints: time to first COPD exacerbation and time to first COPD exacerbation leading to hospitalization.

For COPD exacerbations, the Applicant reports that patients in the tio HH18 group had a significantly longer time to event than patients in the placebo group (p<0.0001, RR 0.86, 95% CI 0.81-0.91). The median time to first exacerbation was 12.5 months in the placebo group and 16.7 months in the tio HH18 group. A Kaplan-Meier estimate of the probability of no exacerbation as provided by the Applicant is presented in Figure 9.

Figure 9: Study 205.235 Kaplan-Meier estimates of the probability of no exacerbation

The Applicant also reports that patients in the tio HH18 group had a statistically significantly longer time to first hospitalization due to COPD exacerbation compared to placebo (p= 0.0024, RR 0.86, 95% CI 0.78, 0.95). The lower quartile for time to first exacerbation requiring hospitalization was 28.6 months in the placebo group and 35.9 months in the tio HH group. Since only 27% of the placebo group and 25% of the tio HH18 group experienced exacerbations leading to hospitalizations, the median time to first exacerbation was calculated based on the first 25% of patients with exacerbations. A Kaplan-Meier estimate of the probability of no exacerbation resulting in hospitalization as provided by the Applicant is presented in Figure 10.

Figure 10: Protocol 205.235 Kaplan-Meier estimates of the probability of no exacerbation leading to hospitalization

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Reviewer comment:

Significance was not achieved for the co-primary endpoints; however, the key secondary endpoints showed a significant difference from placebo with an unadjusted p-value of <0.0001. Strictly speaking, because the trial adjusted for multiplicity using a step-wise approach, i.e. allowing testing of secondary endpoints only if the primary endpoints were met, the trial could be considered "failed" for the secondary endpoints as well. Adjusting for multiplicity in a more-conventional way, a p<0.01 would be considered to show statistical significance. [See Statistical Review by Dr. Joan Buenconsejo, NDA 21-395, S029]

Clinically, the exacerbation endpoints are clinically important, and the failure of the study to show an improvement in disease progression does not detract from the finding of improvement in exacerbations, which was also replicated in a second, independent study (Protocol 205.235). If the exacerbation finding had been less robust, adjustments for multiplicity would pose a greater concern. As a litmus test for evaluating impact of primary versus secondary endpoints, if the study had been designed differently, with COPD

exacerbations as the primary endpoint and rate of decline in FEV1 as a secondary endpoint, the conduct of study and analyses would have been the same.

This same argument also applies to labeling claims regarding lung function, which from a statistical standpoint also represent secondary endpoints with a failed primary. In addition, it would be difficult to provide a description of the study in the label without discussing lung function. Regardless of efficacy, it is important to describe the UPLIFT in the product label due to the safety implications of such a large, long-term trial.

Other secondary

PFT endpoints

Mean pre- and post-bronchodilator FEV1 at each visit was estimated using a repeated measure ANOVA model with visit as a discrete variable and baseline value as a covariate. The tio HH18 group had a significantly higher pre- and post-bronchodilator FEV1 compared to placebo at all timepoints. Pre-bronchodilator FEV1 was a trough level performed after wash-out of appropriate pulmonary medications (see section on PFT measurements). For mean pre-bronchodilator FEV1, the estimated mean difference between tio HH18 and placebo groups ranged from 87 to 103 ml ($p<0.0001$), with an overall mean difference of 94 ml. See Table 42. Post bronchodilator FEV1 was measured after four puffs of albuterol, four puffs of ipratropium and administration of study drug. For post-bronchodilator FEV1, the treatment difference ranged from 47 to 65 ml ($p<0.0001$), with an overall mean difference of 57 ml.

Table 42: Protocol 205.235 FEV1

Test Day	Broncho-dilator	Placebo [L]	Tio HH18 [L]	Treatment difference [L]	p-value	95% CI
Day 1	Pre	1.116	1.116			
	Post	1.347	1.347			
Month 1	Pre	1.134	1.221	0.087	<0.0001	0.077, 0.098
	Post	1.372	1.418	0.047	<0.0001	0.037, 0.057
Month 6	Pre	1.126	1.225	0.099	<0.0001	0.087, 0.110
	Post	1.365	1.423	0.058	<0.0001	0.047, 0.069
Month 12	Pre	1.111	1.213	0.103	<0.0001	0 091, 0.115
	Post	1.345	1.398	0.054	<0.0001	0.042, 0.065
Month 18	Pre	1.101	1.192	0.091	<0.0001	0.078, 0.104
	Post	1.326	1.379	0.053	<0.0001	0.040, 0.066
Month 24	Pre	1.079	1.173	0.094	<0.0001	0.081, 0.107
	Post	1.294	1.356	0.062	<0.0001	0.049, 0.075
Month 30	Pre	1.061	1.156	0.095	<0.0001	0.081, 0.109
	Post	1.274	1.335	0.061	<0.0001	0.047, 0.075
Month 36	Pre	1.045	1.144	0.099	<0.0001	0.085, 0.114
	Post	1.250	1.315	0.065	<0.0001	0.051, 0.080
Month 42	Pre	1.034	1.129	0.095	<0.0001	0.080, 0.110
	Post	1.236	1.297	0.061	<0.0001	0.045, 0.076
Month 48	Pre	1.024	1.112	0.088	<0.0001	0.073, 0.103
	Post	1.219	1.268	0.049	<0.0001	0.033, 0.065
Overall mean	Pre	1.080	1.174	0.094	<0.0001	0.084, 0.105
	Post	1.298	1.354	0.057	<0.0001	0.046, 0.067

Pre-BD N=2363 placebo, N=2494 tio HH18; Post-BD N=2374 placebo, N=2516 tio HH18
Mean and 95% CI estimated using repeated measured ANOVA adjusted for D1 baseline overall mean value.

[m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/0202-0235-01-15-study-report-body.pdf/page 109-111]

Reviewer comment:

Bronchodilatory effect of tio HH18 is slightly lower than that observed in both the Spiriva HandiHaler and Spiriva Respimat Phase 3 programs. For Spiriva HandiHaler Phase 3 pivotal trials the FEV_1 trough response was 0.110-0.130L. For Spiriva Respimat Phase 3 pivotal trials (205.251 and 205.252), the trough response was 0.109-0.124L. Overall, however, the results are comparable. The spirometry results from this study demonstrate bronchodilator efficacy in a more "real world" patient population in which there was high use of concomitant respiratory medications. In addition, the results (trough FEV1 treatment difference of 0.09-0.10L) are similar to that observed in Spiriva HandiHaler Protocol 205.266, a Phase 3 trial conducted in a Veteran's Affairs setting (NDA 21-395, S024), with similar "real world" inclusion criteria.

Rate of decline in PFT measurements

A number of additional rate of decline endpoints were examined in this trial. These included:

- rate of decline in pre-bronchodilator FEV1 from Day 1 until end of trial (30 days post-treatment)
- rate of decline in post-bronchodilator FEV1 from Day 1 until end of trial (30 days post-treatment)
- rate of decline in pre-bronchodilator FVC from Day 1 until end of trial (30 days post-treatment)
- rate of decline in pre-bronchodilator FVC from Day 1 until end of trial (30 days post-treatment)
- rate of decline in pre-bronchodilator SVC from Day 1 until end of trial (30 days post-treatment)
- rate of decline in post-bronchodilator SVC from Day 1 until end of trial (30 days post-treatment)
- rate of decline in pre-bronchodilator FEV1 from Day 1 until end of trial (30 days post-treatment)—nonparametric approach
- change in FEV1 from Day 1 to Day 30 and from Day 30 until completion of treatment
- rate of decline in pre-bronchodilator FVC from Day 30 until completion of treatment
- rate of decline in post-bronchodilator FVC from Day 30 until completion of treatment
- rate of decline in pre-bronchodilator SVC from Day 30 until completion of treatment
- rate of decline in post-bronchodilator SVC from Day 30 until completion of treatment

The rate of decline in FEV1 from Day 1 (randomization) until the end of trial after the 30 day washout was estimated using the following equation: (FEV1 at end of trial – FEV1 on Day 1)/(duration between Day 1 and end of trial). The limitation of this endpoint was that many patients did not have the end of trial visit, and therefore were excluded from the analysis (approximately 44% of patients).

All of the rate of decline variables showed no significant difference between treatment groups with the exception of post-bronchodilator FEV1 from Day 1 until end of trial. For this parameter, there was a median decline of 32 ml/year in the placebo group compared to 27 ml/year in the tio HH18 group (p=0.0145).

[m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/0202-0235-01-15-study-report-body.pdf/page 111-116]

FVC measurements

Mean pre- and post-bronchodilator FVC values were significantly increased in the tio HH18 group compared to placebo at all time points from Day 30 to Month 48, with treatment differences for pre-bronchodilator (trough) values ranging from 0.17-0.20 ($p<0.0001$). The overall mean pre-bronchodilator difference was 0.19L ($p<0.0001$). The differences for post-bronchodilator (peak) values ranged from 0.03-0.07L ($p=0.04$, $p<0.0001$), with an overall mean difference of 0.05L ($p<0.0001$).

[m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/0202-0235-01-15-study-report-body.pdf/page 112-113]

SVC measurements

Mean pre-bronchodilator (trough) SVC values were significantly increased in the tio HH18 group compared to placebo at all time points from Day 30 to Month 48, with treatment differences ranging from 0.15 to 0.19L ($p<0.0001$). The overall mean pre-bronchodilator difference was 0.17L ($p<0.0001$). The mean post-bronchodilator (peak) SVC values were significantly increased in the tio HH18 group compared to placebo out to Month 36, becoming non significant at months 42 and 28. The differences ranged from 0.03-0.05L. The overall mean post-bronchodilator SVC difference was 0.035L ($p=0.0006$).

[m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/0202-0235-01-15-study-report-body.pdf/pages 114-115]

Reviewer comment:

The increases in FVC and SVC are consistent with the known bronchodilator properties of tiotropium.

St. George's Respiratory Questionnaire (SGRQ) endpoints

For SGRQ scores, an increase indicates a worsening of quality of life, while a decrease indicates an improved quality of life. Both rate of decline in SGRQ and mean SGRQ scores during the trial were evaluated.

There were no differences in rate of decline in SGRQ scores from month 6 until completion of treatment for the activity component, impact component, or total scores. The SGRQ symptom component was significantly increased (worsened quality of life) in the tio HH18 group compared to placebo (treatment difference 0.45, $p=0.02$). The applicant notes that this effect was seen only in the last year of the study, and attributes it to differential drop out rates.

The mean SGRQ scores showed a statistically significant decrease across all domains and timepoints for the tio HH18 group compared to placebo, with a treatment difference ranging from -2.30 to -3.35 ($p<0.0001$) for the total SGRQ score. Overall mean SGRQ scores are provided in Table 43.

Table 43: Protocol 205.235 overall mean SGRQ scores

Score	Placebo Mean (SE)	Tio HH18 Mean (SE)	Difference Mean (95% CI)	p-value
Activity	61.08 (0.282)	58.07 (0.272)	-3.01 (-3.78, -2.43)	<0.0001
Impact	33.85 (0.263)	31.42 (0.253)	-2.43 (-3.14 -1.71)	<0.0001
Symptom	45.83 (0.322)	42.79 (0.309)	-3.04 (-3.91, -2.16)	<0.0001
Total	44.09 (0.240)	41.40 (0.231)	-2.69 (-3.34, -2.04)	<0.0001

Activity: placebo N=2337, tio HH18 N=2478 Impact: placebo N=2337, tio HH18 N=2478
Symptom: placebo N=2363, tio HH18 N=2510 Total: placebo N=2337, tio HH18 N=2478

In a responder analysis, a significantly higher proportion of patients in the tio HH18 group compared to placebo had a ≥ 4 unit decrease (improvement) in SGRQ scores from baseline at 1, 2, 3, and 4 years (tio HH18 45-49% versus placebo 36-41%, p<0.0001). In addition, significantly fewer patients in the tio HH18 group compared to placebo experienced a deterioration in scores from baseline.

[m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/0202-0235-01-15-study-report-body.pdf/pages 116-119]

Reviewer comment:

A clinically meaningful difference in SGRQ total score is reported to be 4 points. This is the difference used in the responders analysis (see secondary endpoints). While the differences between the tiotropium groups and placebo reach a high level of statistical significance, differences of less than 4 may not be clinically meaningful. However, the result is supportive of the improvement observed in FEV1. The treatment difference in SGRQ scores is comparable to that observed in the Spiriva Respimat Phase 3 program (Protocols 205.254 and 205.255).

The Applicant is not making labeling claims regarding SGRQ, nor would the data support such a claim.

COPD exacerbation related endpoints

A number of additional endpoints related to COPD exacerbations were examined, including:

- number of COPD exacerbations
- time to first exacerbation treated with steroids
- time to first exacerbation treated with antibiotics
- number of patients with at least one COPD exacerbation
- number of exacerbations treated with steroids
- number of exacerbation days

- number of COPD exacerbations leading to hospitalization
- number of patients with at least one exacerbation leading to hospitalization
- number of days hospitalized due to exacerbation per patient year

The endpoints involving number of exacerbation events are calculated per person year, with a correction for overdispersion. Results as calculated by the applicant are presented in Table 44. All recorded COPD events were included in the analysis. The applicant reports that 98.8% of the recorded exacerbation events agreed with the protocol definition.

Table 44: Protocol 205.235 COPD related events endpoints

Endpoint	Placebo	Tio HH18	Risk Ratio	p-value
Exacerbations/pt year	0.85	0.73	0.86	<0.0001
Time to first exacerbation with steroids [median, month]	26.4	36.5	0.84	<0.0001
Time to first exacerbation with antibiotics [median, month]	16.2	19.8	0.87	<0.0001
Pts with exacerbations [%]	68	67	NC	0.3481
Exacerbations with steroids	0.52	0.44	0.84	<0.0001
Exacerbations with antibiotics	0.71	0.62	0.87	<0.0001
Exacerbation days [mean]	13.6	12.1	0.89	0.0011
Exacerbations with hospitalization	0.16	0.15	0.94	0.3413
Pts hospitalized due to exacerbation [%]	27	25	NC	0.1766
Days in hospital due to exacerbations [mean]	3.13	3.17	1.01	0.8624

All endpoints other than time to first event and percent of patients are reported as number of events per patient-year. Poisson regression analysis adjusted for overdispersion was used.
NC=not calculated

[m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/0202-0235-01-15-study-report-body.pdf/pages 119-122]

Reviewer comment:

These exacerbation endpoints are generally in favor of tiotropium, supportive of a claim regarding reduction in COPD exacerbations. The number of exacerbations per patient year is consistent with that found in Study 205.266 (VA study, NDA 21-395, S-024), in which the number of exacerbations per patient year was 0.876 in the placebo group and 0.711 in the tio HH18 group, giving a risk ratio of 0.812. The percent of patients with exacerbations and

hospitalized with exacerbations may be biased against tiotropium due to differential drop out from the placebo group.

This analysis correctly adjusts for overdispersion. The default Poisson regression technique assumes that all patients are homogenous with respect to their rate of exacerbation. The correction for overdispersion takes into account that for COPD, the majority of exacerbations occur in a small portion of patients while the rest of the population has no exacerbations.[4] The method of calculation of exacerbation rate and correction for overdispersion is critical as different statistical methodologies may give very different results.

Efficacy conclusions

The UPLIFT study showed no significant difference between treatment groups in the primary endpoints of rate of decline in pre- and post-bronchodilator FEV1. In a subgroup analysis, patients who were sustained quitters from smoking did experience a significant decrease in rate of decline in FEV1 compared to sustained smokers. This effect was observed across both treatment groups.

The applicant offers two plausible explanations for the failure of the UPLIFT trial to demonstrate a difference in long-term rate of decline in FEV1, confounding by concomitant disease-modifying therapy and differential discontinuation biasing against tiotropium. While these effects may be real, the UPLIFT design overall was significantly strengthened by its "real world" approach to inclusion of multiple concomitant medications, similar to the situation encountered in the COPD population in the United States. Thus, one can conclude that in the setting of high-quality COPD care, the addition of tiotropium is unlikely to impact the natural history of disease.

For the key secondary endpoints of time to first COPD exacerbation and time to first COPD exacerbation leading to hospitalization, tiotropium showed significant decrease compared to placebo. For COPD exacerbations, the Applicant reports that patients in the tio HH18 group had a significantly longer time to event than patients in the placebo group ($p<0.0001$, RR 0.86, 95% CI 0.81-0.91). The median time to first exacerbation was 12.5 months in the placebo group and 16.7 months in the tio HH18 group. Patients in the tio HH18 group also had a statistically significantly longer time to first hospitalization due to COPD exacerbation compared to placebo ($p= 0.0024$, RR 0.86, 95% CI 0.78, 0.95). The lower quartile for time to first exacerbation requiring hospitalization was 28.6 months in the placebo group and 35.9 months in the tio HH group.

A significant improvement in most of the additional COPD exacerbation-related endpoints was also observed. These included the number of COPD exacerbations, time to first exacerbation treated with steroids, time to first exacerbation treated with antibiotics, number of exacerbations treated with steroids, number of exacerbation days, number of COPD exacerbations leading to hospitalization, and number of days hospitalized due to exacerbation per patient year. In conjunction with supportive evidence from Protocol 205.266 (VA study, submitted under NDA 21-395, S-024), these data are generally supportive of an exacerbation claim. The exact wording of the claim will need consideration as various aspects of exacerbation were measured in this trial.

On November 19, 2009, the PADAC voted (11 yes, 1 no) that the UPLIFT and VA trials provide substantial and convincing evidence to support the claim that Spiriva HandiHaler reduces COPD exacerbations. The single negative vote was secondary to the lack of exact wording of the claim in the question and not because evidence of efficacy was lacking for a COPD exacerbation claim in general.

SGRQ endpoints included rate of SGRQ deterioration, as well as total and component SGRQ scores. There were no differences in rate of decline in SGRQ scores from month 6 until completion of treatment for the activity component, impact component, or total scores. The mean SGRQ scores showed a statistically significant but not a clinically important decrease across all domains and timepoints for the tio HH18 group compared to placebo, with a treatment difference ranging from -2.30 to -3.35 ($p<0.0001$) for the total SGRQ score.

Spirometry endpoints included trough FEV_1, FVC, and SVC response and 90 minute FEV_1 FVC, and SVC response. Endpoints were measured every six months throughout the four year treatment period. Consistent with the known bronchodilator properties of the drug, the tio HH18 group generally demonstrated a significant improvement ($p<0.0001$) over placebo for all endpoints and time points tested.

Safety outcomes

Safety outcomes for Study 205.235 included collection of non-serious and serious adverse events, as well as assessment of mortality on all patients including those who discontinued prematurely. All patients who were randomized and received at least one dose of study drug were included in the safety analyses. Adverse events with an onset of up to 30 days after discontinuation of study drug were assigned to the treatment period.

Extent of exposure

A total of 5992 COPD patients were randomized and received at least one dose of study drug. The planned exposure for each patient was 1440 days (approximately 48 months). One eligible patient withdrew at the randomization visit, prior to receiving study drug. One additional patient was randomized twice in error (once to each treatment group).

Mean exposure to study drug for all patients was 1080 days. Significantly fewer ($p<0.0001$) patients in the tio HH18 group prematurely discontinued than in the placebo group [1080 (36.2%) versus 1341(44.6%)]. The highest percentage of discontinuations occurred in the first year of treatment. A summary of patient exposure is provided in Table 45.

[m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/0202-0235-01-15-study-report-body.pdf/pages 125-128]

Table 45: Protocol 205.235 summary of treatment exposure

	Placebo N=3006 n (%)	Tio HH18 N=2986 n (%)	Total N=5992 n (%)
Total treated Exposure (months)			
≥ 1	2867 (95.4)	2915 (97.6)	5782 (96.5)
≥ 3	2740 (91.2)	2816 (94.3)	5556 (92.7)
≥ 6	2618 (87.1)	2726 (91.3)	5344 (89.2)
≥ 9	2513 (83.6)	2634 (88.2)	5147 (85.9)
≥ 12	2418 (80.4)	2565 (85.9)	4983 (83.2)
≥ 15	2344 (78.0)	2496 (83.6)	4840 (80.8)
≥ 18	2249 (74.8)	2432 (81.4)	4681 (78.1)
≥ 21	2161 (71.9)	2363 (79.1)	4524 (75.5)
≥ 24	2090 (69.5)	2293 (76.8)	4383 (73.1)
≥ 27	2013 (67.0)	2236 (74.9)	4249 (70.9)
≥ 30	1947 (64.8)	2177 (72.9)	4124 (68.8)
≥ 33	1891 (62.9)	2117 (70.9)	4008 (66.9)
≥ 36	1831 (60.9)	2060 (69.0)	3891 (64.9)
≥ 39	1779 (59.2)	2001 (67.0)	3780 (63.1)
≥ 42	1723 (57.3)	1970 (66.0)	3693 (61.6)
≥ 45	1665 (55.4)	1904 (63.8)	3569 (59.6)
Treatment Exposure (days)			
Mean	1032.7	1128.1	1080.3
Min	1	1	1
Max	1550	1655	1655

Adverse events

Overall, 92% of patients in the UPLIFT trial experienced an adverse event (AE), and 51% experience a serious adverse event (SAE). The incidence of various categories of AEs was generally balanced between the groups, except for drug-related adverse events (as determined by the investigator), which were more frequent in the tio HH18 group (7.8% placebo versus 10.2% tio HH18). This was largely driven by the increased incidence of dry mouth in the tio HH18 group. See Table 46.

[m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/0202-0235-01-15-study-report-body.pdf/pages 129-131]

Table 46: Protocol 205.235 overall adverse event summary

	Placebo N=3006 N (%)	Tio HH18 N=2986 N (%)	Total N=5992 N (%)
Any AE	2774 (92.3)	2764 (92.6)	5538 (92.4)
Drug-related AEs	233 (7.8)	306 (10.2)	539 (9.0)
AEs leading to discontinuation	735 (24.5)	618 (20.7)	1353 (22.6)
Serious AEs	1509 (50.2)	1540 (51.6)	3049 (50.9)
Fatal	411 (13.7)	381 (12.8)	792 (13.2)
Life threatening	112 (3.7)	103 (3.4)	215 (3.6)
Disabling	75 (2.5)	73 (2.4)	148 (2.5)
Hospitalization	1357 (45.1)	1369 (45.8)	2726 (45.5)
Other	135 (4.5)	158 (5.3)	293 (4.9)

Deaths

Vital status was collected on all patients who prematurely discontinued from the trial extending to 4 years post-randomization. The primary cause of each death was adjudicated by an independent committee. Time to death was defined as time to the end date of the fatal AE (date of death). The primary analysis evaluated deaths with a cut off date of 1440 days (4 years); however, evaluations with a cut off date of 1470 days (4 years plus 30 days) and no cut off date were also conducted. The applicant also presents fatal events in two ways: 1) deaths on treatment and 2) deaths including post-discontinuation vital status. The adjudicated cause of death is presented as the primary analysis, but investigator-reported cause of death is also presented.

Overall, the total number of deaths during treatment (including the last day of study drug plus 30 days) was 792; 411 (13.7%) in the placebo group and 381 (12.8%) in the tio HH18 group. The risk ratio for death from any cause (tiotropium/placebo) was 0.84 [95% CI (0.73, 0.97)]. The risk ratio for death remains significantly or nearly significantly different from placebo regardless of the cut off used or inclusion of vital status data. See Table 47.

Table 47: Protocol 205.235 fatal event summary

	Placebo N (%)	Tio HH18 N (%)	Rate difference	Risk Ratio	Risk Ratio Tio HH18 vs. Placebo 95% CI	p-value
On treatment (Day 1440)	400 (13.3)	361 (12.1)	1.2%	0.83	0.72, 0.95	0.010
On treatment (Day 1470)	402 (13.4)	374 (12.5)	0.9%	0.85	0.74, 0.98	0.024
On treatment (all)	411 (13.7)	381 (12.8)	0.9%	0.84	0.73, 0.97	0.016
Vital status (Day 1440)	491 (16.3)	430 (14.4)	1.9%	0.87	0.76, 0.99	0.034
Vital status (Day 1470)	495 (16.5)	446 (14.9)	1.6%	0.89	0.79, 1.02	0.086
Vital status (all)	514 (17.1)	467 (15.6)	1.5%	0.89	0.78, 1.00	0.058

On-treatment mortality

A Kaplan-Meier estimate of the probability of no death on treatment as presented by the applicant is given in Figure 11. The curves show separation after 12 months out to 48 months.

Figure 11: Protocol 205.235 Kaplan-Meier estimates of probability of no all cause mortality [adjudicated on treatment deaths censored at Day 1470]

The most common causes (adjudicated) of death on-treatment were COPD exacerbation, lung cancer, and death of unknown cause. See Table 48. There were 271 patients who died of lower respiratory causes by Day 1470, 140 (4.7%) in the placebo group and 131 (4.4%) in the tio HH18 group [RR=0.85, 95% CI (0.67, 1.08)]. Forty-nine patients died of cardiac causes, 25 (0.8%) in the placebo group and 24 (0.8%) in the tio HH18 group [RR=0.88, 95% CI (0.50, 1.55)]. The preferred terms of sudden death, sudden cardiac death, and death of unknown cause are coded by MedDRA under the General Disorders System Organ Class; however, these terms are often considered cardiac events. Combining these three preferred terms, 127 patients died with sudden or unknown causes of death. Of these, 70 (2.3%) were in the placebo group and 57 (1.9%) were in the tio HH18 group [RR=0.75, 95% CI (0.53, 1.06)].

Table 48: Protocol 205.235 on-treatment adjudicated cause of death occurring in ≥ 10 patients in either treatment group

Cause of death	Placebo N (%) [n=3006]	Tio HH18 N (%) [n=2986]	Risk Ratio	p-value (95% CI)
COPD exacerbation	121 (4.0)	103 (3.4)	0.79	0.07 (0.60, 1.02)
Lung cancer	66 (2.2)	73 (2.4)	1.02	0.89 (0.73,1.43)
Death (unknown cause)	36 (1.2)	29 (1.0)	0.74	0.23 (0.46, 1.21)
Sudden cardiac death	23 (0.8)	15 (0.5)	0.60	0.13 (0.31, 1.15)
Pneumonia	18 (0.6)	27 (0.9)	1.39	0.28 (0.76, 2.52)
Congestive heart failure	14 (0.5)	15 (0.5)	0.99	0.98 (0.48, 2.05)
Sudden death	12 (0.4)	14 (0.5)	1.08	0.85 (0.50, 2.33)
Cerebrovascular accident	13 (0.4)	12 (0.4)	0.85	0.69 (0.39, 1.87)

Vital status mortality

Vital status information was known for 98% of tiotropium treated patients and 97% of placebo treated patients out to at least 45 months post-randomization. There were a total of 921 deaths, including vital status, for the full 4 year protocol defined study period (1440 days). There were 941 deaths for the period of 4 years plus 30 days (1470 days). See Table 47. Compared to the on-treatment mortality, an additional 149 deaths were collected for patients who discontinued.

Similar to on-treatment causes of death, the most frequent causes of death in the group including vital status were COPD exacerbation, lung cancer, and death of unknown cause.

[m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/0202-0235-01-15-study-report-body.pdf/pages 133-138]

<u>*Reviewer comment:*</u>

The applicant is requesting a claim for mortality. BI proposes the following language for the clinical studies section of the label: "In the 4-year multicenter trial, there was a 16% reduction in the risk of death while on treatment with Spiriva HandiHaler compared to placebo. The incidence rate of death was 4.10 per 100 patient years in the tiotropium group vs. 4.78 per 100 patient years in the placebo group [Hazard Ratio (tiotropium/placebo) = 0.84, 95% CI = 0.73, 0.97]."

Since UPLIFT is a major study that more than doubles the size of the safety database for tio HH18, it is reasonable to describe major findings such as reduction in mortality in the product label. The persistence of the effect across many different analyses strengthens the evidence for a mortality benefit. However, a number of factors come into consideration for this claim:

- *Mortality is a major claim which requires a substantive body of evidence for approval. To support a labeling claim, the Agency typically requires replication of findings in two or more clinical trials. However, according to the Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biologic Products, reliance on a single study is possible in situations in which a trial has demonstrated a clinically meaningful effect on mortality or irreversible morbidity. In addition, the single study would typically be large multicenter center, such as UPLIFT, with consistency across study subsets and statistically very persuasive findings.*

- *A small numerical imbalance in mortality in favor of the placebo group was observed in 3 one-year Phase 3 studies of Spiriva Respimat. Although Spiriva Respimat is a different drug product from an efficacy perspective, it contains the same drug substance as Spiriva HandiHaler, thus the two products would be expected to have a similar systemic safety profile. These data complicate approval of a mortality claim.*

- *A recent meta-analysis by Singh, et al.[1] concludes that anticholinergic medications including tiotropium increase long-term cardiovascular mortality. Dr. Simone Pinheiro of the Office of Surveillance and Epidemiology reviewed the relevant literature, including this meta-analysis. Dr. Pinheiro concluded that the currently available data implicating tiotropium and ipratropium in increasing risk of cardiovascular death, myocardial infarction, and stroke is not compelling. Refer to the Office of Surveillance and Epidemiology briefing document for details.*

The Pulmonary and Allergy Drugs Advisory Committee (PADAC), in their meeting on November 19, 2009, concluded that UPLIFT was a compelling and important study, demonstrating generally beneficial effects on mortality. Although the Respimat results were felt to be somewhat concerning and additional data are needed, the Respimat results do not necessarily convey to the HandiHaler.

Serious adverse events

Serious adverse events (SAEs) occurred in 50.9% of the overall study population, including 51.6% of the tio HH18 group and 50.2% of the placebo group. The most common SAEs were COPD exacerbation, pneumonia, and respiratory failure. SAEs occurring in more than 1% in either treatment group are given in Table 49. SAEs were generally balanced between treatment groups.

For some of the most common adverse events, the applicant appropriately grouped MedDRA terms in order to create a single category which incorporates a variety of different terms for the same or very similar conditions. These grouped terms included angina, atrial

fibrillation, myocardial infarction, bronchitis, COPD exacerbation, dyspnea, and pneumonia. As part of the review process, the clinical reviewer also grouped terms for some of the more common SAEs as follows:

- Cardiac failure: cardiac failure, cardiac failure acute, cardiac failure chronic, cardiac failure congestive, acute right ventricular failure, left ventricular dysfunction, left ventricular failure, right ventricular failure
- Coronary artery disease: coronary artery disease, coronary artery embolism, coronary artery insufficiency, coronary artery occlusion, coronary artery restenosis, coronary artery stenosis, coronary artery thrombosis
- Gall bladder disease: bile duct obstruction, bile duct stone, biliary colic, biliary dyskinesia, cholangitis, cholangitis acute, cholecystitis, cholecystitis acute, cholecystitis chronic, cholelithiasis, cholelithiasis obstructive, cholestasis, gallbladder disorder
- Sepsis: enterococcal sepsis, escherichia sepsis, klebsiella sepsis, neutropenic sepsis, pneumococcal sepsis, sepsis, sepsis syndrome, septic shock, staphylococcal sepsis, wound sepsis
- Bladder cancer: bladder adenocarcinoma stage unspecified, bladder cancer, bladder cancer recurrent, bladder cancer stage II, bladder cancer stage IV, bladder neoplasm, bladder transitional cell carcinoma
- Prostate cancer: prostate cancer, prostate cancer metastatic, prostate cancer stage I, prostate cancer stage III
- Stroke: this combined term is handled separately under adverse events of interest
- Respiratory failure: acute respiratory failure, chronic respiratory failure, respiratory failure

While a combination of terms resulted in an increase in the percentage of patients with the event over the 1% threshold for each event other than bladder cancer which remained at 0.7% overall, the combination did not result in identification of new safety signals. Combination of the respiratory failure term did not result in diminution of the treatment difference between groups in favor of tiotropium.

Table 49: Protocol 205.235 serious adverse events occurring in ≥ 1% of patients in either treatment group (as reported by applicant)

MedDRA System Organ Class MedDRA Preferred Term	Placebo N (%)	Tio HH18 N (%)	Total N (%)
Total Treated N (%)	3006 (100)	2986 (100)	5992 (100)
Total with serious adverse events	1509 (50.2)	1540 (51.6)	3049 (50.9)
Cardiac disorders	350 (11.6)	322 (10.8)	672 (11.2)
Angina#	31 (1.0)	48 (1.6)	79 (1.3)
Atrial fibrillation#	67 (2.2)	69 (2.3)	136 (2.3)
Cardiac failure	42 (1.4)	57 (1.9)	99 (1.7)
Cardiac failure congestive	42 (1.4)	27 (0.9)	69 (1.2)
Coronary artery disease	32 (1.1)	20 (0.7)	52 (0.9)
Myocardial infarction#	84 (2.8)	65 (2.2)	149 (2.5)
Neoplasms	170 (5.7)	197 (6.6)	367 (6.1)
Prostate cancer	22 (0.7)	31 (1.0)	53 (0.9)
Respiratory system disorders* (Lower)	985 (32.8)	911 (30.5)	1896 (31.6)
Acute respiratory failure	31 (1.0)	29 (1.0)	60 (1.0)
Bronchitis#	27 (0.9)	35 (1.2)	62 (1.0)
COPD exacerbation#	742 (24.7)	688 (23.0)	1430 (23.9)
Dyspnea#	54 (1.8)	36 (1.2)	90 (1.5)
Pneumonia#	290 (9.6)	296 (9.9)	586 (9.8)
Respiratory failure	113 (3.8)	85 (2.8)	198 (3.3)
Respiratory system disorders* (Other)	156 (5.2)	170 (5.7)	326 (5.4)
Lung neoplasm malignant	34 (1.1)	40 (1.3)	74 (1.2)
Pulmonary embolism	29 (1.0)	25 (0.8)	54 (0.9)

BI Collapsed Preferred Terms include multiple MedDRA Preferred Terms.

*All system organ classes are defined by MedDRA with the exception of respiratory, thoracic and mediastinal disorders which have been divided into 3 separate classes of respiratory system disorders lower, upper, and other.

Reviewer comment:

Based on the SAE data, the applicant is requesting a claim for reduction in respiratory failure. BI proposes the following language for the clinical studies section of the label: "In the 4-year multicenter trial….Treatment with tiotropium reduced the risk of respiratory failure by 19% (2.09 vs. 1.68 cases per 100 patient years [relative risk (tiotropium/placebo) = 0.81, 95% CI 0.65, 1.00]."

While the incidence of SAEs of respiratory failure is reduced in the tio HH18 group, the difference is marginally significant and there are multiple related preferred terms that have been analyzed separately. Unlike mortality, which is a hard endpoint and was pre-specified in the protocol as an event of interest (including vital status collection and an independent adjudication committee), the term "respiratory failure" is undefined and subject to investigator interpretation. In addition, multiplicity is a concern since many adverse event variables were evaluated in the safety analysis and the effect is only marginally significant. Inclusion of the term respiratory failure may be appropriate as part of adverse event

reporting for the study; however, there is insufficient evidence to justify a specific claim that Spiriva HandiHaler reduces respiratory failure.

Serious adverse events of interest

Stroke is an adverse event of interest based on a potential safety signal observed in an analysis of combined tiotropium HandiHaler and Respimat trials. Stroke-related adverse events were not increased in the tiotropium groups in Protocol 205.235. See Table 50.

Table 50: Protocol 205.235 stroke adverse events

	Tio HH18 N=2986		Placebo N=3006		
	N	Rate/100 pt yrs	N	Rate/100 pt yrs	Risk Ratio (95% CI)
AE	82	0.88	80	0.93	0.95 (0.70, 1.29)
SAE	66	0.70	63	0.73	0.97 (0.69, 1.37)
Fatal (on treatment)	12	0.13	13	0.15	0.85 (0.39, 1.87)
Fatal (vital status, D1470)	14	0.13	17	0.15	0.82 (0.40, 1.66)

[m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/0202-0235-01-15-study-report-body.pdf/pages 141-142]

Reviewer comment:

In recently completed pooled analyses of tiotropium clinical trial data, the Applicant identified stroke as occurring at higher rates in patients receiving tiotropium compared with patients receiving placebo (RR 1.37, 95% CI 0.73-1.56). This data was submitted to FDA in November 2007 and an Early Communication was issued by FDA for Spiriva HandiHaler on March 18, 2008. This pooled trial population presented information on 13,344 patients from 29 clinical trials, contributing 4,572 person-years of exposure to tiotropium and 3,065 person-years of exposure to placebo. This population included 25 trials from the Spiriva HandiHaler program and 4 trials from the Spiriva Respimat program (205.251, 205.252, 205.254, and 205.255). The analysis also investigated a large number of other adverse events without correction for multiplicity. The pooled trials in the Respimat program did not demonstrate a significantly increased risk (RR 0.87, 95% CI 0.30-2.56), although the confidence intervals were wide.

Likewise, the UPLIFT trial does not show a specific signal for stroke events. The Risk Ratio for adverse events of stroke is less than one, and the upper bound of the confidence interval is less than 1.3, suggesting that if there is any adverse drug effect, it is minimal. Because stroke was a pre-specified term for the adjudication of cause of death, readers can have confidence that fatal strokes were appropriately classified and are not "hiding" under some other preferred term. Serious adverse events and fatal adverse events of stroke are

subgroups and as expected, have slightly wider confidence intervals, although the conclusions are the same.

Adverse events leading to discontinuation

There were 618 (20.7%) patients in the tio HH18 group and 735 (24.5%) patients in the placebo group who discontinued prematurely due to an adverse event. The most frequent AEs leading to discontinuation were all lower respiratory events—COPD exacerbation, dyspnea, pneumonia, and respiratory failure. Fewer patients in the tio HH18 group discontinued due to a lower respiratory AE compared to patients in the placebo group [291 (9.7%) versus 412 (13.7%), respectively]. This was driven by a reduced number of patients in the tio HH18 group with COPD exacerbations and dyspnea. See Table 51.

Table 51: Protocol 205.235 adverse events leading to discontinuation occurring in ≥ 10 patients overall

MedDRA System Organ Class MedDRA Preferred Term	Placebo N (%)	Tio HH18 N (%)	Total N (%)
Total Treated N (%)	3006 (100)	2986 (100)	5992 (100)
Total with AEs leading to discontinuation	735 (24.5)	618 (20.7)	1353 (22.6)
Cardiac disorders	81 (2.7)	70 (2.3)	151 (2.5)
Atrial fibrillation#	7 (0.2)	7 (0.2)	14 (0.2)
Cardiac failure	7 (0.2)	13 (0.4)	20 (0.3)
Cardiac failure congestive	6 (0.2)	5 (0.2)	11 (0.2)
Myocardial infarction#	21 (0.7)	15 (0.5)	36 (0.6)
Gastrointestinal disorders	32 (1.1)	29 (1.0)	61 (1.0)
Dry mouth#	4 (0.1)	9 (0.3)	13 (0.2)
General disorders	38 (1.3)	47 (1.6)	85 (1.4)
Death	12 (0.4)	19 (0.6)	31 (0.5)
Sudden death	11 (0.4)	9 (0.3)	20 (0.3)
Nervous system disorders	38 (1.3)	39 (1.3)	77 (1.3)
Cerebrovascular accident	8 (0.3)	11 (0.4)	19 (0.3)
Respiratory system disorders* (Lower)	412 (13.7)	291 (9.7)	703 (11.7)
Acute respiratory failure	10 (0.3)	8 (0.3)	18 (0.3)
COPD exacerbation#	209 (7.0)	152 (5.1)	361 (6.0)
Dyspnea#	118 (3.9)	54 (1.8)	172 (2.9)
Pneumonia#	51 (1.7)	48 (1.6)	99 (1.7)
Respiratory failure	31 (1.0)	21 (0.7)	52 (0.9)
Respiratory system disorders* (Other)	82 (2.7)	89 (3.0)	171 (2.9)
Bronchial carcinoma	5 (0.2)	11 (0.4)	16 (0.3)
Lung neoplasm	5 (0.2)	8 (0.3)	13 (0.2)
Lung neoplasm malignant	19 (0.6)	21 (0.7)	40 (0.7)
Non-small cell lung cancer	7 (0.2)	5 (0.2)	12 (0.2)
Non-small cell lung cancer, malignant	4 (0.1)	6 (0.2)	10 (0.2)
Pulmonary embolism	9 (0.3)	5 (0.2)	14 (0.2)
Small cell lung cancer, stage unspecified	3 (0.1)	7 (0.2)	10 (0.2)

BI Collapsed Preferred Terms include multiple MedDRA Preferred Terms.

*All system organ classes are defined by MedDRA with the exception of respiratory, thoracic and mediastinal disorders which have been divided into 3 separate classes of respiratory system disorders lower, upper, and other.

[m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/0202-0235-01-15-study-report-body.pdf/page 142]

Overall adverse events

Non serious adverse events were reported in almost all patients in both groups (92.3% of placebo patients and 92.6% of tio HH18 patients), an expected finding given the length of the study and the severity of disease in this patient population. In order to account for differential drop out, the applicant also reported AEs as exposure adjusted rates (number of patients experiencing an event divided by the person-years at risk).

The most frequently reported AEs were COPD exacerbation, pneumonia, dyspnea, nasopharyngitis, and upper respiratory tract infection. If evaluated by exposure adjusted rates, COPD exacerbation, dyspnea, and respiratory failure occurred significantly less frequently in the tio HH18 group compared to placebo. In contrast, dry mouth and insomnia occurred significantly more frequently in the tio HH18 group. Dry mouth is a known anticholinergic side effect of tiotropium. Other known anticholinergic side effects also occurred with greater frequency in the tiotropium group although not significantly so. These included constipation, benign prostatic hypertrophy, dizziness, sinusitis, nasopharyngitis, cough, and urinary tract infection. See Table 52.

All AEs with a risk ratio ≥3 in the tio HH18 group compared to placebo are presented in Table 53. Analysis of these events reveals that while the risk ratio may be high, the number of patients with each event is very low and in most cases there is no biologic plausibility for a causal relationship. The risk ratio reached statistical significance for only one event, intestinal obstruction. Events that could be secondary to anticholinergic effects include atrial tachycardia, tachyarrhythmia, intestinal obstruction, and prostate infection. Supraventricular tachyarrythmic events in general did not appear to be increased overall in the tio HH18 group, with atrial fibrillation occurring in 113 (3.8%) patients in the placebo group and 119 (4.0%) patients in the tio HH18 group [RR 0.97, 95% CI (0.75, 1.26)] and tachycardia occurring in 43 (1.4%) patients in the placebo group and 40 (1.3%) patients in the tio HH18 group [RR 0.86, 95%CI (0.56, 1.32)].

[m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/0202-0235-01-15-study-report-body.pdf/pages 130-133]

Table 52: Protocol 205.235 frequency and incidence rates (per 100 patient years) of patients with AEs occurring in >3% of either treatment group

	Placebo N=3006		Tio HH18 N=2986		Tio HH18/ placebo
	N (%)	Incidence Rate	N (%)	Incidence Rate	Rate Ratio (95% CI)
Total with AE	**2774 (92.3)**		**2764 (92.6)**		
COPD exacerbation#	1986 (66.1)	45.5	1934 (64.8)	38.1	0.84 (0.79, 0.89)
Pneumonia#	418 (13.9)	5.14	433 (14.5)	4.94	0.96 (0.84, 1.10)
Dyspnea#	443 (14.7)	5.49	364 (12.2)	4.09	0.75 (0.65, 0.86)
Nasopharyngitis	324 (10.8)	4.06	373 (12.5)	4.33	1.07 (0.92, 1.24)
Upper respiratory tract infection#	290 (9.6)	3.57	298 (10.0)	3.38	0.95 (0.81, 1.11)
Hypertension	284 (9.4)	3.45	275 (9.2)	3.08	0.89 (0.75, 1.05)
Bronchitis#	233 (7.8)	2.82	232 (7.8)	2.57	0.91 (0.76, 1.10)
Cough	213 (7.1)	2.57	238 (8.0)	2.64	1.03 (0.86, 1.24)
Back pain	188 (6.3)	2.25	198 (6.6)	2.18	0.97 (0.79, 1.18)
Urinary tract infection#	169 (5.6)	2.00	190 (6.4)	2.08	1.04 (0.85, 1.28)
Sinusitis#	160 (5.3)	1.90	194 (6.5)	2.14	1.12 (0.91, 1.39)
Influenza	158 (5.3)	1.87	158 (5.3)	1.73	0.92 (0.74, 1.15)
Headache	136 (4.5)	1.61	171 (5.7)	1.88	1.17 (0.94, 1.47)
Edema#	130 (4.3)	1.52	145 (4.9)	1.57	1.03 (0.82, 1.31)
Constipation	111 (3.7)	1.29	151 (5.1)	1.63	1.26 (0.99, 1.61)
Diarrhea	122 (4.1)	1.43	138 (4.6)	1.5	1.04 (0.82, 1.33)
Cataract	123 (4.1)	1.45	120 (4.0)	1.3	0.90 (0.70, 1.15)
Atrial fibrillation#	113 (3.8)	1.32	119 (4.0)	1.28	0.97 (0.75, 1.26)
Dry mouth#	80 (2.7)	0.93	152 (5.1)	1.68	1.80 (1.37, 2.36)
Depression	98 (3.3)	1.14	131 (4.4)	1.42	1.25 (0.96, 1.62)
Insomnia	91 (3.0)	1.06	131 (4.4)	1.42	1.34 (1.02, 1.75)
Arthralgia	94 (3.1)	1.10	125 (4.2)	1.36	1.24 (0.95, 1.62)
Benign prostatic hyperplasia	96 (3.2)	1.12	122 (4.1)	1.32	1.18 (0.90, 1.54)
Rhinitis	112 (3.7)	1.32	101 (3.4)	1.09	0.83 (0.63, 1.08)
Abdominal pain#	96 (3.2)	1.12	113 (3.8)	1.22	1.09 (0.83, 1.43)
Respiratory failure	120 (4.0)	1.39	88 (2.9)	0.94	0.67 (0.51, 0.89)
Hypercholesterolemia	97 (3.2)	1.13	104 (3.5)	1.12	0.99 (0.75, 1.31)
Nausea	94 (3.1)	1.09	93 (3.1)	1.00	0.91 (0.69, 1.22)
Dizziness	81 (2.7)	0.94	103 (3.4)	1.11	1.18 (0.88, 1.58)

BI Collapsed Preferred Terms include multiple MedDRA Preferred Terms.
*All system organ classes are defined by MedDRA with the exception of respiratory, thoracic and mediastinal disorders which have been divided into 3 separate classes of respiratory system disorders lower, upper, and other.

Table 53: Protocol 205.235 frequency and incidence rates (per 100 patient years) of patients with AEs with a risk ratio of ≥3

	Placebo N=3006		Tio HH18 N=2986		Tio HH18/ placebo
	N (%)	Incidence Rate	N (%)	Incidence Rate	Rate Ratio (95% CI)
Total with AE	2774 (92.3)		2764 (92.6)		
Atrial tachycardia	1 (0.0)	0.01	8 (0.3)	0.08	7.39 (0.92, 59.1)
Tachyarrhythmia	2 (0.1)	0.02	8 (0.3)	0.08	3.70 (0.79, 17.4)
Tricuspid valve incompetence	1 (0.0)	0.01	6 (0.2)	0.06	5.54 (0.67, 46.1)
Epigastric discomfort	1 (0.0)	0.01	5 (0.2)	0.05	4.62 (0.54, 39.6)
Intestinal obstruction*	2 (0.1)	0.02	12 (0.4)	0.13	5.55 (1.24, 24.8)
Large intestinal perforation	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Peritonitis	1 (0.0)	0.01	5 (0.2)	0.05	4.62 (0.54, 39.6)
Tongue disorder	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Ulcer	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Bile duct stone	2 (0.1)	0.02	8 (0.3)	0.08	3.70 (0.79, 17.4)
Abscess	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Appendicitis	2 (0.1)	0.02	9 (0.3)	0.10	4.16 (0.90, 19.3)
Osteomyelitis	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Prostate infection	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Foreign body trauma	1 (0.0)	0.01	5 (0.2)	0.05	4.62 (0.54, 39.6)
Tendon rupture	2 (0.1)	0.02	9 (0.3)	0.10	4.16 (0.90, 19.3)
Ulna fracture	1 (0.0)	0.01	5 (0.2)	0.05	4.62 (0.54, 39.6)
INR increased	1 (0.0)	0.01	5 (0.2)	0.05	4.62 (0.54, 39.6)
Vitamin B12 deficiency	2 (0.1)	0.02	7 (0.2)	0.07	3.24 (0.67, 15.6)
Costochondritis	2 (0.1)	0.02	9 (0.3)	0.10	4.16 (0.90, 19.3)
Lumbar spinal stenosis	2 (0.1)	0.02	7 (0.2)	0.07	3.24 (0.67, 15.6)
Musculoskeletal discomfort	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Intercostal myalgia	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Non-Hodgkin's lymphoma	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Esophageal carcinoma	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Neurosis	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Restlessness	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Urethral stenosis	2 (0.1)	0.02	7 (0.2)	0.07	3.24 (0.67, 15.6)
Metastases to lung	2 (0.1)	0.02	7 (0.2)	0.07	3.24 (0.67, 15.6)
Small cell lung cancer, metastatic	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Rash generalized	1 (0.0)	0.01	6 (0.2)	0.06	5.55 (0.67, 46.1)
Skin disorder	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)

*p=0.02

Reviewer comment:

The adverse events observed in the UPLIFT trial are consistent with the known adverse event profile of Spiriva HandiHaler. The findings of significant reductions in COPD exacerbation, dyspnea, and respiratory failure are supportive of the efficacy findings in the trial. Intestinal obstruction has not been mentioned previously in the Spiriva HandiHaler label, but could be consistent with the known anticholinergic side effect of constipation. No particular cardiac signals or stroke signals were identified.

Laboratory findings

There were no laboratory evaluations performed in this trial aside from pregnancy testing conducted at screening for women of childbearing potential.

ECG findings

There were no ECGs performed in this trial.

Physical examination

Vital signs were performed as part of the complete physical examination at the start and end of each patient's participation in the trial. Any new or clinically relevant worsening of baseline conditions detected at the follow up physical examination were reported as adverse events. The applicant did not conduct additional analyses of vital sign or physical examination data.

Safety conclusions

Overall, the total number of deaths during treatment (including the last day of study drug plus 30 days) was 792; 411 (13.7%) in the placebo group and 381 (12.8%) in the tiotropium group. Vital status information was known for 98% of tio HH18 treated patients and 97% of placebo treated patients including discontinued patients out to at least 45 months post-randomization. Compared to the on-treatment mortality, an additional 149 deaths were collected for patients who discontinued. The risk ratio for death from any cause (tiotropium/placebo) on treatment was 0.84 [95% CI (0.73, 0.97)]. The risk ratio for death remains significantly or nearly significantly different from placebo regardless of the cut off used or inclusion of vital status data.

The primary cause of each death in the UPLIFT trial was adjudicated by an independent committee. The most common causes (adjudicated) of death both on-treatment and including vital status were COPD exacerbation, lung cancer, and death of unknown cause. Combining the preferred terms of sudden death, sudden cardiac death, and death of unknown cause, 127 patients died with sudden or unknown causes of death. Of these, 70 (2.3%) were in the placebo group and 57 (1.9%) were in the tio HH18 group [RR=0.75, 95% CI (0.53, 1.06)]. The Risk Ratio for adverse events of stroke is less than one, and the upper bound of the confidence interval is less than 1.3, suggesting that if there is any adverse drug effect, it is minimal. Because stroke was a pre-specified term for the adjudication of cause of death, readers can have confidence that fatal strokes were appropriately classified and are not "hiding" under some other preferred term. Serious

adverse events and fatal adverse events of stroke are subgroups and as expected, have slightly wider confidence intervals, although the conclusions are the same.

Serious adverse events (SAEs) occurred in 50.9% of the overall study population, including 51.6% of the tio HH18 group and 50.2% of the placebo group. The most common SAEs were COPD exacerbation, pneumonia, and respiratory failure. SAEs were generally balanced between treatment groups. While the incidence of SAEs of respiratory failure is reduced in the tio HH18 group, the difference is marginally significant and there are multiple related preferred terms that have been analyzed separately. Unlike mortality, which is a hard endpoint and was pre-specified in the protocol as an event of interest (including vital status collection and an independent adjudication committee), the term "respiratory failure" is undefined and subject to investigator interpretation. There is insufficient evidence to justify a specific claim that Spiriva HandiHaler reduces respiratory failure.

There were 618 (20.7%) patients in the tio HH18 group and 735 (24.5%) patients in the placebo group who discontinued prematurely due to an adverse event. The most frequent AEs leading to discontinuation were all lower respiratory events—COPD exacerbation, dyspnea, pneumonia, and respiratory failure. A reduced number of patients in the tio HH18 group discontinued due to COPD exacerbations and dyspnea compared to the placebo group.

The most frequently reported AEs were COPD exacerbation, pneumonia, dyspnea, nasopharyngitis, and upper respiratory tract infection. If evaluated by exposure adjusted rates, COPD exacerbation, dyspnea, and respiratory failure occurred significantly less frequently in the tio HH18 group compared to placebo. In contrast, dry mouth and insomnia occurred significantly more frequently in the tio HH18 group. Dry mouth is a known anticholinergic side effect of tiotropium. In addition, although the numbers were small, intestinal obstruction occurred significantly more frequently in the tio HH18 group and could represent an anticholinergic side effect related to constipation.

Stroke is an adverse event of interest based on a potential safety signal observed in an analysis of combined tiotropium HandiHaler and Respimat trials. Stroke-related adverse events (AEs, SAEs, or fatal events) were not increased in the tio HH18 group relative to placebo.

Cardiovascular events are also adverse events of interest based on a potential safety signal observed in a meta-analysis literature report. There was no increase in adverse events of myocardial infarction in the tiotropium group compared to placebo, with a Risk Ratio of 0.71, 95% CI (0.52, 0.99). Overall, there was a borderline significant decrease in AEs in the cardiac SOC [RR 0.84, 95% CI (0.73, 0.98)], driven by a decrease in congestive heart failure and MI. Likewise, there was no increase in deaths due to cardiac disorders, sudden cardiac death, sudden death, or death due to unknown cause.

The PADAC voted that the UPLIFT trial adequately addressed potential safety signals of stroke and cardiovascular events for Spiriva HandiHaler.

10.1.3 Summary and conclusions

The UPLIFT study showed no significant difference between treatment groups in the primary endpoints of rate of decline in pre- and post-bronchodilator FEV1. In a subgroup analysis, patients who were sustained quitters from smoking did experience a significant decrease in rate of decline in FEV1 compared to sustained smokers. This effect was observed across both treatment groups.

The applicant offers two plausible explanations for the failure of the UPLIFT trial to demonstrate a difference in long-term rate of decline in FEV1, confounding by concomitant disease-modifying therapy and differential discontinuation biasing against tiotropium. While these effects may be real, the UPLIFT design overall was significantly strengthened by its "real world" approach to inclusion of multiple concomitant medications, similar to the situation encountered in the COPD population in the United States. Thus, one can conclude that in the setting of high-quality COPD care, the addition of tiotropium is unlikely to impact the natural history of disease.

For the key secondary endpoints of time to first COPD exacerbation and time to first COPD exacerbation leading to hospitalization, tiotropium showed significant decrease compared to placebo. For COPD exacerbations, the Applicant reports that patients in the tio HH18 group had a significantly longer time to event than patients in the placebo group ($p<0.0001$, RR 0.86, 95% CI 0.81-0.91). The median time to first exacerbation was 12.5 months in the placebo group and 16.7 months in the tio HH18 group. Patients in the tio HH18 group also had a statistically significantly longer time to first hospitalization due to COPD exacerbation compared to placebo ($p= 0.0024$, RR 0.86, 95% CI 0.78, 0.95). The lower quartile for time to first exacerbation requiring hospitalization was 28.6 months in the placebo group and 35.9 months in the tio HH group.

A significant improvement in most of the additional COPD exacerbation-related endpoints was also observed. These included the number of COPD exacerbations, time to first exacerbation treated with steroids, time to first exacerbation treated with antibiotics, number of exacerbations treated with steroids, number of exacerbation days, number of COPD exacerbations leading to hospitalization, and number of days hospitalized due to exacerbation per patient year. In conjunction with primary evidence from Protocol 205.266 (VA study, submitted under NDA 21-395, S-024), these data are generally supportive of an exacerbation claim. The exact wording of the claim will need consideration as various aspects of exacerbation were measured in this trial.

SGRQ endpoints included rate of SGRQ deterioration, as well as total and component SGRQ scores. There were no differences in rate of decline in SGRQ scores from month 6 until completion of treatment for the activity component, impact component, or total scores. The mean SGRQ scores showed a statistically significant but not clinically important decrease across all domains and timepoints for the tio HH18 group compared to placebo, with a treatment difference ranging from -2.30 to -3.35 ($p<0.0001$) for the total SGRQ score.

Spirometry endpoints included trough FEV_1, FVC, and SVC response and 90 minute FEV_1 FVC, and SVC response. Endpoints were measured every six months throughout the four year treatment period. Consistent with the known bronchodilator properties of the drug, the tio HH18 group generally demonstrated a significant improvement ($p<0.0001$) over placebo for all endpoints and time points tested.

Overall, the total number of deaths during treatment (including the last day of study drug plus 30 days) was 792; 411 (13.7%) in the placebo group and 381 (12.8%) in the tiotropium group. Vital status information was known for 98% of tio HH18 treated patients and 97% of placebo treated patients including discontinued patients out to at least 45 months post-randomization. Compared to the on-treatment mortality, an additional 149 deaths were collected for patients who discontinued. The risk ratio for death from any cause (tiotropium/placebo) on treatment was 0.84 [95% CI (0.73, 0.97)]. The risk ratio for death remains significantly or nearly significantly different from placebo regardless of the cut off used or inclusion of vital status data.

The primary cause of each death in the UPLIFT trial was adjudicated by an independent committee. The most common causes (adjudicated) of death both on-treatment and including vital status were COPD exacerbation, lung cancer, and death of unknown cause. Combining the preferred terms of sudden death, sudden cardiac death, and death of unknown cause, 127 patients died with sudden or unknown causes of death. Of these, 70 (2.3%) were in the placebo group and 57 (1.9%) were in the tio HH18 group [RR=0.75, 95% CI (0.53, 1.06)].

Overall, these data are supportive of a mortality claim, as UPLIFT is a major study that doubles the size of the safety database, prespecified mortality endpoints and vital status collection were appropriately collected and adjudicated, and the salutary effect on mortality is robust across multiple different analyses. In addition, the mortality benefit was driven by a reduction in fatal COPD exacerbations, suggesting a plausible mechanism of action. However, outstanding issues with regards to mortality with Spiriva Respimat temper such a claim. Also, the mortality benefit was observed in only a single, albeit very large, trial. The Pulmonary and Allergy Drugs Advisory Committee (PADAC), in their meeting on November 19, 2009, concluded that UPLIFT was a compelling and important study, demonstrating generally beneficial effects on mortality. Although the Respimat results were felt to be somewhat concerning and additional data are needed, the Respimat results do not necessarily convey to the HandiHaler.

Serious adverse events (SAEs) occurred in 50.9% of the overall study population, including 51.6% of the tio HH18 group and 50.2% of the placebo group. The most common SAEs were COPD exacerbation, pneumonia, and respiratory failure. SAEs were generally balanced between treatment groups. While the incidence of SAEs of respiratory failure is reduced in the tio HH18 group, the difference is marginally significant and there are multiple related preferred terms that have been analyzed separately. Unlike mortality, which is a hard endpoint and was pre-specified in the protocol as an event of interest (including vital status collection and an independent adjudication committee), the term “respiratory failure” is undefined and subject to investigator interpretation. There is insufficient evidence to justify a specific claim that Spiriva HandiHaler reduces respiratory failure.

There were 618 (20.7%) patients in the tio HH18 group and 735 (24.5%) patients in the placebo group who discontinued prematurely due to an adverse event. The most frequent AEs leading to discontinuation were all lower respiratory events—COPD exacerbation, dyspnea, pneumonia, and respiratory failure. A reduced number of patients in the tio HH18 group discontinued due to COPD exacerbations and dyspnea compared to the placebo group.

The most frequently reported AEs were COPD exacerbation, pneumonia, dyspnea, nasopharyngitis, and upper respiratory tract infection. If evaluated by exposure adjusted rates, COPD exacerbation, dyspnea, and respiratory failure occurred significantly less frequently in the tio HH18 group compared to placebo. In contrast, dry mouth and insomnia occurred significantly more frequently in the tio HH18 group. Dry mouth is a known anticholinergic side effect of tiotropium. In addition, although the numbers were small, intestinal obstruction occurred significantly more frequently in the tio HH18 group and could represent an anticholinergic side effect related to constipation.

Stroke is an adverse event of interest based on a potential safety signal observed in an analysis of combined tiotropium HandiHaler and Respimat trials. Stroke-related adverse events (AEs, SAEs, or fatal events) were not increased in the tio HH18 group relative to placebo.

Cardiovascular events are also adverse events of interest based on a potential safety signal observed in a meta-analysis literature report. There was no increase in adverse events of myocardial infarction in the tiotropium group compared to placebo, with a Risk Ratio of 0.71, 95% CI (0.52, 0.99). Overall, there was a borderline significant decrease in AEs in the cardiac SOC [RR 0.84, 95% CI (0.73, 0.98)], driven by a decrease in congestive heart failure and MI. Likewise, there was no increase in deaths due to cardiac disorders, sudden cardiac death, sudden death, or death due to unknown cause.

The PADAC voted that the UPLIFT trial adequately addressed potential safety signals of stroke and cardiovascular events for Spiriva HandiHaler.

10.2 Line-by-Line Labeling Review

10.2.1 PLR format

In addition to the proposed exacerbation claim language, Boehringer Ingelheim proposes changing the Spiriva HandiHaler label into the new PLR format. The following clinical comments were provided to the Applicant on November 5, 2009 in addition to a number of small edits directly to the text of the label.

<u>General Labeling Comments</u>

13. We have not included comments regarding your proposed language for the UPLIFT trial (Protocol 205.235). We will provide comments regarding the UPLIFT trial after

the Pulmonary Allergy Drugs Advisory Committee meeting to be held on November 19, 2009.

Highlights of Prescribing Information

14. The Adverse Reactions section of HIGHLIGHTS should contain a list of adverse reactions that are included in Table 1. Inclusion of adverse reactions from the Spiriva HandiHaler placebo controlled trials is acceptable.

Full Prescribing Information

15. In Section 4, Contraindications, include hypersensitivity to tiotropium or any ingredients in Spiriva HandiHaler. Include descriptions of hypersensitivity reactions that have occurred in patients receiving Spiriva HandiHaler from clinical trials and post-marketing. For example, "In clinical trials and post-marketing experience with Spiriva HandiHaler, cases of X, X, X have been reported."

16. In Section 5.2, Warnings and Precautions, Immediate Hypersensitivity Reactions, include a brief list of hypersensitivity reactions that have occurred in clinical trials or post-marketing with Spiriva HandiHaler or refer back to Section 4 for the list.

17. Delete Section 5.4 and create two separate sections (5.4 and 5.5) to highlight the potential eye and urinary issues with Spiriva HandiHaler. For example:

    5.4 Worsening of Narrow-Angle Glaucoma

    5.5 Urinary Retention.

18. In the two distinct sections noted in Comment #5 above, include relevant information from clinical trials or post-marketing regarding these potential effects. Include information for prescribers and patients, e.g. "Prescribers and patients should be alert for be signs of acute narrow-angle glaucoma, e.g. eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema. Instruct patients to consult a physician immediately should any of these signs and symptoms develop."

19. In Section 6, Adverse Reactions, revise the 3rd bullet regarding anticholinergic effects to be consistent with the revised sections 5.4 and 5.5.

20. We note that you have [redacted] (b) (4) Replace these data in Table 1 and the sentence immediately after Table 1 as per the currently approved label. The purpose of inclusion of these data is to provide a more complete picture of the Spiriva HandiHaler adverse reaction profile. While we generally do not include active controlled clinical trial information in product labels, inclusion of active controlled clinical trial information can be useful in certain situations, e.g. transitioning from a short acting to long acting product, such as Spiriva HandiHaler.

21. Include a brief description of demographic data from your trials in Section 6.1, Adverse Reactions, Clinical Trial Experience. Include a description of the overall clinical trial database from which adverse reaction data have been drawn, including a

discussion of overall exposure (number of patients, dose schedule, duration) and demographics of the exposed population.

22. The multiple different presentations of adverse reaction data in Section 6, Adverse Reactions, seem disjointed, i.e. Table 1, ≥3% but <1% greater than placebo, 1-3%, <1% and Additional Adverse Reactions. Consider combining some of the information to improve the readability of the section.

23. We have revised Section 12.2, Clinical Pharmacology, Pharmacodynamics, to include QT study language that was approved for Supplement S-027 on November 13, 2008.

Patient's Instructions for Use

24. Revise the Patient Instructions for Use (PIU) to include language that was approved for Supplement S-014 on March 3, 2009. Also include figures in the PIU you submitted as an amendment to S-029 on July 28, 2009.

10.2.2. New language

Numerous comments regarding labeling can be found throughout this review, and the proposed language from the Applicant has changed over the course of the review period. General comments regarding new language in the label include the following:

- Reduction in COPD exacerbations is considered a new label indication. List reduction in COPD exacerbations in the indications section in addition to a description in the clinical trials section.
- Efficacy data from Spiriva Respimat do not apply to Spiriva HandiHaler because the two locally acting formulations are considered different drug products (b) (4)
- The VA study is the primary trial supporting efficacy for COPD exacerbations and should be described in the label.
- The claim for a (b) (4) is not supported. (b) (4)

REFERENCES

Reference List

1. Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease. JAMA 2008; 300(12):1439-1450.

2. Anthonisen NR, Connett JE, Kiley JP et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1: the Lung Health Study. JAMA 1994; 272:1497-1505.

3. Fletcher C, Peto R. The natural history of chronic airflow obstruction. British Medical Journal 1977; 1:1645-1648.

4. Suissa S. Statistical treatment of exacerbations in therapeutic trials of chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine 2008; 173:842-846.

5. Smeeth L, Haines A, Ebrahim S. Numbers needed to treat derived from meta-analyses--sometimes informative, usually misleading. British Medical Journal 1999; 318:1548-1541.

6. Singh S, Loke YK, Furberg CD. Corrections to Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease. JAMA 2009; 301(12):1227-1230.

7. Lanes SGW, Mikl J. Ipratropium and the Lung Health Study. American Journal of Respiratory and Critical Care Medicine 2003; 167:801-802.

8. Wilson CB, Jones PW, O'Leary CJ, Cole PJ, Wilson R. Validation of the St. George's Respiratory Questionnaire in bronchiectasis. American Journal of Respiratory and Critical Care Medicine 1997; 156:536-541.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21395	SUPPL-29	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	SPIRIVA HANDIHALER

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

THERESA M MICHELE
11/30/2009

SALLY M SEYMOUR
12/01/2009
I concur.

MEDICAL OFFICER REVIEW
Division Of Pulmonary and Allergy Products (HFD-570)

APPLICATION:	NDA 21-395 SE8-029	**TRADE NAME:**	Spiriva® HandiHaler
APPLICANT/SPONSOR:	Boehringer Ingelheim	**USAN NAME:**	Tiotropium bromide
MEDICAL OFFICER:	Theresa M. Michele, M.D.		
TEAM LEADER:	Sally Seymour, M.D.	**CATEGORY:**	Anticholinergic bronchodilator
DATE:	January 16, 2009	**ROUTE:**	Inhaled

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
Nov 17, 2008	Nov 17, 2008	NDA 21-395, SE08-029	NDA efficacy supplement

RELATED APPLICATIONS

Document Date	Application Type	Comments
Jan 14, 2008	NDA 21-395, SE08-024	NDA efficacy supplement
Nov 17, 2008	IND 46,687, Doc 322	Clinical study report 205.235
Nov 16, 2007	NDA 21-936	Tiotropium inhalation spray using Respimat
Dec 12, 2001	NDA 21-395	Tiotropium inhalation powder using HandiHaler

REVIEW SUMMARY:

This NDA is an efficacy supplement for tiotropium bromide dry powder inhaler. The applicant is Boehringer Ingelheim Pharmaceuticals, Inc. The current indication is for once-daily maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. Tiotropium is a long-acting anticholinergic intended for use with the HandiHaler at a dose of 18 mcg (1 inhalation) once daily. The sponsor proposes the following new efficacy claims in the clinical trials section of the product label: 1) description of the long-term effects on lung function, 2) reduction in exacerbations, 3) reduction in mortality, and 4) reduction in respiratory failure.

A single large 4-year placebo-controlled clinical trial of tiotropium HandiHaler was conducted in support of the exacerbations claim (UPLIFT trial), and was submitted as part of this application. In addition, the sponsor proposes to use data from the VA trial (205.266), previously reviewed under S024, to provide supportive data for the exacerbations claim.

The data from the UPLIFT trial submitted in this application (205.235) is important for evaluation of the recent mortality, stroke, and cardiovascular signals observed with tiotropium. It is anticipated that this application and potential safety issues with Spiriva will be discussed at a Pulmonary Advisory Committee meeting.

The submission is adequate to allow for clinical review. The submission is fileable. The clinical team has requested additional information regarding the UPLIFT study (205.235) from the sponsor.

OUTSTANDING ISSUES:

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS:	**FILEABLE**___X____	**NOT FILEABLE**_____	
	APPROVAL_____	**APPROVABLE**_____	**NOT APPROVABLE**_____
OTHER ACTION:	**COMMENTS FOR SPONSOR**_____X_		

1. GENERAL INFORMATION

Tiotropium bromide dry powder inhaler (HandiHaler inhalation device, 18 mcg tiotropium) was approved on January 30, 2004 (NDA 21-395) for the long-term, once-daily maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. Tiotropium is a specific antagonist at muscarinic acetylcholine receptors, often called anticholinergic. The applicant, Boehringer Ingelheim Pharmaceuticals, Inc., now seeks additional efficacy claims for the HandiHaler with an additional 3 years of marketing exclusivity. Requested efficacy claims included in the clinical trials section are: 1) description of the long-term effects on lung function, 2) reduction in exacerbations, 3) reduction in mortality, and 4) reduction in respiratory failure.

The application is provided electronically. A paper submission of the clinical trial report from this NDA is provided under IND 46,687 Document Number 322.

2. CLINICAL DEVELOPMENT PROGRAM

The sponsor has conducted one study (205.235, UPLIFT) in support of the labeling claims, which are presented in Table 1. In addition, Study 205.266 in support of the exacerbation claim was previously reviewed under NDA 21-395 S024.

Table 1: Clinical studies submitted for NDA 21-395 SE024

Trial No.	Trial description	Patient population	N	Country
Spiriva HandiHaler Phase 3b program				
205.235	4-year, randomized, double-blind, placebo-controlled , parallel group trial (UPLIFT)	COPD	5993	multinational
205.266	6-month trial with proportion of patients with at least one COPD exacerbation as primary endpoint	COPD (Veterans Affairs)	1829	US

Reviewer comment:

The UPLIFT study provides long-term data on nearly 3000 patients exposed to tiotropium over a 4 year period, doubling the size of the safety database. In addition to the efficacy parameters evaluated, it provides key safety data that has implications for both Spiriva HandiHaler (the product evaluated in this NDA) and Spiriva Respimat (NDA 21-936, Complete Response September 16, 2008).

3. FOREIGN MARKETING AND REGULATORY HISTORY

The HandiHaler formulation of tiotropium bromide was approved on January 30, 2004 for the chronic treatment of bronchospasm associated with COPD, and is marketed worldwide. The

sponsor is requesting a full waiver from pediatric studies for this application. A waiver for pediatric studies was previously granted for the HandiHaler program.

In efficacy supplement S024, Boehringer Ingelheim requested that claims be added to the clinical studies section of the label regarding reduction of COPD exacerbations based on Study 205.266 (See Table 1). This application received a Complete Response letter on November 13, 2008 because the efficacy data was not replicated. The current application (S029) is expected to form the basis for a complete response for S024, although BI has not yet submitted a formal complete response. Three potential safety signals are under FDA evaluation for tiotropium: 1) mortality, 2) stroke, and 3) cardiovascular events.

An increased number of deaths in the tiotropium groups compared to placebo were observed in the Phase 3 pivotal trials for Spiriva Respimat (205.254 and 205.255), reviewed under NDA 21-936. This issue was reviewed by the Drug Safety Oversight Board on June 15, 2006, as well as in an internal Regulatory Briefing on July 18, 2008. No increase in mortality has been observed in the HandiHaler program, but the issue is relevant because both products contain the same active ingredient, tiotropium bromide. On the basis of this potential safety signal, Spiriva Respimat NDA 21-936 received a Complete Response action on September 16, 2008. It is anticipated that the current submission will form the primary basis of the complete response to NDA 21-936, which has not yet been submitted.

In November 2007, BI submitted an information amendment to the IND providing data regarding an increased incidence of stroke with tiotropium in a pooled analysis of 29 studies involving both the HandiHaler and Respimat devices. FDA issued an early communication regarding this potential safety issue on March 18, 2008, which was updated on October 10, 2008.

The third potential safety signal, increased cardiovascular events, is based on two recent publications which reported increased risk for cardiovascular events and cardiovascular mortality in patients who received tiotropium or ipratropium (a short-acting anticholinergic). Singh et al.[1] performed a systematic review and meta-analysis of 17 clinical trials enrolling 14,783 patients treated with inhaled anticholinergic drugs used for the treatment of chronic obstructive lung disease. Lee et al.[2] performed a case-control study of 32,130 patients (320,501 controls) treated with inhaled medications, including an anticholinergic, for the treatment of chronic obstructive lung disease.

Reviewer comment:

An application for a full waiver was submitted to the Pediatric Review Committee. Because COPD is a disease that occurs only in the adult population, granting of a full waiver is anticipated.

The data from the trial submitted in this application (205.235) is important for evaluation of the mortality, stroke, and cardiovascular signals observed with tiotropium. It is anticipated that this application and potential safety issues with Spiriva will be discussed at a Pulmonary Advisory Committee meeting.

4. ITEMS REQUIRED FOR FILING (21 CFR 314.50)

The following items pertinent to a clinical review are included in the submission.

- Application form (FDA 356h) [m1/us/356h.pdf]

- Index [m5/clintoc.pdf]
- Summary—not provided
- Clinical technical section
  - Clinical study reports
    - Study report 205.235 [m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235]
    - Reports of analyses of data from more than one study [m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5353-rep-analys-data-more-one-stud]
  - Integrated summary of efficacy –not applicable
  - Integrated summary of safety—not applicable (although majority of information provided under reports of analyses of data form more than one study)
  - Good Clinical Practice certification [m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/0205-0235—01-15-study-report-body.pdf, Section 5.2, page 41]
  - Debarment certification [m1/us/debar-certification.pdf]
  - Pediatric use [m1/us/pediatric-waiver.pdf]
- Labeling [m1/us/labeling]
- Case report forms [m5/53-clin-stud-rep/535-rep-effic-safety-stud/COPD/5351-stud-rep-contr/0205-0235/crfs]
- Financial disclosure [m1/us/financial-cert-and-disclosure.pdf]

5. CLINICAL STUDIES

The sponsor is referencing 2 clinical trials in this application. See Table 1. One trial, 205.266, evaluated the effect of tiotropium HandiHaler on COPD exacerbations in a Veterans Affairs population. This study was previously submitted and reviewed under S024. Study 205.235 (UPLIFT) was submitted and will be reviewed under this application, S029. Both studies referenced in this submission are summarized below.

5.1. Study 205.266

Study 205.266 was a randomized, double-blind, placebo-controlled, parallel group trial assessing the proportion of patients experiencing an exacerbation and proportion of patients hospitalized for an exacerbation over 6 months during treatment with tio HH in patients with COPD in a Veterans Affairs setting. A total of 1829 patients with moderate to severe COPD ($FEV_1 \leq 60\%$ predicted) were randomized, 914 to tio HH and 915 to placebo. Of these, 1640 (89.7%) completed the study. The co-primary endpoints were the proportion of patients with an exacerbation of COPD and the proportion of patients hospitalized for a COPD exacerbation during the 6-month treatment period. Secondary endpoints included time to exacerbations, number of days of exacerbation therapies, total number of exacerbations, hospitalizations, and

trough FEV_1 and FVC. A significantly smaller proportion of patients in the tio HH group had a COPD exacerbation (27.9% vs. 32.3%, respectively, p=0.0368). While a smaller proportion of patients in the tio HH group were hospitalized for a COPD exacerbation, this result did not reach statistical significance. There was also a significant decrease in mean number of exacerbations per patient-year, number of exacerbation days, number of days of antibiotics used to treat exacerbations, number of days of steroids, and number of unscheduled visits for exacerbations. The time to first exacerbation was significantly increased in the tio HH group compared to placebo.

Due to the extensive safety database available for the HandiHaler, only serious adverse events were systematically collected for this trial. The proportion of SAEs was similar between the treatment groups (17.7% tio HH vs. 17% placebo). There were 67 deaths during the trial, 5 during the screening period, 41 during the treatment period, and 21 during the post-treatment period. Deaths occurring during the treatment period were generally balanced between the treatment groups (22 in the tio HH and 19 in the placebo group). The majority of deaths were secondary to respiratory events. [Module 5, Volume 1.17, Study report 205.266, pages 3-7]

Reviewer comment:

Analysis of results was also performed for the following subgroups in study 205.266: race, age, smoking history, inhaled corticosteroid use, theophylline use, COPD severity, prior COPD hospitalizations, steroid use, antibiotic use, home oxygen use, and long-acting ß-agonist use.

5.2. Study 205.235 (UPLIFT)

Study 205.235 was a randomized, double-blind, placebo-controlled parallel group trial assessing the rate of decline of lung function over 4 years with tio HH in patients with COPD. The short title of this study is UPLIFT: Understanding Potential Long-term Impacts on Function with Tiotropium. A total of 5993 patients with moderate to severe COPD ($FEV_1 \leq 70\%$ predicted) were randomized, 2986 to tio HH and 3006 to placebo. Of these, 3535 (59.0%) completed all 4 years of the study, 1648 (45.2%) in the placebo group and 1887 (63.2%) in the tio HH group. The co-primary endpoints were the yearly rate of decline in trough (pre-bronchodilator) FEV_1 and yearly rate of decline in post-bronchodilator FEV_1. Key secondary endpoints were time to first COPD exacerbation and time to first COPD exacerbation leading to hospitalization. A number of other exacerbation endpoints, various other lung function endpoints, and the St. George's Respiratory Questionnaire (SGRQ) were also included. There was no difference in rate of decline of either pre- or post-bronchodilator FEV_1, although benefits in lung function and SGRQ were maintained throughout the study. Tio HH significantly increased the time to first COPD exacerbation and time to first COPD exacerbation leading to hospitalization. In addition, patients in the tio HH group had significantly fewer COPD exacerbations (0.85 vs. 0.73, p<0.0001) and exacerbation days (13.6 vs. 12.1, p=0.001) per patient year.

The safety endpoints included all adverse events, all-cause mortality, and lower respiratory mortality. All deaths were adjudicated by a central committee, and patients who discontinued trial medication were followed for outcome. Vital status was known for 97.6% of randomized patients. No increased incidence of stroke, cardiovascular events, or pneumonia was observed in the tio HH group compared to placebo. There was a lower rate of death during treatment with tio HH than with placebo (Hazard Ratio 0.84; 95% CI, 0.73-0.97).

Reviewer comment:

Analyses of FEV1 and mortality results were also performed for the following subgroups in study 205.266: age, gender, smoking status, inhaled corticosteroid use, LABA use, COPD severity (GOLD stage), race, region, reversibility of FEV1, and body mass index (BMI). Subgroup analyses were not performed for other endpoints in the study Evaluation by subgroup will also be required for COPD exacerbation (major labeling claim) and adverse events, including stroke and cardiovascular events.

6. BRIEF REVIEW OF PROPOSED LABELING

Proposed package labeling has been included in this submission [m1/us/labeling]. A brief review of the proposed labeling was performed. The content and format of the proposed labeling is presented in the new Physicians Labeling Rule (PLR) format, building on the submitted (unapproved) label from the S024 supplement. Two other labeling supplements were outstanding as of the time of this submission: 1) S-014 providing for a new Patient Package Insert (originally submitted August 3, 2006), and 2) S-027 providing for revised text in the Clinical Pharmacology Electrophysiology section (originally submitted April 5, 2006). The submitted label for this S-029 supplement includes current text from all 3 outstanding supplements. S-027 has subsequently been approved, and S-014 is nearing completion of the approval process.

The applicant has not requested any new indications. Requested efficacy claims included in the clinical trials section of the label are: 1) description of the long-term effects on lung function, 2) reduction in exacerbations, 3) reduction in mortality, and 4) reduction in respiratory failure. The efficacy evaluation of this application will focus on these claims.

7. DSI REVIEW AND AUDIT

The UPLIFT study in this submission is a key study in the Spiriva program due both to its length and scope. Based on this study, several important efficacy claims are under evaluation. Of even more importance are the safety implications of a 6000 patient, 4 year study. The study was conducted multinationally and included a total of 5 world regions (US, Western Europe, Eastern Europe, Latin America, and Asia), 37 countries, and 487 sites. Given the size and importance of the study, preliminary discussions were held with Dr. Tejashri Purohit-Sheth in DSI regarding site selection for audit. She suggested that for this study, a larger number of sites should be audited than for most applications (3-4 sites in the US and 3-4 sites ex-US).

Sites were reviewed for audit selection based on the following criteria: 1) enrollment, 2) region, 3) previous audit (BI or FDA), and financial disclosure. In addition, Dr. Joan Buenconsejo, FDA statistician for this application, is reviewing sites for outliers based on mortality and FEV1. The application did not contain information on death and protocol violations by site. This information has been requested from BI.

Based on the information reviewed to date, a preliminary list of sites has been identified for inspection. See Table 2. This list will be refined based on the statistical review and information request from the applicant.

Table 2: Preliminary audit choices

Site Number	Investigator	Location	# Enrolled
		US Sites	
3732	Eichenhorn	Henry Ford-Detroit	127
3701	Altose	VA-Cleveland	78
3741	Greenwald	Rancho Mirage, CA	58
		Ex-US Sites	
1317	Szalai	Mosonmagyarovar, Hungary	38
1802	Bagdonas	Kaunas, Lithuania	36
2004	Valay	Monterrey, Mexico	32
1402	Yu	Kowloon, Hong Kong	25

8. SUMMARY

This NDA is an efficacy supplement for tiotropium bromide dry powder inhaler. The applicant is Boehringer Ingelheim Pharmaceuticals, Inc. The current indication is for once-daily maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. Tiotropium is a long-acting anticholinergic intended for use with the HandiHaler at a dose of 18 mcg (1 inhalation) once daily. The sponsor proposes the following new efficacy claims in the clinical trials section of the product label: 1) description of the long-term effects on lung function, 2) reduction in exacerbations, 3) reduction in mortality, and 4) reduction in respiratory failure.

A single large 4-year placebo-controlled clinical trial of tiotropium HandiHaler was conducted in support of the exacerbations claim (UPLIFT trial), and was submitted as part of this application. In addition, the sponsor proposes to use data from the VA trial (205.266), previously reviewed under S024, to provide supportive data for the exacerbations claim.

The data from the UPLIFT trial submitted in this application (205.235) is important for evaluation of the recent mortality, stroke, and cardiovascular signals observed with tiotropium. It is anticipated that this application and potential safety issues with Spiriva will be discussed at a Pulmonary Advisory Committee meeting.

The submission is adequate to allow for clinical review. The submission is fileable. The clinical team has requested additional information regarding the UPLIFT study (205.235) from the sponsor.

9. REVIEW TIMELINE

The schedule for review is provided in Table 3. Write-up will be concomitant with the review process. Clinical review will focus on the UPLIFT study (205.235). The review will culminate with the proposed label. It is anticipated that the primary clinical review will be included in the background package for the AC meeting. Therefore, the time frame for completing the review is moved up. The initial draft review will be complete by May 15, 2009, and the final draft review

(for inclusion in the AC background package) will be completed on June 1, 2009. The review will be finalized July 24, approximately two months in advance of the action date.

Table 3: Review timeline for NDA 21-936

Milestone	Target date for completion
(b) (4)	(b) (4)

10. REFERENCES

1. Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease. JAMA 2008; 300 (12): 1439-1450.

2. Lee TA, Pickard S, et al. Risk of Death Associated with Medications for Recently Diagnosed Chronic Obstructive Pulmonary Disease. Annals of Internal Medicine 2008; 149: 380-390.

11. INFORMATION REQUEST SENT TO THE SPONSOR

The following information requests were sent to the sponsor:

1. Provide summary tables and data listings by investigative site for the following:
   a. Protocol violations
   b. Deaths

2. Provide subgroup analyses for the following endpoints, using the same subgroups as per your subgroup analyses for mortality and FEV1.
   a. Time to first COPD exacerbation
   b. Time to first COPD exacerbation leading to hospitalization
   c. Number of COPD exacerbations per patient year
   d. Adverse events: individual, serious, cardiovascular events, stroke events
3. Provide the following documents:
   a. Data Safety Monitoring Board Charter and meeting minutes
   b. Mortality Adjudication Committee Charter and meeting minutes
   c. Data Handling Guidelines
   d. Clinical Data Monitoring Plan

12. COMMENTS FOR THE SPONSOR

At this time, no additional comments are to be communicated to the sponsor.

Reviewed by:

_____
Theresa M. Michele, M.D.
Medical Officer, Division of Pulmonary and Allergy Products

_____
Sally Seymour, M.D.
Medical Team Leader, Division of Pulmonary and Allergy Products

cc: Original NDA
HFD-570/Division File
HFD-570/Seymour/Medical Team Leader
HFD-570/Chowdhury/Director
HFD-570/Michele/Medical Reviewer
HFD-715/Buenconsejo/Biometrics Reviewer
HFD-570/Pei/Pharmacology-Toxicology Reviewer
ONDQA/Raghavachari/CMC Reviewer
OCP/Suarez/Clinical Pharmacology Reviewer
HFD-570/Raggio/CS

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/s/

Theresa M Michele
1/16/2009 01:00:30 PM
MEDICAL OFFICER

Sally Seymour
1/20/2009 10:18:36 AM
MEDICAL OFFICER
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-395/S029

CHEMISTRY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
OFFICE OF NEW DRUG QUALITY ASSESSMENT

POST-MARKETING EVALUATION
CMC ASSESSMENT FORM

APPLICANT: BOEHRINGER PHARMS	NDA NUMBER: 021395	DOC TYPE: SE8	SEQ NUMBER: 029	SUBMISSION TYPE: ORIGINAL
PROPRIETARY NAME: SPIRIVA HANDIHALER		ESTABLISHED NAME: TIOTROPIUM BROMIDE		
DOSAGE FORM: AER	STRENGTH/POTENCY: 18 MCG/INHALATION		PHARMACOLOGICAL CATEGORY:	
LETTER DATE: 11/17/2008	STAMP DATE: 11/18/2008	PDUFA GOAL DATE: 12/18/2009	SUBMISSION (CHECK ONE) FIRM: PA FINAL: PA	
DIVISION IV BRANCH: VII	OND DIVISION: 570	MANAGED BY: OND	PAL: Raghavachari MEDIA SUBMISSION: Electronic	
SUPPLEMENT PROVIDES FOR: Clinical trial report for a multi-center study and labeling changes to the Clinical Trials and Adverse Reactions sections. Exacerbation claims.				
BUNDLED: No				
CHANGE CATEGORY: Efficacy Supplement				
LABELING INVOLVED: Yes - PI only	PAT: No	COMPARABILITY PROTOCOL: No	PHASE 4 COMMITMENT:	
REVIEW PATH: 6 - OND Multi-Discipline Review				
CONSULTS:				

Review: The applicant has proposed labeling changes based on the clinical studies report U08-3718-03 (205.235). This is an efficacy supplement for exacerbation claims and there are no CMC changes proposed.
Also the applicant has proposed conversion to SPL labeling format under PLR.

The applicant has requested categorical exclusion from preparing an Environmental Assessment for this supplement under 21 CFR 25.31(b). The applicant states that the total estimated drug substance concentration at the point of entry into the aquatic environment will be below one part per billion i.e. 0.0003 µg /L (ppb). The applicant also states that they have no knowledge of any extraordinary circumstances to suggest that the proposed action would affect the quality of the human environment, under 21 CFR 25.15(d).

Evaluation and Comments:
Based on the information provided categorical exclusion may be granted.

PAL ACTION: PA (Path-6)
BRANCH CHIEF: James D. Vidra
COMMENTS:

Based on the information provided categorical exclusion may be granted.
From CMC point of view this supplemental application is recommended for approval.

BRANCH CHIEF ACTION: Recommends approval from CMC point of view.
REVIEWER: Ramesh
REVIEWER ACTION:

From CMC point of view recommended for approval.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21395	SUPPL-29	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	SPIRIVA HANDIHALER

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/s/

RAMESH RAGHAVACHARI
12/01/2009

JAMES D VIDRA
12/01/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-395/S029

PHARMACOLOGY REVIEW(S)

INTEROFFICE MEMO

TO: NDA 21-395
Sequence number/date/type of submission: S029/November 17, 2008/SE8

FROM: Jean Q Wu, M.D., Ph.D.
Acting Pharmacology/Toxicology Supervisor
Division of Pulmonary and Allergy Products

DATE: July 30, 2009

Spiriva HandiHaler is an approved and currently marketed product. The supplement contained no new nonclinical data. In Dr. Luqi Pei's primary review dated July 15, 2009, the nonclinical sections of the labeling were reviewed and the labeling changes were recommended to make the new label conform the Physician Labeling Rule. I concur with the recommendations made in Dr. Pei's primary review for this supplement.

_____
Jean Q Wu, M.D., Ph.D.
Acting Pharmacology/Toxicology Supervisor

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 21395	SUPPL 29	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	SPIRIVA HANDIHALER

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/s/

JEAN Q WU
07/30/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

Labeling Review

NDA NUMBER:	**21-395**
SERIAL NUMBER:	**029/SE8**
DATE RECEIVED BY CENTER:	**November 17, 2008**
PRODUCT:	**Spiriva® Handihaler® (Tiotropium Bromide) Powder Inhaler**
INTENDED CLINICAL POPULATION:	**Bronchospasm and dyspnea associated with chronic obstructive pulmonary disease (COPD)**
SPONSOR:	**Boehringer Ingelheim Pharmaceutical Inc.**
DOCUMENTS REVIEWED:	**Proposed labeling – nonclinical sections**
REVIEW DIVISION:	**Pulmonary and Allergy Products**
PHARM/TOX REVIEWER:	**Luqi Pei, Ph.D.**
PHARM/TOX SUPERVISOR (Acting):	**Jean Wu, M.D., Ph.D.**
DIVISION DIRECTOR:	**Badrul Chowdhury, M.D., Ph.D.**
PROJECT MANAGER:	**Miranda Raggio**

Date of review submission to Division File System (DFS): July 15, 2009

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

Not applicable. Spiriva HandiHaler is an approved and currently marketed product. There is no new, significant nonclinical data that could affect the safety assessment of the drug.

B. Recommendation for nonclinical studies

None.

C. Recommendations on labeling

Edits were made to nonclinical sections of the proposed labeling. The edits were made so that the newly approved labeling will conform to the Draft Guidance for Industry "Labeling for Human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements" (January 2006). The edits and rationales for the edits can be found in the Labeling Review of the document (next page).

II. Summary of nonclinical findings

Not applicable. The supplement contained no new, additional nonclinical data.

Labeling Review

Edits and revisions of nonclinical sections of the proposed product label submitted on November 17, 2008 (Supplement 029/SE8) are recommended. These edits were made to ensure that newly approved labeling will conform to the Draft Guidance for Industry "Labeling for Human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements" (January 2006).

The proposed labeling retained the content of the labeling of the currently marketed product. The format of the labeling was generally in compliance with the new labeling initiative. It included appropriate sections and headings such as Sections 8.1 (Pregnancy), 10 (Overdosage), 13 (Nonclinical Toxicology) and 13.1 (Carcinogenicity …). It, however, lacked Section 13.2 – Animal Toxicology and Pharmacology.

The major edits and revisions to the proposed labeling included the following aspects: 1) creation of Section 13.2 – Animal Toxicology and Pharmacology/reproductive toxicology, 2) relocation of the proposed text of Section 8.1 to Section 13.2, 3) creating new text for Section 8.1 and 4) changing the acronym RHDD to RHDID (the recommended human daily inhalation dose). Suggested inserts are presented as underlines and suggested deletions are presented as strikeouts.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects:~~,~~ Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women. SPIRIVA HandiHaler should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

No evidence of structural alterations was observed in rats and rabbits at inhalation tiotropium doses of up to ~~1.471 and 0.007 mg/kg/day, respectively. These doses correspond to~~ approximately 660 and 6 times the maximum recommended human daily inhalation dose (RHDID) on a mg/m^2 basis. However, in rats, tiotropium caused fetal resorption, litter loss, decreases in the number of live pups at birth and the mean pup weights, and a delay in pup sexual maturation ~~were observed~~ at inhalation ~~tiotropium~~ doses of ~~≥0.078 mg/kg (~~approximately 35 times the RHDID on a mg/m^2 basis~~)~~. In rabbits, tiotropium caused an increase in post-implantation loss ~~was observed~~ at an inhalation dose of ~~0.4 mg/kg/day (~~approximately 360 times the RHDID on a mg/m^2 basis~~)~~. Such effects were not observed at inhalation tiotropium doses ~~of 0.009 and up to 0.088 mg/kg/day in rats and rabbits, respectively. These doses correspond to~~ approximately 4 and 80 times the RHDID on a mg/m^2 basis, respectively. These dose multiples may be over-estimated due to difficulties in measuring deposited doses in animal inhalation studies.

~~There are no adequate and well-controlled studies in pregnant women. SPIRIVA HandiHaler should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.~~

10 OVERDOSAGE

…

No mortality was observed at inhalation tiotropium doses up to 32.4 mg/kg in mice, 267.7 mg/kg in rats, and 0.6 mg/kg in dogs. These doses correspond to 7,300, 120,000, and 850 times the recommended human daily dose on a mg/m^2 basis, respectively. These dose multiples may be over-estimated due to difficulties in measuring deposited doses in animal inhalation studies.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of tumorigenicity was observed in a 104-week inhalation study in rats at tiotropium doses up to 0.059 mg/kg/day, in an 83-week inhalation study in female mice at doses up to 0.145 mg/kg/day, and in a 101-week inhalation study in male mice at doses up to 0.002 mg/kg/day. These doses correspond to approximately 25, 35, and 0.5 times the Recommended Human Daily inhalation Dose (RHDID) on a mg/m^2 basis, respectively. These dose multiples may be over-estimated due to difficulties in measuring deposited doses in animal inhalation studies.

Tiotropium bromide demonstrated no evidence of mutagenicity or clastogenicity in the following assays: the bacterial gene mutation assay, the V79 Chinese hamster cell mutagenesis assay, the chromosomal aberration assays in human lymphocytes *in vitro* and mouse micronucleus formation *in vivo*, and the unscheduled DNA synthesis in primary rat hepatocytes *in vitro* assay.

In rats, decreases in the number of corpora lutea and the percentage of implants were noted at inhalation tiotropium doses of 0.078 mg/kg/day or greater (approximately 35 times the RHDID on a mg/m^2 basis). No such effects were observed at 0.009 mg/kg/day (approximately 4 times than the RHDID on a mg/m^2 basis). The fertility index; however, was not affected at inhalation doses up to 1.689 mg/kg/day (approximately 760 times the RHDID on a mg/m^2 basis). These dose multiples may be over-estimated due to difficulties in measuring deposited doses in animal inhalation studies.

13.2 Animal Toxicology and Pharmacology

Reproductive Toxicology Studies

No evidence of structural alterations was observed in rats and rabbits at inhalation tiotropium doses of up to 1.471 and 0.007 mg/kg/day, respectively. These doses correspond to approximately 660 and 6 times the recommended human daily inhalation dose (RHDID) on a mg/m^2 basis. However, in rats, fetal resorption, litter loss, decreases in the number of live pups at birth and the mean pup weights, and a delay in pup sexual maturation were observed at inhalation tiotropium doses of ≥0.078 mg/kg (approximately 35 times the RHDID on a mg/m^2 basis). In rabbits, an increase in post-implantation loss was observed at an inhalation dose of 0.4 mg/kg/day (approximately 360 times the RHDID on a mg/m^2 basis). Such effects were not observed at inhalation doses of 0.009 and up to 0.088 mg/kg/day in rats and rabbits,

respectively. These doses correspond to approximately 4 and 80 times the RHDID on a mg/m^2 basis, respectively. These dose multiples may be over-estimated due to difficulties in measuring deposited doses in animal inhalation studies.

Luqi Pei, Ph.D.
Senior Pharmacologist

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/s/

Luqi Pei
7/15/2009 11:42:20 AM
PHARMACOLOGIST

Jean Wu
7/15/2009 03:06:27 PM
PHARMACOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-395/S029

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF TRANSLATIONAL SCIENCE
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES (TERTIARY REVIEW)

NDA:	21-395/N024 and N029
Name of drug:	Spiriva HandiHaler (tiotropium bromide)
Indication:	Maintenance treatment of bronchospasms associated with COPD, including chronic bronchitis and emphysema
Applicant:	Boehringer Ingelheim
Dates:	Letter November 17, 2008; Original PDUFA September 15, 2009; New PDUFA December 17, 2009
Review priority:	S
Biometrics division:	Division of Biometrics II
Statistical reviewer:	Thomas Permutt, Director, Division of Biometrics II
Medical division:	Division of Pulmonary and Allergy Products
Clinical team:	Theresa Michele, M.D.
	Sally Seymour, M.D.
Project manager:	Miranda Raggio

Keywords: NDA review, clinical studies

This tertiary review considers the primary review by Joan Buenconsejo, Ph.D. and a secondary review by Qian Li, Ph.D., team leader. I find Dr. Buenconsejo's analysis of the issues in dispute to be balanced and cogent. Dr. Li raises some relevant arguments, but she overstates them.

The important differences of opinion relate, first, to the claim of reduced exacerbations and, second, to the interpretation of the survival data. The applicant seeks a claim of reduced exacerbations based on nominally significant findings in a study which failed to find a significant effect on the primary endpoints. Dr. Buenconsejo correctly points out that according to the protocol, these secondary results cannot be considered statistically significant. Dr. Li suggests that the protocol itself is at fault for specifying a "wrong decision rule." Other methods, if they had been specified, would have led to significant findings on the same data. This is always the case when nominally significant results are excluded by a gatekeeper strategy. Furthermore, if the primary analysis had succeeded, the rule would not have been called "wrong," and the primary claim would presumably have been allowed. There is incontrovertibly an inflation of the probability of error in allowing the primary analysis if successful and some other, even superior, analysis if not. I agree with Dr. Li that the increment in the probability of error seems small in this case, considering the strong nominal significance, the corroboration from the VA study, and the relatedness of the secondary claim to known effects of tiotropium. Nevertheless, the results do not meet the usual standard for an Agency-endorsed claim.

With regard to survival, Drs. Buenconsejo and Li both find the evidence equivocal, and so do I. Most troubling is the contradictory finding from a study of the Spiriva Respimat. If the difference is random, then there is little basis for a claim that Spiriva HandiHaler improves survival. If the difference is not random, then tiotropium under some conditions may worsen survival, and it is not so apparent what the conditions are as to justify a firm conclusion.

Dr. Li, however, raises an additional concern based on her interpretation of the hazard function, and I believe her interpretation is erroneous. The hazard function is approximately the derivative of the survival function. (It is precisely the derivative of the logarithm of the survival function, but taking the logarithm or not makes no meaningful difference here.) Small, short-term fluctuations in the slope of the survival function translate to wild fluctuations in the hazard when it is calculated over short periods. Furthermore, the hazards may overlap for most of their length and still indicate a meaningful, consistent difference in survival, as long as they differ substantially somewhere, especially early. The survival advantage of tiotropium was of questionable significance given the multiplicity of possible tests as well as the inconsistency between formulations, but the survival function as plotted by Dr. Buenconsejo is a better description of the results than Dr. Li's hazard, which she misinterprets.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21395	SUPPL-29	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	SPIRIVA HANDIHALER

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/s/

THOMAS J PERMUTT
12/04/2009

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

SECONDARY STATISTICAL REVIEW

NDA/Serial Number:	21-395/S-029
Drug Name:	Tiotropium Bromide Inhalation Powder (SPIRIVA HandiHaler®)
Indication(s):	Maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema in Patients 40 years of age and above
Applicant:	Boehringer Ingelheim Pharmaceuticals, Inc.
Date(s):	Received 11/17/08
Review Priority:	Goal date: 12/17/09 – Standard clock with 3 month extension subsequent to additional information submission
Biometrics Division:	Division of Biometrics II
Secondary Statistical Reviewer:	Qian H. Li, Sc.D.
Statistics Supervisor:	Thomas Permutt, Ph.D.
Medical Division:	Division of Pulmonary and Allergy Products
Clinical Reviewer:	Theresa Michele, M.D.
Project Manager:	Miranda Raggio

SUMMARY

This review evaluates whether sufficient evidence exists to support proposed label revisions in clinical study section of tiotropium inhalation powder 18 mcg (tiotropium), also known as Sprivia Handihaler, a drug product approved in 2002 for maintenance treatment to patients with chronic obstructive pulmonary disease (COPD). The currently approved label contains the effect of tiotropium on lung function. The sponsor proposed to add long-term effects on lung functions as well as reduction on exacerbations and respiratory failure in COPD patients treated with tiotropium. The support of the proposed claims is primarily based on the results of a recently completed 4-year randomized, double-blinded, and placebo-controlled study which enrolled about 6,000 COPD patients. This study is referred to as the UPLIFT study, which stands for Understanding Potential Long-term Impacts on Function with Tiotropium.

Dr. Joan Buenconsejo conducted the primary statistical review of the UPLIFT study. Because of the differences of views in interpreting the study results, a secondary review is written. The key difference is in whether the conclusions should be based on pre-specified decision rules in individual studies or collective evidence from multiple studies.

A closed step-down testing procedure is pre-specified in the UPLIFT study. The procedure required the primary endpoints to show statistically significant treatment difference before testing the secondary endpoints. The primary endpoints were the rates of decline in forced expiratory volume in one second (FEV_1) measured before and after the administration of the study drugs, i.e., the slopes of the FEV_1 curves. UPLIFT failed to show treatment differences between tiotropium and placebo in the rates of decline in either of the pre- or post-study drug pulmonary function measurements. The study also failed to show reduction in frequency of severe COPD exacerbation leading to hospitalization. The two primary endpoints as well as the rates of severe exacerbation leading to hospitalization are pre-specified to be tested in the first layer of the closed testing hierarchical procedure. Because the study failed on the first layer of the closed testing procedure, the primary reviewer believes no additional claims should be considered to prevent the potential inflation of type I error. Therefore the primary reviewer believes that there is insufficient evidence to support the proposed claims, except the long term effect on lung function.

This secondary statistical review emphasizes evidence based evaluation using collective evidence from multiple studies and multiple endpoints. When evidence is evaluated collectively from multiple studies, consistent evidence across studies will ensure the error rate of false claims to be controlled. Because the error rate can be tightly controlled with collective evidence from multiple studies, the pre-specified multiplicity procedures from individual studies are no longer needed in the evidence based evaluation. The collective evidence from multiple studies with treatment duration ranging from 6 months to 4 years consistently shows that tiotropium maintains better effect on lung function over four-year period in COPD patients compared with placebo. Based on results of two large studies including UPLIFT, tiotropium delayed the onsite of the first exacerbation, and reduced

the frequency and duration of the exacerbations compared with placebo. However, there is inconsistent evidence to support the effect of tiotropium on the severe exacerbation leading to hospitalization, which is a subset of the exacerbation. There is not sufficient evidence to support the protective effect of respiratory failure using tiotropium. Although UPLIFT showed statistically significant reduction in mortality risk compared with placebo based on logrank test, the facts that the hazard functions are almost completely overlapping between tiotropium and placebo and that imbalanced mortality risk against tiotropium respimat formulation observed in three 1-year studies make it less convincing that tiotropium reduced the mortality risk.

This review first provides a brief overview of the design and results of the UPLIFT study, then discusses the problems of pre-specified decision rules and the importance of evidence based decision rules when multiple studies are available. The collective evidence from multiple studies for the long term effect of lung function and reduction in exacerbations is presented next.

OVERVIEW OF THE UPLIFT STUDY

The primary objective of the UPLIFT study is to compare the rates of decline of pulmonary function in patients with COPD treated with tiotropium or placebo. Close to 6,000 COPD patients were randomized in 1:1 ratio to tiotropium and placebo and treated over 4-year duration. The study allowed patients to take their usual pulmonary treatments available on market except the regular use of the approved anticolinergic products. The uniqueness of the study design is that at the administration of study drugs, 80 mcg ipratropium was co-administrated with the study drugs, and 60 minutes later post-study drugs, 400 mcg salbutamol was also administrated in both treatment groups. The primary endpoints are the rates of decline measured by pre- and post-study drug FEV_1. Other endpoints include time to the first exacerbation and the frequency (also referred to as rate in this review) and duration of exacerbation as well as endpoints on severe exacerbations leading to hospitalization. The frequency is assessed based on the number of exacerbations experienced in a patient. The duration is assessed by number of exacerbation days. Some other pulmonary function parameters were also measured. Safety endpoints including vital status were obtained. A closed step-down testing procedure is pre-specified in the trial statistical analysis plan. The first layer of the procedure is to test if tiotropium slows down the deterioration of lung function measured as pre- and post-study drug FEV_1 in comparison with placebo. The significance level for the two co-primary endpoints are set at 0.048, which means the first layer can be passed if the p-values obtained by testing the two co-primary endpoints is smaller than 0.048. In case this is not achieved, tiotropium could have another chance passing the first layer if the frequency of severe exacerbation leading to hospitalization is statistically significantly lower in tiotropium than in placebo at the level of 0.001. Once the tests pass the first layer successfully, tests to see if tiotropium delays the onset of the first exacerbation and the onset of the first severe exacerbation leading to the hospitalization will be performed.

The results of the UPLIFT study do not pass through the first layer of the step-down closed testing procedure. There was no difference in the rates of decline of lung function between tiotropium and placebo in almost all pulmonary function assessments. The rates of decline were 30 mL/year for both tiotropium and placebo in pre-study drug (trough) FEV_1 and 40 and 42 mL/year for tiotropium and placebo, respectively, in 90 minutes post-study drug FEV_1. No difference was observed in the frequencies of severe exacerbations leading to hospitalization either between the two treatment groups. The rates of severe exacerbations leading to hospitalization were 0.15 and 0.16 per person-year in tiotropium and placebo, respectively, with a p-value of 0.341 based on a Poisson regression model controlling over-dispersion.

Multiple endpoints on the effect of exacerbations were assessed, reflecting the frequency and duration of exacerbations. Time to the first exacerbation was also assessed to see if tiotropium delayed the onset of the first exacerbation compared with placebo. The severity of exacerbation was assessed separately with endpoints associated with the severe exacerbation leading to hospitalization. The multiple endpoints in fact provide collective views of tiotropium's effect on exacerbations. However, it worth to note that the proportion of patients who experienced at least one exacerbation will not provide an adequate assessment on the effect of exacerbations as many patients dropped out from treatments prematurely during the four years of treatment. The median time to the first exacerbation was 16.7 months for tiotropium and 12.5 months for placebo with a p-value of <0.001 based on the log-rank test. The ratio of exacerbation rates for tiotropium to placebo was 0.86, representing 14% reduction of placebo's rate. The reduction was statistically significant (p-value of <0.001) based on a Poisson regression model. The average exacerbation days for each patient over one year were 12.1 days in tiotropium and 13.6 days in placebo. The reduction of the exacerbation days in tiotropium was 1.5 day compared with placebo for a patient treated over 1-year and was statistically significant (p-value=0.001). For the severe exacerbation leading to hospitalization, tiotropium delayed the onset of the first severe exacerbation leading to hospitalization compared with placebo with a p-value of 0.002 based on the log-rank test. The time to the first severe exacerbation at the 25 percentile was 35.9 months for tiotropium and 28.6 months for placebo. As mentioned earlier, there was no difference in the frequency of the severe exacerbations between the two treatment groups (p-value is 0.341). There was no difference in the number of hospitalization days due to exacerbation between the two treatment groups (p-value is 0.862). The results reported here are based on the sponsor's study report.

The pulmonary function tests were assessed at pre- and 90 minutes post-study drugs. As expected, because the co-administration of ipratropium with study drugs and later salbutamol in both treatment groups, there was little room to show further immediate improvement by tiotropium at 90 minutes post-study drug FEV_1 assessment, which was 30 minutes post-salbutamol administration. The bronchodilator effect of tiotropium was maintained on average 80 mL for trough FEV_1 over the 4-year treatment period, and 40 mL for 90 minutes post-study drug FEV_1.

The original proposed label revisions also included a claim in the reduction of mortality risk as a statistically significant reduction in mortality risk relative to placebo was seen in the tiotropium arm in the UPLIFT study. This claim was later removed by the sponsor during this review cycle, primarily due to the fact that additional imbalance was observed in mortality against tiotropium respimat formulation in a recently completed 1-year study. Such imbalance was also seen in two previously conducted 1-year studies in tiotropium respimat formulation. In the UPLIFT study, the sponsor reported a total of 981 deaths either during treatment or follow-up, of which, 467 from tiotropium and 514 from placebo. The average risk ratio including all events was 0.89 for tiotropium versus placebo (p-value=0.058). The cumulative mortality rates over four years were 17% for placebo and 15.6% for tiotropium. To understand the risks of mortality over time between treatment groups, Figure 1 displays the two hazard functions over time for tiotropium and placebo. The risk is calculated using two week intervals. As can be seen from Figure 1, the two hazard functions are overlapping over time and there is no clear pattern of reduction in mortality risk in the tiotropium group (in black) compared with the placebo group (in red). The Kaplan-Meier curves of the two treatments with all events are displayed in Figure 2. As there was a debate on whether it is correct to examine the hazard functions in understanding mortality risks among statistical review team, additional discussions on hazard functions are included in this review in the Appendix. Note that the analysis on overall survival includes deaths occurred during follow-up after withdrawals of treatments. This analysis may take care of the problem of potential informative censoring which may occur if patients were not followed after discontinuation of treatments, however, could be conservative if survival benefit indeed exists in tiotropium as the mortality risk may increase once patients discontinued the tiotropium treatment but decrease in placebo patients once they stopped placebo treatment.

Figure 2. Kaplan-Meier Curves by Treatments

According to the study report, overall, the UPLIFT study showed less serious adverse effect in tiotropium than in placebo. The safety profile of tiotropium has been carefully evaluated by medical reviewers. The risk of respiratory failure is mentioned here to see if adequate evidence available as the proposed label revisions include the claim of protective effect of tiotropium on respiratory failure. A total of 198 patients reported respiratory failures, 113 in placebo and 85 in tiotropium. The risk ratio of tiotropium to placebo was 0.69 with 2-sided 95% CI [0.52, 0.92] excluding 1. While searching the reported adverse event database, it appears that a patient could experience more than one event with different severity and duration. The analyses which were based only on the first event may not provide a complete picture of the "protective" effect. In addition, analyses on many serious adverse events had been performed by the sponsor. The chance of observing some difference between treatment groups can be high. Without consistent evidence from other sources to further confirm this finding, it is pre-mature to place this claim on label.

PRE-SPECIFIED DECISION RULES VS. EVIDENCE BASED DECISION RULES

Although it is important to pre-specify in study protocols detailed experimental procedures and data analyses to ensure carefully planned studies, increased emphasis on pre-specified statistical decision rules to reduce inflation of type I error in individual clinical studies may introduce more confusion than clarity in drug evaluations. Pre-specified decision rules are particularly problematic when they are based on the expectation of study outcomes, which are often hypotheses and subject to test. The applicability of a particular decision rule to the final outcome may be uncertain. So evaluating a drug solely based on decision rules pre-specified at the design stage, when little information is available, is not invariably a sound scientific practice.

With the case of UPLIFT, it might be guessed wrong that tiotropium would slow down the decline of pulmonary function compared with placebo because of limited understanding in drug effect. As the study allowed almost all usual COPD treatments with unlimited use as concomitant therapies except the regular use of approved anticolinergic products, the results of no difference in decline rates of pulmonary function between the treatment groups are not a surprise.

Does this wrong decision rule imply that the data collected from the study are no longer valid? There is no reason to believe that the data collected in this study are invalid as no issue has been identified in the conduct and data collection of the UPLIFT study. In fact the conclusion of no treatment difference in the rate decline of pulmonary function has to be made on valid data. The validity of information depends on the study design and conduct, rather than the expectation of the study results.

While it does not always make sense to use a pre-specified decision rule which was made when we have little information and ignores the body of new information obtained, we do need to reconcile the concern of the type I error rate inflation as it is important to control the error rate of placing spurious finding in label. This may be difficult to achieve if we have only one study, but can be an easy task if we have multiple studies. When looking for replicated and consistent evidence from the multiple studies, the error rate of false claims can be tightly controlled. An intuitive way of understanding this is that the chance for all studies to consistently show treatment effect in a drug will be very low if in truth this drug is ineffective. Mathematically, it is not difficult to calculate the probability of the error rates under the setting of collective evidence. The application of collective evidence in fact is simple and intuitive as illustrated below.

COLLECTIVE EVIDENCE FOR TIOTROPIUM'S EFFECT

Evidences from 6 randomized, double blind, and placebo controlled studies including UPLIFT are gathered together to collectively evaluate the effect of tiotropium in lung functions compared with placebo. Two studies, Studies 205.117 and 205.128, are one-year studies, Studies 205.130, 205.137, and 205.266 are six-month studies, and Study

205.235, the UPLIFT study, is a four-year study. Studies 205.117, 205.128, 205.130, and 205.137 were submitted in the original new drug application submission in December 2001. Study 205.266 was submitted in January 2008 and conducted in Veterans Affairs medical centers across US with less than 2% females available in this patient population. This study is also referred to as the VA study. Study 205.235 was submitted in this submission cycle. All studies allowed patients to receive certain concomitant medications. However, the VA and UPLIFT studies particularly specified in study protocols that patients were allowed to receive all usual medical care for COPD with the exception of regular use of market available anticholinergics. As mentioned before, the pulmonary function assessment in Study 235 was different from all other studies. Due to co-administration of ipratropium and salbuterol, the effect of tiotropium on the post-study drug FEV_1 is not expected to be large.

Long term effect on pulmonary function

To understand if there is sufficient evidence for the effect of tiotropium in lung function maintenance, FEV_1 assessments overtime from all 6 studies are displayed in Table 1. The trough FEV_1 collected in this table was the FEV_1 assessed 1 hour prior to the administration of study drugs and the post-dose FEV_1 was collected 1 hour post study drugs for all studies with one-year duration and less except for Study 205.266. The trough FEV_1 in Studies 205.235 (UPLIFT) and 205.266 (VA) was collected before the administration of study medications and the post-study drug FEV_1 was collected 90 minutes post study drugs.

All pre- and post-dose FEV_1 in tiotropium treatment groups are statistically significantly greater than that in the placebo groups in Table 1. Despite the fact that the studies were designed and conducted differently and in different time periods, all study showed that tiotropium maintained better lung function in COPD patients compared with placebo measured by both pre- and post- study drug FEV_1. The evidence is overwhelming within 1-year treatment duration as all of the studies except UPLIFT had treatment duration up to 1 year. Effect on lung functions longer than 1 year was only observed in the UPLIFT study.

On the surface it may appear that evidence for pulmonary function after 1 year treatment is lacking compared with what we have over the first year of the treatment period. As we have concluded that tiotropium maintained better lung function over 1-year treatment period based on the collective evidence, this further validates the results of the UPLIFT study in lung function. If results in the first year of the UPLIFT study are valid, there is no reason to believe that the results after one year in lung function from the UPLIFT study are invalid. The only concern perhaps is the gradually increased dropout rates over time in understanding the long term effect in pulmonary function. To understand the impact of missing data due to the discontinuation of treatment, analyses with data from the UPLIFT study imputed with last-observation-carried-forward (LOCF) are performed by this reviewer. The treatment differences based on LOCF approach was in fact larger than that based on the completer analyses as shown in Table 1. The analyses based on LOCF may still be considered conservative as the patients who discontinued may have even worse FEV_1 than the last observation, had they stayed in the study longer, and the

dropout rate in the placebo group is higher compared with the rate in the tiotropium group. The sustained effect of tiotropium on lung function is confirmed at every time points that FEV_1 was assessed.

Table 1. Trough and post-dose FEV_1 over time based on completer analyses.

Study	Treatment	6 months	12 months	18 months	24 months	30 months	36 months	42 Months	48 months
				Trough FEV_1 (L)					
205.117	Tiotropium(n=268)	1.11	1.11						
	Placebo(n=174)	0.97	0.96						
	Difference	0.14	0.16						
205.128	Tiotropium(n=250)	1.11	1.10						
	Placebo(n=154)	0.96	0.96						
	Difference	0.15	0.15						
205.130	Tiotropium(n=202)	1.15							
	Placebo(n=179)	1.02							
	Difference	0.13							
205.137	Tiotropium(n=175)	1.17							
	Placebo(n=176)	1.05							
	Difference	0.12							
205.235	Tiotropium(n=2986)	1.20	120	1.18	1.17	1.16	1.16	1.14	1.14
	Placebo(n=3006)	1.11	1.10	1.10	1.08	1.08	1.07	1.08	1.07
	Difference	0.09	0.10	0.08	0.09	0.08	0.09	0.06	0.07
205.266	Tiotropium(n=904)	2.39							
	Placebo(n=908)	2.18							
	Difference	0.21							
				Post-study drug FEV_1 (L)					
205.117	Tiotropium(n=268)	1.20	1.20						
	Placebo(n=174)	0.99	0.99						
	Difference	0.21	0.21						
205.128	Tiotropium(n=250)	1.21	1.20						
	Placebo(n=154)	0.98	0.99						
	Difference	0.23	0.21						
205.130	Tiotropium(n=202)	1.29							
	Placebo(n=179)	1.07							
	Difference	0.22							
205.137	Tiotropium(n=175)	1.31							
	Placebo(n=176)	1.13							
	Difference	0.18							
205.235	Tiotropium(n=2986)	1.40	1.38	1.37	1.36	1.34	1.33	1.32	1.30
	Placebo(n=3006)	1.34	1.33	1.32	1.30	1.30	1.29	1.29	1.28
	Difference	0.06	0.05	0.05	0.06	0.04	0.04	0.03	0.02
205.266	Tiotropium(n=904)	1.24							
	Placebo(n=908)	1.07							
	Difference	0.17							

Sources: Data are obtained from sponsor's study reports submitted under NDA21-395.

Exacerbations

The exacerbation information was collected from the UPLIFT and VA studies. Information from the three aspects of exacerbations including frequency, severity, and duration is summarized in Table 2. The survival analyses for the first events provided information on whether tiotropium delays the first onset of exacerbation as well as the first severe events leading to hospitalization compared with placebo. These endpoints collectively provide more complete pictures of the effect on exacerbation than any one endpoint alone. Notice that the analyses for the proportions of patients who experienced at least one exacerbation are not reported here as the analyses can be biased due to high rates of dropouts during the study. Based on both UPLIFT and VA studies, there is consistent evidence to support the exacerbation effect in tiotropium. Tiotropium delayed the onset of the first exacerbation, reduced the frequency as well as duration of the

exacerbation episodes compared with placebo. The median delay of the onset of the first exacerbation in tiotropium is 4 months. There is at least 14% reduction in the rate of exacerbations in tiotropium compared to placebo. On average, one COPD patient treated with tiotropium over 1 year experienced at least 1.5 day less exacerbation. However, the treatment difference was primarily driven by less severe exacerbations as the effect on the severe exacerbations leading to hospitalization was not seen in either frequency or duration.

Table 2. COPD Exacerbation analyses

	Study 205.235 (UPLIFT)			**Study 205.266 (VA Study)**		
	Tiotropium N=2986	Placebo N=3006	Ratio, (p-value)	Tiotropium N=914	Placebo N=915	Ratio, (p-value)
Exacerbation						
Median time (month)	16.7	12.5	0.86, (<0.001)	--	--	0.83, (0.034)
Total number of events	6691	7183		376	446	
Rate (number/person-year)	0.73	0.85	0.86, (<0.001)	0.71	0.88	0.81, (0.037)
Number of exacerbation days/ person-year	12.1	13.6	0.89, (0.001)	10.0	12.6	0.79, (0.056)
Exacerbation leading to hospitalization						
Time (months) of 25 percentile	35.9	28.6	0.86, (0.002)	--	--	0.72, (0.049)
Total number of events	1403	1379		88	124	
Rate (number/person-year)	0.15	0.16	0.94, (0.341)	0.15	0.21	0.69, (0.054)
Number of hospitalization days due to exacerbation /person-year	3.17	3.13	1.01, (0.862)	1.2	1.7	0.67, (0.249)

CONCLUSION

Based on the principle of collective evidence, there is sufficient evidence that tiotropium maintained long term better effect on pulmonary function in COPD patients compared with placebo. The effect size of trough FEV_1 shown in UPLIFT is about 80 mL on average over the four year treatment period. The effect size of post-study drug FEV_1 in UPLIFT is about 40 mL on average.

There is consistent evidence to support the exacerbation effect in tiotropium from two studies. The effect is examined collectively from three aspects of the exacerbations: the frequency, duration, and severity of exacerbations. Tiotropium delayed the onset of the first exacerbation, reduced the frequency as well as duration of the exacerbation episodes compared with placebo. The median delay of the onset of the first exacerbation in tiotropium is 4 months. There is at least 14% reduction in the rate of exacerbations in tiotropium compared to placebo. On average, one COPD patient treated with tiotropium over 1 year experienced at least 1.5 day less exacerbation. However, the treatment difference was primarily driven by less severe exacerbations as the effect on the severe exacerbations leading to hospitalization was not seen in either frequency or duration.

There is no robust evidence showing that tiotropium reduces mortality risk as the risk functions for tiotropium and placebo are almost completely overlapping. However, the UPLIFT study shows that tiotropium does not have higher mortality risk over placebo. This observation from UPLIFT is inconsistent with the unfavorable results on mortality imbalance observed in tiotropium respimat formulation.

There is insufficient evidence to support the claim in the reduction of respiratory failures. The information on the reduction of the risk of respiratory failure is lacking as multiple failures in a patient have not been taken into consideration in statistical analyses. The statistically significant finding in respiratory failures is the results of many tests in serious adverse events. No replicate information is available from other studies.

Appendix: Hazard Functions

Technical discussions are provided here to help readers understand the importance of examining hazard functions in survival analyses when the Logrank test or proportional hazard models show statistically significant risk reduction and survival curves do not cross. Construction of hazard functions is discussed here. Questions of interpreting mortality risk are raised when hazard functions are overlapping and fluctuating overtime.

The reason of examining hazard functions in survival analyses is simple. It has been well understood that the Logrank test and proportional hazard models test the average risk ratio over time when the risk ratio of two hazard functions is not constant. The Kaplan-Meier survival curves represent the cumulative decreases in survival over time. The average risk ratio and the survival curves are not always sufficient in understanding risk changes over time between two treatment groups. A simple hypothetical example is used to illustrate the importance of examining risk functions. Figure A1 displays two hypothetical hazard functions for treatments A and B over a period of time. During the time period, the risk functions of the two treatments cross at time point t_0. Before crossing, treatment A has lower risk than treatment B, indicating reduced mortality risk in treatment A. After crossing, treatment A in fact does more harm than treatment B. The average risk ratio in this case can still show that treatment A is better than treatment B over the entire treatment period. In fact the survival curves of the two treatments never cross over the treatment period as shown in Figure A2. Despite the favorable results to treatment A over the entire treatment period, treatment A should be stopped at time t_0. The valuable information could not always be gained by simply applying survival analysis and plotting Kaplan-Meier curves, but can be revealed by examining the hazard functions. Despite the importance of inspecting the hazard functions, it is important to point out that the interpretation of hazard functions should not be done with isolation of other information such as the survival analyses and changes of patient population over time due to differential dropout rates from risk sets between two treatment groups.

Figure A1. Two Crossing Hazard Functions

Figure A2. The Two Survival Curves Corresponding to the Crossing Hazards Functions

Although valuable information may be gained from examining hazard functions in survival analysis, the analysis of hazard functions may not always be doable as we need sufficient sample sizes and number of events to perform this analysis. While it is not possible to calculate the transit hazard at each time point, average risk is usually calculated over certain time interval. Although there is not a fixed rule in determining the length of the interval, however, the interval should not be too large so that we will not lose the capability of understanding the risk changes over time. It is also important to understand that using larger interval does not make the estimate more accurate as the average risk represents an average of risk that can be different over time. In the UPLIFT analysis, the risk presented in Figure 1 is the weekly risk averaged by every two weeks. The two hazard functions are almost completely overlapping. Risk reductions as well as increases relative to placebo were observed during the treatment. Smoothing method using the average of three 2-week periods is applied to reduce the variability. The smoothed hazard functions are displayed in Figure A3. As can be seen from Figure A3, the two smoothed hazard functions are still overlapping and fluctuate over time.

Questions arise in interpreting hazard functions that are overlapping and fluctuating over time as illustrated in Figure A3. The fact that the hazard function of tiotropium fluctuates above and below the hazard function of placebo indicates that tiotropium did not reduce the risk of mortality consistently. An exaggerated way of interpreting this is that tiotropium sometimes saves life and sometimes kills patients during treatment. Perhaps it saves a few more than it kills, which makes the average risk ratio and survival curves look like in favor to tiotropium. Does such a drug deserve the status of saving life when in fact it may kill patients during treatment? Or is it ethical to tell a patient that you have to risk your life in order to receive survival benefit? A moderate way of interpreting the overlapping and fluctuation is that the hazard functions varies within their normal range and there is not any obvious treatment difference in the risk of mortality between placebo and tiotropium.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21395	SUPPL-29	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	SPIRIVA HANDIHALER

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/s/

QIAN H LI
12/04/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF TRANSLATIONAL SCIENCE
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	21-395/N024 and N029
Name of drug:	Spiriva HandiHaler (tiotropium bromide)
Indication:	Maintenance treatment of bronchospasms associated with COPD, including chronic bronchitis and emphysema
Applicant:	Boehringer Ingelheim
Dates:	Letter November 17, 2008; Original PDUFA September 15, 2009; New PDUFA December 17, 2009
Review priority:	S
Biometrics division:	Division of Biometrics II
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	Thomas Permutt, Ph.D.
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TABLE OF CONTENTS

1 Executive Summary 5
1.1 Conclusions and recommendations 5
1.2 Brief overview of clinical studies 5
1.3 Statistical issues and findings 6
2 Introduction 9
2.1 Overview 9
2.2 Data sources 10
3 Statistical Evaluation 10
3.1 Evaluation of Efficacy 10
3.1.1 Design and Analysis Plan 10
3.1.2 Disposition of patients, demography and baseline characteristics 15
3.1.3 Primary Efficacy Endpoints 18
3.1.4 Key secondary EndpointS 31
3.1.5 St. George's Respiratory Questionnaire (SGRQ) 34
3.1.6 Other Pulmonary Function Testing 35
3.1.6.1 Forced Vital Capacity (FVC) 35
3.1.6.2 Slow Vital Capacity 36
3.1.7 Efficacy Conclusion 37
3.2 Evaluation of safety 41
4 Findings in Subgroups and Special Populations 47
4.1 COPD Exacerbation 47
4.2 Pre- and Post-bronchodilator Fev_1 53
5 Summary and Conclusions 56
5.1 Statistical issues and collective evidence 56
5.2 Conclusions and recommendations 59
6 Labeling 60
7 Appendix 64

List of Tables

Table 1: Patient Disposition 16
Table 2: Patient Disposition – Discontinued from trial medication after 1350 days 17
Table 3: Patients included for the analysis of the efficacy endpoints 18
Table 4: Rate of decline in pre- or post-bronchodilator FEV_1 from Day 30 until completion of double-blind treatment 20
Table 5: Estimated* mean pre- or post-bronchodilator FEV_1 from Day 30 until completion of double-blind treatment - Treated set with at least 3 measurements between Visits 3 – 19 (or Months 1 – 48) 24
Table 6: Analysis of COPD exacerbation 32
Table 7: Patient with at least one exacerbation by Disposition 33
Table 8: Analysis of COPD exacerbation leading to hospitalization 34
Table 9: Rate of increase in SGRQ scores from Month 6 until completion of treatment – treated set with at least 2 acceptable measurements 35
Table 10: Rate of decline in pre- or post-bronchodilator FVC 35
Table 11: Rate of decline in pre- or post-bronchodilator SVC 36
Table 12: Analysis of COPD exacerbation – UPLIFT Study 38
Table 13: Analysis of COPD exacerbation –VA Study 40
Table 14: Fatal Adverse Event Summary – Treated Set 42
Table 15: Subgroup Analysis on on−treatment death − treated set 43
Table 16: Incidence density of fatal AE by treatment, selected preferred terms − adjudicated primary cause; on−treatment death − treated set 44
Table 17: Incidence density of fatal AE by treatment, selected preferred terms − adjudicated primary cause; on−treatment death including Vital Status (1470 cut-off) − treated set 45
Table 18: Subgroup Analyses of Pneumonia - on−treatment death − treated set 46
Table 19: Analysis of COPD exacerbation – Number of Patients with Exacerbation (%) and Median Time to First Exacerbation (in months) 48
Table 20: Analysis of COPD exacerbation leading to Hospitalization – Number of Patients with Exacerbation (%) and Lower Quartile Time to First Exacerbation (in months) 50
Table 21: Estimated Rate of Patients with Exacerbation per Patient-Year 52
Table 22: Estimated* mean pre-bronchodilator FEV_1 from Day 30 until completion of double-blind treatment - Treated set with at least 3 measurements between Visits 3 – 19 (or Months 1 – 48) 53
Table 23: Estimated* mean post-bronchodilator FEV_1 from Day 30 until completion of double-blind treatment - Treated set with at least 3 measurements between Visits 3 – 19 (or Months 1 – 48) 54

List of Figures

Figure 1: Time course of FEV_1 prior to bronchodilators on the test days 21
Figure 2: Time course of FEV_1 post-bronchodilators on the test days 22
Figure 3: Estimated* mean FEV_1 pre-bronchodilators by Visits – treated set with at least 3 measurements between Visits 3 – 19 (or Months 1 – 48) 23
Figure 4: Estimated* mean FEV_1 post-bronchodilators by Visits – treated set with at least 3 measurements between Visits 3 – 19 (or Months 1 – 48) 23
Figure 5: Proportion of Responders* (i.e. 15% Improvement from baseline) Pre-Bronchodilator FEV_1 by Visits – treated set with at least 3 measurements between Visits 3 – 19 (or Months 1 – 48) and have baseline score 25
Figure 6: Proportion of Responders (i.e. 15% Improvement from baseline) Post-Bronchodilator FEV_1 by Visits – treated set with at least 3 measurements between Visits 3 – 19 (or Months 1 – 48) and have baseline score 26
Figure 7: Response Profile Pre-Bronchodilator FEV_1 by Visits – treated set with at least 3 measurements between Visits 3 – 19 (or Months 1 – 48) and have baseline score 27
Figure 8: Response Profile Post-Bronchodilator FEV_1 by Visits – treated set with at least 3 measurements between Visits 3 – 19 (or Months 1 – 48) and have baseline score 29
Figure 9: Kaplan-Meier estimates of the probability of no COPD exacerbation – treated set 31
Figure 10: Kaplan-Meier estimates of the probability of no COPD exacerbation leading to hospitalization – treated set 34
Figure 11: Kaplan-Meier estimates of the probability of no all-cause mortality – adjudicated; on-treatment deaths-treated set-censored at Day 1470 42

1 EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

Spiriva HandiHaler (tiotropium bromide inhalation powder) was approved on January 30, 2004 for long-term maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema.

The primary objective of the clinical program is to supplement the Clinical Studies section of the product information with additional information to prescribers concerning the long-term (4 year) efficacy and safety of tiotropium in the treatment of patients with COPD, based on the results from the UPLIFT study. The requested efficacy claims are: 1) description of the long-term effects on lung function, 2) reduction in exacerbations, 3) reduction in mortality, and 4) reduction in respiratory failure.

From a statistical perspective, because of multiplicity issue in the UPLIFT study, there is insufficient evidence that tiotropium 18 mcg is effective in reducing risk of COPD exacerbation and delaying the onset of COPD exacerbation. On the other hand, there is evidence from the UPLIFT study supporting the labeling claim for long-term effect on lung function. As noted in the clinical review, reduction in respiratory failure is not supported because the improvement is marginally significant and is not predefined.

A Pulmonary and Allergy Drug Advisory Committee meeting is scheduled on November 19, 2009. The Division plans to discuss the results from the UPLIFT study along with the RESPIMAT data.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

On November 17, 2008, the Applicant, Boehringer Ingelheim (BI), submitted an efficacy supplement to the Spiriva Handihaler NDA 21-395 (under Serial No. 029). In this submission, they provided the clinical trial report from the 4-year multi-center study, titled 'A randomized double-blind, placebo-controlled, parallel group trial assessing the rate of decline of lung function with tiotropium 18 mcg inhalation capsule once daily in patients with COPD' and the associated draft labeling based on the results of this study. Of note, this 4-year multi-national clinical trial is also referred to as the UPLIFT Study, i.e., Understanding Potential Long-term Impacts on Function with Tiotropium.

On January 30, 2009, the Applicant submitted a Complete Response to the FDA November 13, 2008 Complete Response letter for NDA 21-395 Serial No. 024. In this submission, they referred to the data and summaries from the UPLIFT clinical trial (Serial No. 029) to address the Division's comments regarding the reduction in COPD exacerbations, as well as stroke. On June 24, 2009, the Applicant formally withdrew the unapproved supplement Serial No. 024, and formally submitted the information supporting the proposed indication for the reduction of COPD exacerbations from Serial No. 24 to Serial No. 29. On July 22, 2009, the Applicant amended the efficacy supplement to remove the mortality claim. According to the Applicant, there was no new Spiriva Handihaler data contributing to this decision.

The UPLIFT study evaluated 5,992 patients with COPD. Study treatment (tiotropium or placebo) was administered to these patients in addition to their usually prescribed therapy for COPD

(including short- and long-term inhaled beta-adrenergics, steroids, or theophyllines but excluding inhaled anticholinergics).

1.3 STATISTICAL ISSUES AND FINDINGS

The Applicant proposed to add 'Long-Term Effect of Lung Function', 'Exacerbation' and 'Survival and Respiratory Failure' in the Clinical Section of the SPIRIVA Handihaler label.

On January 11, 2008, the Applicant submitted the results of a six-month clinical trial with Spiriva HandiHaler (Study 266 or VA study) as pivotal evidence to support inclusion of the 'exacerbation' language in the labeling of Spiriva Handihaler. After careful review of the application, the Division concluded that the submitted data failed to provide substantial evidence of efficacy to support labeling claim for reduction of exacerbation in patients with COPD. In the Action Letter, it stated the following deficiency that precludes approval of the application.

> The submitted data do not provide substantial evidence of efficacy to support the labeling claim for reduction of exacerbation in COPD patients. Replicate findings from two adequate and well controlled studies are necessary to support a COPD exacerbation labeling claim. The results from combined analysis of clinical studies 205.254 and 205.255 are not acceptable for replication because these studies were conducted with Spiriva Respimat, which is a distinct product in terms of efficacy. To support the proposed claim of reduction of COPD exacerbation, provide data from an adequate and well controlled clinical study that shows statistically significant reduction in COPD exacerbation with Spiriva HandiHaler compared to placebo.

The Division Director's Memo summarized the results from Study 266

> The submitted data failed to show substantial evidence to support a reduction of COPD exacerbation claim for Spiriva HandiHaler. Results of the co-primary efficacy variables for study 266 are shown in Table 13. One of the two co-primary efficacy variables was met in this study and the other efficacy variable showed positive trend. Secondary efficacy variable generally trended in the right direction, but the results were not consistent (additional data not shown in this review). This study, while it may be considered positive, is not sufficiently robust to support approval of the labeling claim.

On January 30, 2009, the Applicant submitted a Complete Response to the FDA November 13, 2008 Complete Response letter for NDA 21-395 Serial No. 024. In this submission, they referred to the data and summaries from the UPLIFT clinical trial (Serial No. 029) to address the Division's comments regarding the reduction in COPD exacerbations, as well as stroke.

In the UPLIFT Study Report, the Applicant claimed the following:

> Tiotropium did result in significant improvement in lung functions (i.e. FEV_1, FVC, and SVC, and this improvement was maintained over the four years of the trial. They also claimed that tiotropium reduced the risk of the first COPD exacerbation and the risk of the first COPD exacerbation leading to hospitalization by 14% each. Tiotropium significantly reduced the number of COPD exacerbations by 14%, and reduced the number of exacerbation days by 11%. The two treatment groups had comparable numbers of COPD exacerbations leading to hospitalization and comparable numbers of hospitalization days.

In the UPLIFT study, the co-primary endpoints directly relate to the study objective and these were the focus of the design and power of the study. However, statistical significance was not achieved in favor of tiotropium for these co-primary endpoints in order to continue testing the 'key' secondary endpoints (i.e. time to the first COPD exacerbation and time to the first COPD exacerbation leading to hospitalization) and 'other' endpoints (i.e. estimated mean pre- and post-bronchodilators FEV_1 by visit), based on a pre-specified multiplicity adjustment strategy. In the strictest sense of alpha spending, all the alpha has been spent by the primary efficacy analyses. Furthermore, evaluating the

secondary endpoints (i.e. COPD exacerbation) is "to provide additional clinical characterization of the treatment effect". Although the observed results (i.e. reduction in risk of COPD exacerbation) were in favor of tiotropium, the evidence from this study is insufficient to support the result from the VA study and to warrant a claim 'for reduction of exacerbation in patients with COPD'.
In the VA study, only one of the two 'co-primary' endpoints achieved statistical significance. Similar to the UPLIFT Study, the secondary endpoint (i.e. time-to-first COPD exacerbation) is the basis of the labeling claim 'for reduction of exacerbation in patients with COPD'. Like the UPLIFT study, multiplicity is a problem in interpreting the result of the secondary endpoint analysis because not all primary endpoints achieved statistical significance. However, as Dr. Davi pointed out in her review, there is a correlation between the primary analysis and secondary analysis of the same outcome (i.e. COPD exacerbation) such that it is unlikely the result of the time-to-first COPD exacerbation analysis is a spurious finding. Nevertheless, the overall conclusion by the Division was that the evidence is insufficient to warrant a claim from the VA study.

Therefore the statistical evidence taken collectively from the VA Study and the UPLIFT study, in particular because of the multiplicity issue in the UPLIFT study, does not support labeling claim for reduction of exacerbation in patients with COPD.

Aside from 'COPD exacerbation', the Applicant proposed to add the long-term effect in lung function (FEV_1) in the Clinical Section of the label. They claimed that "SPIRIVA HandiHaler maintained improvements in pulmonary function throughout 4 years. Specifically, SPIRIVA HandiHaler sustained improvements in trough (pre-dose) FEV_1 (adjusted means over time: 87 – 103 mL) throughout the 4 years of the study." Like COPD exacerbation, multiplicity is a problem in interpreting the results of these secondary analyses (i.e. estimated mean pre- or post-bronchodilator FEV_1). Furthermore, 'maintenance' and 'sustainability' are hard to quantify when group means are used instead of individual response. In other words, there are no pre-defined criteria that would allow us to determine 'maintenance' of effect.

Nonetheless, the current approved label indicated that

> SPIRIVA HandiHaler, administered once-daily in the morning, provided improvement in lung function (forced expiratory volume in one second, FEV_1), with peak effect occurring within 3 hours following the first dose.

In addition, the label described the results from the one-year and the six-month placebo controlled studies. It stated that there is evidence that improvement of lung function was maintained for 24 hours after a single dose and consistently maintained over the 1-year and the 6-month treatment period, respectively.

The result from UPLIFT study was consistent with the one-year and six-month studies when the mean trough FEV_1 scores were calculated throughout the 4-year period. When continuous responder analyses were performed for each Visit until Month 48, there is evidence that a higher proportion of patients treated with tiotropium responded better compared to the placebo as early as Month 1. Visually, the difference was maintained until Month 48 for the pre-bronchodilator FEV_1, and until at least until Month 24 for the post-bronchodilator FEV_1. Therefore the evidence from the UPLIFT study does support labeling claim for long-term effect in lung function.

The Applicant also proposed to include the following result in the Clinical Section of the label:

> Improvement in symptom scores was also seen in patients treated with SPIRIVA HandiHaler compared to placebo.

Based on statistical review of the UPLIFT study, the evidence that there is improvement in symptom score is insufficient to warrant inclusion in the Clinical Section of the Label.

Lastly, the Applicant proposed to add mortality and respiratory failure claims in the Clinical Section of the label. The following is the proposed language:

> In the 4-year multicenter trial, there was a 16% reduction in the risk of death while on treatment with SPIRIVA HandiHaler compared to placebo. The incidence rate of death was 4.10 per 100 patient years in the tiotropium group vs. 4.78 per 100 patient years in the placebo group [Hazard Ratio (tiotropium/placebo) = 0.84, 95% CI = 0.73, 0.97]. Treatment with tiotropium reduced the risk of respiratory failure by 19% (2.09 vs. 1.68 cases per 100 patient years [relative risk (tiotropium/placebo) = 0.81, 95% CI = 0.65, 1.00].

Like COPD exacerbation and long-term effect in lung function, mortality and respiratory failure are classified as secondary endpoints. However, unlike COPD exacerbation and lung function, the general consensus is that mortality can reach the status of a primary endpoint, if analyzed properly and supported by other study. In papers written by Dr. D'Agostino Sr.[1] and Dr. O'Neill[2] and several other researchers, they have alluded that a statistical significant finding on mortality has clinical impact. They also stated that the usual reason for designating mortality as a secondary endpoint is that the trialist believes *a priori* that there is little chance a treatment effect will be observed, given the sample sizes and the power to detect a clinically important effect on mortality.

In the UPLIFT Study, there is evidence of a benefit of tiotropium on on-treatment mortality. However, because a different result was observed in another SPIRIVA application using RESPIMAT delivery system, the result from UPLIFT needs to be explored further. Of note, in the RESPIMAT application, an increased number of deaths were observed in the Spiriva Respimat treatment groups compared to placebo for 1-year pivotal trials. As stated in the overview, the Applicant amended the efficacy supplement to remove the mortality claim.

The following is from Dr. Michele's review about the 'respiratory failure claim.

> Based on the SAE data, the applicant is requesting a claim for reduction in respiratory failure. BI proposes the following language for the clinical studies section of the label: "In the 4-year multicenter trial. Treatment with tiotropium reduced the risk of respiratory failure by 19% (2.09 vs. 1.68 cases per 100 patient years [relative risk (tiotropium/placebo) = 0.81, 95% CI 0.65, 1.00]."
> While the incidence of SAEs of respiratory failure is reduced in the tio HH18 group, the difference is marginally significant and there are multiple related preferred terms that have been analyzed separately. Unlike mortality, which is a hard endpoint and was pre-specified in the protocol as an event of interest (including vital status collection and an independent adjudication committee), the term "respiratory failure" is undefined and subject to investigator interpretation. Inclusion of the term respiratory failure may be appropriate as part of adverse event reporting for the study; however, there is insufficient evidence to justify a specific claim that Spiriva HandiHaler reduces respiratory failure.

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[1] Ralph D'Agostino Sr., "Controlling alpha in a clinical trial: the case for secondary endpoints", Statistics in Medicine, 2000 19: 763-766

[2] Robert T. O'Neill, "Secondary Endpoints Cannot be Validly Analyzed if the Primary Endpoint Does Not Demonstrate Clear Statistical Significance", Controlled Clinical Trials, 1997 18: 550-556

2 INTRODUCTION

2.1 OVERVIEW

Spiriva HandiHaler (tiotropium bromide inhalation powder) was approved on January 30, 2004 for long-term maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema.

> The approved product consists of a dry powder containing tiotropium bromide in the Spiriva capsule, and the inhalation device, the HandiHaler, which is used to deliver the dry powder from the capsule. The recommended dose is inhalation of one Spiriva capsule, once-daily, with the HandiHaler inhalation device. One Spiriva capsule contains 18 mcg tiotropium, which is equivalent to 22.5 mcg tiotropium bromide monohydrate.

On January 11, 2008, Boehringer Ingelheim (BI) submitted an efficacy supplement (Serial No. 024) for Spiriva HandiHaler to add the following labeling claim to the Clinical Studies Section of the product label:

> In a 6-month clinical trial of COPD patients in a Veterans Affairs setting, Spiriva HandiHaler significantly reduced the proportion of COPD patients who experienced exacerbations compared to placebo and significantly delayed the time to first exacerbation. These findings are supported by a pre-specified combined analysis of two one-year clinical trials using Spiriva Respimat.

The Applicant submitted the results of a six-month clinical trial with Spiriva HandiHaler (Study 266 or VA study) as pivotal evidence to support inclusion of the following language in the labeling of Spiriva Handihaler. In addition, the sponsor references two one-year phase 3 clinical studies with Spiriva Respimat (studies 254 and 255) as supportive evidence; however, the Division of Pulmonary and Allergy Products has determined that these studies are not adequate to support labeling of Spiriva Handihaler as the efficacy performance can be different for different formulations and/or devices. The efficacy results and safety profile from the VA study were reviewed by Ruthanna Davi, Ph.D., a mathematical statistician within the Office of Biostatistics, and Theresa Michele, M.D. and Sally Seymour, M.D. of the Division of Pulmonary and Allergy Products. A Complete Response letter was issued on November 13, 2008. In that letter, the Division provided two comments. Comment 1 identifies the deficiency that precludes approval of this application. Comment 2 is an additional comment, which is not a deficiency that precludes approval of this application.

> 1. The submitted data do not provide substantial evidence of efficacy to support the labeling claim for reduction of exacerbation in COPD patients. Replicate findings from two adequate and well controlled studies are necessary to support a COPD exacerbation labeling claim. The results from combined analysis of clinical studies 205.254 and 205.255 are not acceptable for replication because these studies were conducted with Spiriva Respimat, which is a distinct product in terms of efficacy.
>
> To support the proposed claim of reduction of COPD exacerbation, provide data from an adequate and well controlled clinical study that shows statistically significant reduction in COPD exacerbation with Spiriva HandiHaler compared to placebo.
>
> 2. Increased frequencies of stroke were observed in patients treated with tiotropium bromide compared to placebo in a pooled analysis of clinical study data with Spiriva HandiHaler and Spiriva Respimat. Provide data from an adequate and well-controlled study to address the concerns of stroke. The study should be of adequate duration and power that will allow evaluation of the safety concern.

On November 17, 2008, the Applicant submitted an efficacy supplement to the Spiriva Handihaler NDA 21-395 (under Serial No. 029). In this submission, they provided the clinical trial report from the 4-year multi-center study, titled 'A randomized double-blind, placebo-controlled, parallel group trial assessing the rate of decline of lung function with tiotropium 18 mcg inhalation capsule once daily in patients with COPD' and the associated draft labeling based on the results of this study. Of note, this 4-year multi-national clinical trial is also referred to as the UPLIFT Study, i.e., Understanding Potential Long-term Impacts on Function with Tiotropium.

On January 30, 2009, the Applicant submitted a Complete Response to the FDA November 13, 2008 Complete Response letter for NDA 21-395 Serial No. 024. In this submission, they referred to the data and summaries from the UPLIFT clinical trial (Serial No. 029) to address the Division's comments regarding the reduction in COPD exacerbations, as well as stroke. On June 24, 2009, the Applicant formally withdrew the unapproved supplement Serial No. 024, and formally submitted the information supporting the proposed indication for the reduction of COPD exacerbations from Serial No. 24 to Serial No. 29. On July 22, 2009, the Applicant amended the efficacy supplement to remove the mortality claim. According to the Applicant, there was no new Spiriva Handihaler data contributing to this decision.

2.2 DATA SOURCES

The electronic submission of this NDA can be found at:
\\Fdswa150\nonectd\N21395\S_029\2008-11-17\
\\Fdswa150\nonectd\N21395\S_024\2009-01-30\

3 STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

3.1.1 DESIGN AND ANALYSIS PLAN

The primary objective of the clinical program is to supplement the Clinical Studies section of the product information with additional relevant information to prescribers concerning the long-term (4 year) efficacy and safety of tiotropium in the treatment of patients with COPD, based on the results from the UPLIFT study.

In the original efficacy supplement dated January 11, 2008, the Applicant included reports from one 6-month clinical trial with Spiriva HandiHaler (Study 266). In addition, the sponsor references two one-year phase 3 clinical studies with Spiriva Respimat (studies 254 and 255) as supportive evidence; however, the Division of Pulmonary and Allergy Products has determined that these studies are not adequate to support labeling of Spiriva Handihaler as the efficacy performance can be different for different formulations and/or devices. Statistical review of the efficacy results was conducted by Ruthanna Davi, Ph.D. Please refer to Dr. Davi's review of the design, analysis plan, and efficacy

results of Study 266. Any additional claims by the Applicant in the updated label that were not included in Dr. Davi's review will be presented in this review.

The following is taken from Dr. Davi's review (Conclusions and Recommendations Section).

> Study 266 provides evidence that the odds of a COPD exacerbation are reduced by Spiriva Handihaler relative to placebo. The percent of patients with a COPD exacerbation (i.e., one of the primary efficacy endpoints) was statistically significantly lower for Spiriva Handihaler compared to placebo (28% and 32%, respectively with p=0.04). The proportion of patients with hospitalization for exacerbation (i.e., the second primary efficacy endpoint) was numerically lower for those patients receiving Spiriva Handihaler than those receiving placebo; however, with a strict alpha of 0.05, the comparison did not reach statistical significance (7% and 10%, respectively with p=0.06).
>
> Time-to-event analyses of the primary efficacy endpoints were supportive of the efficacy of Spiriva Handihaler. Analysis of the time-to-first COPD exacerbation endpoint is of particular interest in this submission as the sponsor is proposing this claim in labeling. Because of the expected and observed correlation between this secondary analysis and the primary analysis and because this analysis was a selection from one of a limited number of secondary efficacy endpoints, it is unlikely that the significant result for the time-to-first COPD exacerbation analysis is an artifact of multiplicity. In addition, this type of analysis may be considered more appropriate than the primary analysis in that patients who dropped out of the study are censored.
>
> Numerical results for the primary efficacy endpoints sub-grouped by race and age did not reveal any substantively differing treatment effects.

In this submission, the document provides results from a four-year, multinational, randomized, double-blind, placebo-controlled, Phase 3 study (Study 235), comparing the rate of decline in FEV1 in patients with COPD receiving tiotropium to those receiving placebo in addition to their usual care for COPD (including short- and long-acting inhaled beta-adrenergics, steroids, and theophyllines but excluding inhaled anticholinergics). The study design is summarized as follows:

> Following an initial screening period, qualifying patients were randomized to tiotropium or placebo at Visit 2 (allocation ratio of 1:1). The randomization was in blocks of four by country and by site in sequence to prevent imbalanced allocation.
>
> Patients were seen after 1 month on treatment (Visit 3), at 3 months (Visit 4), and then every 3 months until study drug termination (at 4 years). At study drug termination, patients received open-label ipratropium for 30 days. The final visit occurred approximately 30 days post-treatment.
>
> Pulmonary function testing was conducted at the screening visit (Visit 1), randomization visit (Visit 2), Day 30 (Visit 3), and then every 6 months (Visits 5, 7, 9, 11, 13, 15, 17, and 19) until the end of treatment. Final pulmonary function testing was performed 30 days post-treatment.
>
> The St. George's Respiratory Questionnaire (SGRQ) was completed at the randomization visit (Visit 2) and then every 6 months (Visits 5, 7, 9, 11, 13, 15, 17, and 19) until the end of treatment. COPD exacerbations, concomitant therapies, and adverse events were monitored throughout the screening period and the 4-year treatment period.
>
> Of note that with the exception of inhaled anticholinergic agents, randomized patients were permitted to continue to use all of their previously prescribed respiratory medications during the treatment period. These concomitant respiratory medications included stable doses of inhaled corticosteroids, theophyllines, short-acting and long-acting beta agonists, and modest doses of oral corticosteroids.

Two primary efficacy endpoints were examined, which the Applicant referred to as 'co-primary endpoints'. They are:

1. Yearly rate of decline in trough FEVl from day 30 (steady state) until completion of double-blind treatment. Trough FEVl is the pre dose value measured approximately 24 hours after the previous dose of study drug.

2. Yearly rate of decline in FEVl measured 90 minutes after inhalation of study drug and ipratropium (and 30 minutes after inhalation of salbutamol) from day 30 (steady state) until completion of double-blind treatment.

The key secondary endpoints were time to first COPD exacerbation and time to first COPD exacerbation leading to hospitalization. A COPD Exacerbation was defined as an increase or new onset of more than one of the following respiratory symptoms (cough, sputum, sputum purulence, wheezing, dyspnea) with a duration of three or more days requiring treatment with antibiotics and/or systemic (oral, intramuscular or intravenous) steroids. According to the Applicant,

> This is based on data contained in the COPD module of the AE case report form. This will be confined to on-treatment exacerbation only, i.e. the starting date of exacerbation is after the treatment start day, and before the treatment end date (not including the 30-day washout period). All events recorded in the exacerbation module will be included in the efficacy analyses whether or not they meet all components of the protocol definition. Overlapping exacerbations were collapsed into one event. Unless otherwise specified, two exacerbations were considered distinct events if there was at least seven exacerbation-free days between the end of one event and the start of the next.

Other secondary endpoints the Applicant examined were:

1. Yearly rate of decline in trough FVC and slow vital capacity (SVC) from day 30 until completion of double-blind treatment. Trough FVC and SVC are the pre dose values measured approximately 24 hours after the previous dose of study drug.

2. Yearly rate of decline in FVC and SVC measured 90 minutes after inhalation of study drug and ipratropium (and 30 minutes after salbutamol) from day 30 until completion of double-blind treatment.

3. Yearly rate of decline in FEV1, FVC, and SVC prior to ipratropium and salbutamol inhalation from day 1 until completion of the trial (30 days post study drug treatment).

4. Yearly rate of decline in FEVl, FVC, and SVC measured 90 minutes after inhalation of ipratropium (and 30 minutes after inhalation of salbutamol) from day 1 until completion of the trial (30 days post study drug treatment).

5. Estimated mean pre- and post-bronchodilator FEVl, FVC, and SVC from day 30 until completion of double-blind treatment.

6. The rate of decline in trough FEV1, representing lung function 24 hours after inhalation of tiotropium, was chosen as one

7. Yearly rate of decline in St. George's Respiratory Questionnaire (SGRQ) total, impact, symptom, and activity scores from 6 months until completion of double-blind treatment.

8. Estimated mean SGRQ total, impact, symptom, and activity scores from 6 months until completion of double-blind treatment.

9. Some additional endpoints for COPD exacerbations and associated hospitalizations

The analysis plan is described as follows:

> Unless otherwise specified for specific analyses, all treated patients with at least 3 acceptable

spirometry test sets from Day 30 onward were included in the analyses for the pulmonary function testing endpoints. Sensitivity analyses were performed for decline in pre- and post-bronchodilator FEV1, FVC, and SVC in patients with at least 1 PFT measurement from Day 30 onward.

The co-primary endpoints of the yearly rate of decline in trough (pre-bronchodilator) FEV1 and the yearly rate of decline in post-bronchodilator FEV1 from Day 30 (steady state) to the end of double-blind treatment were analyzed using the random-effects model with center included as random effects. The pre- and post-bronchodilator FEV1 were assumed to follow linear trends over time. In the random-effects model, the intercept and slope were random coefficients, and their covariance matrix was assumed to be unstructured. Additional analyses for these endpoints include using the two-sample Wilcoxon (Mann-Whitney) rank sum test to compare the treatment groups from Day 1 until completion of the trial, and using a repeated measures ANOVA model with visit as a discrete variable to estimate and compare the mean of pre- and post-bronchodilator FEV1 at each visit from Day 30 between the two treatment groups.

As part of secondary analyses to the primary endpoints, a piecewise linear model with random effects was used to analyze the change of FEV1 from Day 1 to Day 30, and the rate of decline from Day 30 onward. The primary analysis was also carried out with adjusting for baseline covariates. In addition, to accommodate the FDA comments dated May 29, 2008, individual rate of decline from day 30 until completion of double-blind treatment will be calculated by taking the difference between the last on-treatment visit and visit 3 (day 30) divided by the time difference and this difference will be compared using Wilcoxon rank sum test.

The primary endpoint was also analyzed for the subgroups (age, gender, smoking status, baseline concomitant medication use, COPD severity according to GOLD stages, race, region, reversibility, BMI) using a random-effects model. Tables of baseline and demographic data and COPD background characteristics were created for each category of the subgroup analyses.

The two key secondary endpoints of time to the first COPD exacerbation and time to the first COPD exacerbation leading to hospitalization were compared between treatment groups using the log rank test. Additional analyses for these endpoints include: an estimate of the hazard ratio between treatment groups using Cox regression with a single covariate of treatment; the Kaplan-Meier estimate of the probability of not having the event (first COPD exacerbation or first COPD exacerbation requiring hospitalization) for each treatment group.

It was specified in the protocol that the number of COPD exacerbations and the number of hospitalizations for exacerbations will be compared between tiotropium and placebo using the Wilcoxon rank-sum test. For the interim analysis, the Poisson regression adjusted for overdispersion and exposure to treatment was requested for analyzing these two variables. Therefore, for the trial report, in addition to the specified analysis in the protocol, Poisson regression adjusted for overdispersion and exposure to treatment will be performed. In addition to the protocol-specified Wilcoxon rank sum test, the number of exacerbation days and number of days hospitalized due to exacerbation will be analyzed with the Poisson regression adjusted for overdispersion.

To accommodate the FDA comments dated May 29, 2008, all the exacerbation endpoints will be analyzed using the exacerbation data with seven days between distinct events. This data would allow for clear distinction between events. Number of exacerbation and number of exacerbations leading to hospitalization based on the Poisson model will also be analyzed using an exacerbation data with 1 day between events as sensitivity analysis.

Other spirometric endpoints (i.e. FVC or SVC) and SGRQ will be analyzed similar to the co-primary endpoints. Time-to-event will be analyzed using log-rank test and hazard ratio estimated using Cox regression. Count data between treatment groups, calculated by patient-year, will be estimated and compared using Poisson regression adjusting for overdispersion with Pearson's method. Treatment exposure was adjusted as the offset of the model. Count data between treatment groups, calculated per patient will be estimated and compared using Wilcoxon (MannWhitney) rank-sum test. For other count data (e.g. number of patients with at least one COPD exacerbation) will be compared using Fisher's exact test.

Of note, missing data were not imputed for the efficacy analyses.

In consideration of multiplicity in hypothesis testing, the following multiple testing strategies were used:

> 1. As defined in the protocol, hierarchical testing was performed for the co-primary endpoints. First, the rate of decline in pre-bronchodilator FEV1 was compared between the tiotropium and the placebo groups at a significance level of 0.049. If significance was achieved in favor of tiotropium, the rate of decline in postbronchodilator FEV1 results was compared between groups at a significance level of 0.049.
>
> 2. In parallel with the testing of the co-primary endpoints, the number of COPD exacerbations leading to hospitalizations per patient year was compared between treatment groups at the significance level of 0.001.
>
> 3. If statistical significance was achieved in favor of tiotropium for the co-primary endpoints, hierarchal testing of two key secondary endpoints, time to the first COPD exacerbation and time to the first COPD exacerbation leading to hospitalization, was performed using the log-rank test. First, the time to first exacerbation was tested at 0.049 level of significance. If significance was achieved, the time to the first COPD exacerbation leading to hospitalization was tested at 0.049 level of significance.
>
> 4. P-values for testing the co-primary endpoints, the number of COPD exacerbations leading to hospitalizations per patient year, and the two key secondary endpoints were adjusted for interim looks. For the other endpoints, p-values are reported at nominal p-values.
>
> By following this procedure, the overall probability of type I error is protected at 0.05 for the two co-primary endpoints, the number of COPD exacerbations leading to hospitalization per patient year, and the two key secondary endpoints.

Interim analyses were not planned in the protocol. However, after the protocol was finalized, a DSMB Charter was developed and interim analyses were planned. In their report, they stated that

> As specified in the DSMB Charter, independent interim safety analyses were conducted and reviewed by the DSMB at approximately 12 months, 24 months, 36 months, 48 months, and 54 months after trial initiation. Also as specified in the DSMB Charter, independent interim efficacy analyses were conducted and reviewed by the DSMB at approximately 24 and 36 months after the trial initiation. At 48 and 54 months, efficacy analyses were conducted and data packages were provided to the DSMB for review in the event they felt it was necessary.
>
> For the final efficacy analyses, the p-values for the co-primary endpoints, number of exacerbations leading to hospitalization, and the two key secondary endpoints were adjusted accordingly (for the DSMB efficacy data reviews at 24 and 36 months).
>
> For the interim analyses, stopping rules were based on the following efficacy endpoints: rates of decline in trough and 90 minutes post-bronchodilator FEV1 (co-primary endpoints) and the number of hospitalizations due to COPD exacerbations. As specified in the DSMB Charter, the type I error for the two co-primary endpoints was controlled at 0.049 level (two-tailed). The type I error for the number of hospitalizations due to COPD exacerbations per patient year was controlled at 0.001 level (two-tailed). The Lan-DeMets spending function for generating O'Brien-Fleming type stopping boundaries was used.

The sample size of 2916 patients per group (or 5832 total) was estimated to detect a difference of 15 mL in the rate of decline in FEV1 between tiotropium and placebo (standard deviation 90 mL) with 90% power assuming 35% patients dropout or without adequate data, and in order to conduct subgroup analyses with adequate power (e.g. 40% current smokers). The assumptions were based on data from previous long-term studies in patients with COPD and data from the one-year and six-month studies of tiotropium. Thus, a total of 6000 patients were planned.

During the course of the trial, the protocol was amended on three occasions. Amendment 1 (dated May 16, 2003) was made to include a validated generic quality of life instrument, the EQ-5D questionnaire. However, because this was added more than midway through the recruitment period, only the last 1235 patients from 13 countries with significant enrollment remaining were included in the study. Amendment 2 (dated November 15, 2005) was made to include the monitoring of long-term outcomes, specifically vital status information (i.e. 4-year mortality follow-up) on all randomized patients who prematurely discontinued from the study. Amendment 3 (dated April 25, 2007) was made to establish an external committee to independently assess the primary cause of death for all fatal cases. Changes in the planned analysis are summarized in Appendix 1.

3.1.2 DISPOSITION OF PATIENTS, DEMOGRAPHY AND BASELINE CHARACTERISTICS

In Study 235, a total of 8020 patients from 490 centers worldwide were screened for participation in the study. Of this, 5,993 patients were randomized into the study and took at least from 487 centers in 37 countries. The first patient was randomized on January 9, 2003. The last patient completed February 22, 2008. According to the Applicant,

> Several patients that had completed Visit 1 (screening) assessments and failed the screening period were incorrectly reported as randomizations. As a result, recruitment was stopped December 2003 and re-opened in January 2004 in order to reach the overall recruitment goal. Complete enrollment was achieved in 14 months.

One eligible patient withdrew at the randomization visit, prior to receiving study medication. One patient was randomized twice in error: once to placebo for 18 days (patient number 24741) and once to tiotropium for approximately 3 years (patient number 24780). For this patient, data have been included separately for both treatment exposures.

Table 1 summarizes the patient disposition and Appendix 2 summarizes the treatment exposure.

A total of 2457 (41%) patients prematurely discontinued study medication. Of note, patients were considered 'not prematurely discontinued' if they completed at least 1350 days of treatment and were not discontinued due to adverse events. Like in Study 266 (VA study), fewer patients in the tiotropium group (1,099 patients, 37%) prematurely discontinued trial medication than in the placebo group (1,358 patients, 45%). The highest percentage of discontinuations occurred in the first year of treatment (14% tiotropium, 20% placebo). In the tiotropium group there were 627 (21%) discontinuations due to adverse events and 412 (14%) discontinuations due to administrative reasons; while in the placebo group there were 746 (25%) patients who discontinued due to adverse events and 554 (18%) for administrative reasons. The most common adverse event is the worsening of the disease (i.e. COPD).

Table 1: Patient Disposition

	Placebo N (%)	Tio 18 mcg N (%)	Total N (%)
Screened	--	--	8016[1]
Not entered / randomized	--	--	2023[1]
Entered / randomized	3006	2987	5993[2]
Not treated	0	1	1
Treated	3006 (100.0)	2986 (100.0)	5992 (100.0)
Not prematurely discontinued from trial medication[3]	1648 (54.8)	1887 (63.2)	3535 (59.0)
Prematurely discontinued from trial medication	1358 (45.2)	1099 (36.8)	2457 (41.0)
Adverse event	746 (24.8)	627 (21.0)	1373 (22.9)
Worsening of disease under study	368 (12.2)	238 (8.0)	606 (10.1)
Worsening of other pre-existing disease	41 (1.4)	40 (1.3)	81 (1.4)
Other adverse event	337 (11.2)	349 (11.7)	686 (11.4)
Administrative	554 (18.4)	412 (13.8)	966 (16.1)
Non compliant with protocol	75 (2.5)	48 (1.6)	123 (2.1)
Lost to follow up	76 (2.5)	64 (2.1)	140 (2.3)
Consent withdrawn	403 (13.4)	300 (10.0)	703 (11.7)
Other	58 (1.9)	60 (2.0)	118 (2.0)

Source data: Table 15.1.1: 2

[1]Reflects the number of patients with case report form data available. Four additional patients were registered in IVRS. Actual total number of patients screened = 8020; actual total number of patients not entered = 2027.
[2]One patient was randomized twice in error.
[3]Patients were considered "not prematurely discontinued" if they completed at least 1350 days of treatment and were not discontinued due to an adverse event.

The following patients discontinued the trial due to 'Worsening of disease under study', but did not have an adverse event leading to treatment discontinuation coinciding with the date of termination of trial medication: Tiotropium: 18251, 21672, 21758, 23103, 23166, 26577. Placebo: 17991, 18479, 19013, 19018, 21499, 21812, 26130, 26143

Source: Clinical Study Report page 96 and Table 15 1 1:2, page 166

When patient disposition was analyzed using data provided by the Applicant, there is a discrepancy with patient 22842. In the report, patient 22842 was classified as 'Not prematurely discontinued from trial'. When the data was summarized according to the disposition, although this patient is classified as 'not stopped medication', this patient's extent of exposure is 1330 days and is classified as 'non-completer'. Therefore, there should be 1100 patients who prematurely discontinued from the study not 1099 as reported.

There are total of 93 subjects who dropped out of the study after 1350 days (Table 2). Of these, 43 subjects discontinued due to AE and these subjects are included in Table 1 and 50 subjects dropped out for other reasons. These 50 subjects are classified as 'not prematurely discontinued from trial medication' according to the definition provided by the Applicant. Of note, there are slightly more subjects in Tiotropium group who discontinued after 1350 days compared to placebo; but these proportions are very small.

Table 2: Patient Disposition – Discontinued from trial medication after 1350 days

	Placebo N=3006	Tio 18 mcg N = 2986	Total N = 5992
Administrative	9 (0.3%)	19 (0.6%)	28 (0.5%)
Lost to follow-up	2	4	6
Non compliance to Protocol	3	4	7
Refused to continue medication	4	11	15
Other	7 (0.2%)	15 (0.5%)	22 (0.4%)
AE*	31 (1%)	33 (1%)	64 (1%)
Worsening of disease under study	10	7	17
Worsening of other pre-existing disease	2	2	4
Other AE	19	24	43

* Discontinued due to AE included in Table 1

The Applicant reported several protocol violations (see Appendix 3 and Appendix 4). Treatment allocation was unblinded for 22 patients during the study (9 in the tiotropium group and 13 in the placebo group). All these patients had experienced at least one adverse event: 8 were related to exacerbations of COPD (6 in the placebo group and 2 in the tiotropium group) and 2 were due to sudden death (1 in each group). A total of 440 patients were reported to have protocol violations; 8% (223 patients) of the tiotropium group and 7% (217 patients) of the placebo group. The majority of protocol violations were due to use of anticholinergics on at least 2 consecutive visits, improper wash out of medication, failure to meet the inclusion criteria of post-bronchodilator FEV1 <70 % of predicted or post-bronchodilator FEV1 <70% of FVC at Visits 1 and 2, or respiratory infection/COPD exacerbation in the 4 weeks prior to screening (Visit 1) or between Visits 1 and 2.

In the Statistical Analysis Plan, the Applicant reported fraudulent PFT data for the following patients and visits: patient 18956 visits 9 and 10, patient 18933 visit 9, patient 18974 visits 7 and 9, patient 18932 visits 3 and 5. This was revealed during an audit at one of the investigator sites (specifically Site #5555, Dr. Kemmerich in Germany). There are 28 patients enrolled in Site DE005555.

Sensitivity analyses will be performed to the efficacy endpoints by excluding patients from Site 5555, by excluding patients who were unblinded, and by excluding patients with protocol violations.

Demographic characteristics of subjects at baseline were generally well balanced across treatment groups (Appendix 5). The majority of subjects were men (75%) and Caucasian (90%). The mean age was 65 years and median weight was 78 kg. The majority of subjects was ex-smokers (70%) and on average smoked 49 packs per year. The average duration of COPD is 10 years. The disease characteristics at baseline, including spirometric endpoints like FEV_1 (Appendix 6) and SGRQ scores (Appendix 7) were also generally similar across the randomized groups. Use of pulmonary medication at baseline, defined as within 2 months of entry, is displayed in Appendix 8. Patients taking pulmonary medication were balanced between the treatment groups. At baseline, a total of 67% patients were taking inhaled corticosteroids (ICS), and 60% patients were on long-acting beta adrenergics (LABA). Overall, 93% patients were taking a pulmonary medication.

The following criteria are used to identify the study population to be analyzed:

- For the analysis of rate of decline in pre- or post-bronchodilator FEV1, FVC, or SVC, treated patients with at least three corresponding acceptable PFT measurements after (including) Day 30 (Visit 2) until the completion of double-blinded treatment (Visit 19) were included. As a sensitivity analysis, the analysis of rate of decline was conducted for patients with at least 1 acceptable PFT measurement between Day 30 and completion of double-blinded treatment.
- For the analysis of rate of decline in the SGRQ activity, impact, symptom and total scores, patients with at least 2 measurements between (including) months 6 (Visit 5) and the completion of double-blinded treatment (Visit 19) were included. As a sensitivity analysis, rate of decline for the SGRQ endpoints was estimated for patients with at least 1 measurement between Visits 5 and 19. Turkish patients (N=128, or 2% of the treated set) were not included for the analysis of SGRQ endpoints due to a missing question in the Turkish version of the questionnaire.
- Evaluation of the secondary endpoints associated with COPD exacerbation and COPD exacerbation leading to hospitalization was performed for the treated set defined as all patients who were randomized and treated with at least one dose of the study medication.

The following (Table 3) summarizes the number of patients included for the analysis of the efficacy endpoints.

Table 3: Patients included for the analysis of the efficacy endpoints

	Placebo N (%)	Tio 18 mcg N (%)	Total N (%)
Total treated (treated set)	3006 (100.0)	2986 (100.0)	5992 (100.0)
PFT*			
Post-bronchodilator FEV_1	2410 (80.2)	2554 (85.5)	4964 (82.8)
Post-bronchodilator FVC	2410 (80.2)	2554 (85.5)	4964 (82.8)
Post-bronchodilator SVC	2383 (79.3)	2527 (84.6)	4910 (81.9)
Pre-bronchodilator FEV_1	2413 (80.3)	2557 (85.6)	4970 (82.9)
Pre-bronchodilator FVC	2413 (80.3)	2557 (85.6)	4970 (82.9)
Pre-bronchodilator SVC	2374 (79.0)	2531 (84.8)	4905 (81.9)
SGRQ**			
Activity score	2362 (78.6)	2505 (83.9)	4867 (81.2)
Impact score	2362 (78.6)	2505 (83.9)	4867 (81.2)
Symptom score	2364 (78.6)	2512 (84.1)	4876 (81.4)
Total score	2362 (78.6)	2505 (83.9)	4867 (81.2)

Source data: Table 15.1.3: 1.
* Including patients with at least 3 acceptable measurements between Visits 3 and 19;
** Including patients with at least 2 measurements between Visits 5 and 19; excluding Turkish patients.

Source: Clinical Study Report, Table 11.1:1 page 101

3.1.3 PRIMARY EFFICACY ENDPOINTS

The two primary endpoints, rates of decline of pre- and post-bronchodilator FEV_1, did not achieve statistical significance (Table 4). When sensitivity analyses (1 – 3) were performed, similar results of no significant treatment difference were observed. Additional analyses (Sensitivity #4 – #5) were conducted by the Applicant. These are done by applying nonparametric test to compare the change in lung function (i.e. FEV_1) from Day 1 until completion of the trial, and from Day 30 until

completion of the double-blind treatment period. Although the treatment difference for post-bronchodilator was statistically significant when comparing the change in FEV1 from Day 1 until completion of the trial (p-value=0.0145), 44% of patients did not have end of trial visit and were excluded from the analysis. Therefore, the result may not be reliable. I also conducted additional analyses to the primary endpoint (Sensitivity Analyses # 6 to # 8) by excluding patients from Site 5555, by excluding patients who were unblinded, and by excluding patients with protocol violations, respectively. Similar results of no significant treatment difference were observed.

The Applicant also conducted subgroup analyses on the primary endpoints. The subgroups were pre-specified as follows: age (<55; 55-<65; 65-<75; ≥75 years), gender (male; female), smoking status (smoker; ex-smoker), baseline LABA use (yes; no), baseline ICS use, baseline use of ICS and LABA combination, baseline anticholinergic use, GOLD stage (I/II; III; IV), race (Asian; Black; White), region (Asia; Eastern Europe; Western Europe; Latin America; USA), reversibility, and BMI (<20; 20-<25; 25-<30; ≥30 kg/m^2). The results from subgroup analyses are summarized in Appendix 9. There were no significant treatment-by-subgroup interactions detected in any subgroups. There was a treatment difference in the rate of decline in post-bronchodilator FEV1 observed in GOLD stage I/II patients. None of the other subgroups showed any treatment difference.

Additional subgroup analysis was conducted by the Applicant based on the change of smoking status (i.e. sustained ex-smokers, sustained smokers, and intermittent smokers/ex-smokers). The rates of decline in pre- or post-bronchodilator were comparable between the treatment groups for all smoker subgroups.

Table 4: Rate of decline in pre- or post-bronchodilator FEV_1 from Day 30 until completion of double-blind treatment

	Placebo		Tiotopium		Difference		
	N	Mean (SE) [ml/yr]	N	Mean (SE) [ml/yr]	Mean (SE) [ml/yr]	95% CI	p-value
Primary							
Pre-BD	**2413**	**-30 (1)**	**2557**	**-30 (1)**	**0 (2)**	**(-4, 4)**	**0.9524**
Post-BD	**2410**	**-42 (1)**	**2554**	**-40 (1)**	**2 (2)**	**(-2, 6)**	**0.2074**
Sensitivity #1							
Pre-BD	2863	-29 (1)	2906	-29 (1)	-0 (2)	(-4, 4)	0.9791
Post-BD	2851	-41 (1)	2904	-39 (1)	2 (2)	(-2, 6)	0.2367
Sensitivity #2							
Pre-BD	2413	-30 (1)	2557	-30 (1)	0 (2)	(-4, 4)	0.9017
Post-BD	2410	-43 (1)	2554	-40 (1)	3 (2)	(-1, 7)	0.1662
Sensitivity #3							
Pre-BD	2413	-31 (1)	2557	-31 (1)	0 (2)	(-4, 4)	0.8886
Post-BD	2410	-43 (1)	2554	-41 (1)	3 (2)	(-1, 7)	0.1738
Sensitivity #4							
Pre-BD	2385	-28	2532	-29			0.4357
Post-BD	2389	-41	2534	-38			0.1072
Sensitivity #5							
Pre-BD	1618	-17	1803	-15			0.2488
Post-BD	1613	-32	1805	-27			0.0145
Sensitivity #6							
Pre-BD	2403	-30 (1)	2547	-30 (1)	0 (2)		0.9349
Post-BD	2400	-42 (1)	2544	-40 (1)	3 (2)		0.1886
Sensitivity #7							
Pre-BD	2405	-30 (1)	2549	-30 (1)	0 (2)		0.9293
Post-BD	2403	-42 (1)	2546	-40 (1)	2 (2)		0.1940
Sensitivity #8							
Pre-BD	2233	-31 (1)	2368	-30 (1)	0 (2)	(-4, 4)	0.8626
Post-BD	2229	-42 (1)	2364	-40 (1)	2 (2)	(-2, 6)	0.2026

Pre-BD: pre-bronchodilator FEV_1 Post-PB: post-bronchodilator FEV_1
Statistical Method: Random effects model with intercept and slope as random coefficients, assuming pre- and post-bronchodilator FEV_1 following linear trend and assuming covariance matrix as unstructured.
Primary: treated set with at least 3 measurement after (including) day 30 until completion of double-blind treatment.
Sensitivity #1: analysis of primary endpoint based on treated set with at least 1 measurement after (including) day 30
Sensitivity #2: analysis of primary endpoint with center as random effect
Sensitivity #3: analysis of primary endpoint when adjusted for baseline covariates, including post-bronchodilator FEV_1, age, sex, height and smoking status in the random effect model.
Sensitivity #4: Re-analysis of the rate of decline in FEV1 from Day 30 until end of treatment using non-parametric approach. Median scores are reported for the difference in FEV1 at last on-treatment visit and on Day 30, divided by the duration between visits. P-values were calculated based on Wilcoxon Rank Sum test.
Sensitivity #5: Rate of decline in FEV1 from Day 1 until end of trial using non-parametric approach. Median scores are reported for the difference in FEV1 at last trial visit and on Day 1, divided by the duration between visits. P-values were calculated based on Wilcoxon Rank Sum test.
Sensitivity #6: Reviewer's excluding site 5555 (Dr. Kemmerich) from the primary analysis
Sensitivity #7: Reviewer's excluding patients that were unblinded from the primary analysis
Sensitivity #8: Reviewer's excluding patients that had protocol violations from the primary analysis
Source: Clinical Study Report, Table 11..4.1.1:1 (page 107), Table 15.2.1:7 (page 386), Table 15.2.1.:13 (page 392), and Table 15.2.1:6 (page 385), Table 15.2.1: 14 (page 393), and . Table 11..4.1.2.2:1 (page 112)

The following two figures describe the time course of the FEV_1 pre- and post-bronchodilator. Of note, these figures include all available data and are based on raw means.

Figure 1: Time course of FEV_1 prior to bronchodilators on the test days

Figure 2: Time course of FEV_1 post-bronchodilators on the test days

Additional Analyses

The Applicant also assessed the pre- and post-bronchodilators FEV_1 by comparing the overall mean treatment difference and by comparing treatment difference of the mean pre- and post-bronchodilators FEV_1 by visit. The results are presented in Figure 3 and Figure 4 and summarized in Appendix 10. There is an initial increase of 105 ml and 71 ml in mean pre- and post-bronchodilator FEV_1, respectively, at Visit 3 (Day 30 – vertical line) from baseline in the tiotropium group compared to 18 ml and 25 ml in mean pre- and post-bronchodilator FEV_1, respectively, in the placebo group. The treatment difference in the mean pre- and post-bronchodilators FEV_1 was evident as early as Day 30 and was maintained throughout the trial. Despite the concurrent administration of ipatropium and salbutamol in both treatment groups after inhalation of study drug, the mean post-bronchodilators FEV_1 was consistently higher in the tiotropium group compared to the placebo group.

For the mean pre-bronchodilator FEV_1, the estimated mean treatment difference ranged from 87 to 103 ml and an overall mean difference of 94 ml. For the mean post-bronchodilator FEV_1, the estimated mean treatment difference ranged from 47 to 65 ml and an overall mean difference of 57 ml.

I conducted additional analyses to assess the sensitivity of the results when some patients are removed from the analysis. The results are summarized in Table 5 for the overall mean difference and are in agreement with the Applicant's results.

Figure 3: Estimated* mean FEV_1 pre-bronchodilators by Visits – treated set with at least 3 measurements between Visits 3 – 19 (or Months 1 – 48)

Source: Clinical Study Report, Figure 11.4.1.2.2:1 page 111; *Estimated (least squares) means are based on repeated measures ANOVA model with visit as a discrete variable and baseline value as a covariate.

Figure 4: Estimated* mean FEV_1 post-bronchodilators by Visits – treated set with at least 3 measurements between Visits 3 – 19 (or Months 1 – 48)

Source: Clinical Study Report, Figure 11.4.1.2.2:2 page 112; *Estimated (least squares) means are based on repeated measures ANOVA model with visit as a discrete variable and baseline value as a covariate.

Table 5: Estimated* mean pre- or post-bronchodilator FEV_1 from Day 30 until completion of double-blind treatment - Treated set with at least 3 measurements between Visits 3 – 19 (or Months 1 – 48)

	Treatment		Difference		
	Placebo Mean (SE)	Titropium Mean (SE)	Mean (SE) [ml/yr]	95% CI	p-value
Original					
Pre-BD	**1.080 (0.004)**	**1.174 (0.004)**	**0.094**	**(0.084, 0.105)**	**<0.0001**
Post-BD	**1.298 (0.004)**	**1.354 (0.004)**	**0.057**	**(0.046, 0.067)**	**<0.0001**
Sensitivity #1					
Pre-BD	1.080 (0.004)	1.174 (0.004)	0.094	(0.084, 0.105)	<0.0001
Post-BD	1.298 (0.004)	1.354 (0.004)	0.057	(0.046, 0.067)	<0.0001
Sensitivity #2					
Pre-BD	1.080 (0.004)	1.175 (0.004)	0.095	(0.084, 0.105)	<0.0001
Post-BD	1.298 (0.004)	1.355 (0.004)	0.057	(0.047, 0.068)	<0.0001
Sensitivity #3					
Pre-BD	1.086 (0.004)	1.180 (0.004)	0.094	(0.084, 0.105)	<0.0001
Post-BD	1.305 (0.004)	1.362 (0.004)	0.057	(0.047, 0.068)	<0.0001
Sensitivity #4					
Pre-BD	1.074 (0.004)	1.168 (0.004)	0.095	(0.085, 0.104)	<0.0001
Post-BD	1.291 (0.004)	1.346 (0.004)	0.055	(0.045, 0.065)	<0.0001

*Estimated (least squares) means are based on repeated measures ANOVA model with visit as a discrete variable and baseline value as a covariate
Sensitivity #1: Excluding site 5555 (Dr Kemmerich) from the analysis
Sensitivity #2: Excluding patients that were unblinded from the analysis
Sensitivity #3: Excluding patients that had protocol violations from the analysis
Sensitivity #4: analysis of endpoint based on treated set with at least 1 measurement after (including) day 30

Responder Analyses

An alternate way to view the treatment effect is to explore the proportion of patients who had at least 15% improvement in pre- and post-bronchodilators FEV_1 at each Visit from baseline. Only patients with baseline score and had at least 3 measurements between Months 1 to 48 are included in the calculation. Patients who discontinued from the study regardless of reason are considered non-responders. Last observed FEV_1 score is imputed to missing post-baseline FEV_1 scores. Of note, patients who responded at one time point do necessarily respond to other time points.

The results are presented in Figure 5 and Figure 6, for pre- and post-bronchodilators FEV_1, respectively.

At Month 1, 33% of patients treated with tiotropium achieved the level of response (i.e. 15% improvement from baseline) in (trough) pre-bronchodilator FEV_1 compared to 16% in the placebo group (i.e. 17% treatment difference in the proportions of responder). At Month 48, there is roughly 7% difference in the proportions of responder between tiotropium (16%) and placebo (9%).

For post-bronchodilator FEV_1, the proportions of responder in both treatment groups are generally smaller compared to when pre-bronchodilator FEV_1 measurements are used. However, the proportion of responder remains higher in the tiotropium group compared to the placebo group across all visits, particularly prior to Year 1 (or Month 12).

Figure 5: Proportion of Responders* (i.e. 15% Improvement from baseline) Pre-Bronchodilator FEV_1 by Visits – treated set with at least 3 measurements between Visits 3 – 19 (or Months 1 – 48) and have baseline score

*Note: Patients who responded at one time point do not necessarily respond across all time points

Figure 6: Proportion of Responders (i.e. 15% Improvement from baseline) Post-Bronchodilator FEV_1 by Visits – treated set with at least 3 measurements between Visits 3 – 19 (or Months 1 – 48) and have baseline score

*Note: Patients who responded at one time point do not necessarily respond across all time points

Continuous responder analyses by Visit are explored for the pre- and post-bronchodilators FEV1 scores (Figure 7 and Figure 8, respectively). In these plots, only patients with baseline score and had at least 3 measurements between Months 1 to 48 are included in the calculation. Patients who discontinued from the study regardless of reason are considered non-responders. Last observed FEV1 score is imputed to missing post-baseline FEV1 scores.

These figures were created to provide a visual display of the relative benefit of tiotropium across the entire range of response, as well over the period of double-blind treatment. The x-axis shows the percent improvement in FEV1 score from baseline to endpoint, and the y-axis shows the corresponding percentage of patients achieving that level of response.

From the plots for pre- and post-bronchodilators FEV_1 scores there is clear evidence that a higher proportion of patients treated with tiotropium responded better compared to the placebo as early as Month 1. Visually, the difference was maintained until Month 48 for the pre-bronchodilator FEV_1, and until at least until Month 24 for the post-bronchodilator FEV_1.

Figure 7: Response Profile Pre-Bronchodilator FEV_1 by Visits – treated set with at least 3 measurements between Visits 3 – 19 (or Months 1 – 48) and have baseline score

Month 1

Month 6

Month 12

Month 18

Month 24

Month 30

Month 36

Month 42

Month 48/EOT

Figure 8: Response Profile Post-Bronchodilator FEV_1 by Visits – treated set with at least 3 measurements between Visits 3 – 19 (or Months 1 – 48) and have baseline score

Month 1

Month 6

Month 12

Month 18

Month 24

Month 30

Month 36

Month 42

Month 48/EOT

3.1.4 KEY SECONDARY ENDPOINTS

Time to the first COPD exacerbation

Figure 9 presents the Kaplan-Meier estimates of the probability of no COPD exacerbation. Although there is no treatment difference in the proportion of patients with at least one COPD exacerbation, data suggests that tiotropium reduced the risk of COPD exacerbation by 14% compared with placebo. This is based on the estimated hazard ratio (using Cox model) of 0.86 [95% CI: (0.81, 0.91)] between tiotropium and placebo. Furthermore, based on Kaplan-Meier estimates, the median time to first COPD exacerbation in the tiotropium group is 16.7 months compared to 12.5 months in the placebo group. This implies a four-month delay in the time to first exacerbation in the tiotropium-treated patients compared to placebo-treated patients.

Additional analyses were conducted to assess the COPD exacerbations and the results are summarized in Table 6. The results that tiotropium reduced the risk of COPD exacerbation by about 14% were consistent when patient-year is applied or when COPD exacerbation were explored in patients treated with steroids or treated with antibiotics.

Figure 9: Kaplan-Meier estimates of the probability of no COPD exacerbation – treated set

Source: Clinical Study Report, Figure 11.4.1.2.1:1, page 109, Table 15.2.5.1:2 page 427, Table 14.2.5.2:4 page 434

Table 6: Analysis of COPD exacerbation

	Placebo N=3006 PY=8499.46	Tiotropium N=2986 PY=9222.31	Ratio or Difference 95% CI	p-value
Median time to first exacerbation (months)*	12.5	16.7	HR: 0.86 (0.81, 0.91)	<0.0001
No. of patients with at least one exacerbation†	2049 (68%)	2001 (67%)		0.3481
Estimated no. (rate) of COPD exacerbations per patient year ‡	7183 (0.85)	6691 (0.73)	Ratio: 0.86 (0.81, 0.91)	<0.0001
Patients treated with steroids				
Median time to first exacerbation (months)*	26.4	36.5	HR: 0.84 (0.78, 0.90)	<0.0001
No. of patients with at least one Exacerbation†	1561 (52%)	1490 (50%)		
Estimated no. (rate) of COPD exacerbations per PY‡	4432 (0.52)	4051 (0.44)	Ratio: 0.84 (0.78, 0.91)	<0.0001
Patients treated with antibiotics				
Median time to first exacerbation (months)*	16.2	19.8	HR: 0.87 (0.81, 0.93)	<0.0001
No. of patients with at least one Exacerbation†	1917 (64%)	1887 (63%)		
Estimated no. (rate) of COPD exacerbations per PY‡	6076 (0.71)	5741 (0.62)	Ratio: 0.87 (0.82, 0.93)	<0.0001

*Hazard ratio based on Cox model with single covariate treatment; p-value was obtained using log-rank test.
†p-value was calculated using Fisher's exact test
‡Ratio and p-value were calculated using Poisson regression adjusting for overdispersion with Pearson's method. Treatment exposure was adjusted as the offset of the model. Of note, two exacerbation events were considered distinct if there were a 7-day gap.
Source: Clinical Study Report Table 15.2.5.1:2, page 427; Table 15.2.5.2:4, page 434, Table 11.4.1.2.2:4, page 121, Table 15.2.5.1:3 page 428, Table 14.2.5.2 :6, page 436, Table 15.2.5.1:4 page 429, Table 14.2.5.2 :7, page 437

When comparing time to first COPD exacerbation between treatment groups, patients who dropped out of the study are considered 'censored' observations, and assume they are noninformative. In fact, the results generated in Figure 9 and Table 6 all considered dropouts as being noninformative. However, COPD exacerbation is an adverse event and most likely correlated with other adverse events. This implies that patients who discontinued from the study due to adverse events and did not have exacerbation may likely to exacerbate if they continue from the study. In Table 7, with and without COPD exacerbation are explored by patient disposition. The objective is to explore if there is a difference in the proportion of discontinued patients (particularly due to AE) among those with exacerbation and without exacerbation. Although a higher proportion of patients in the 'without exacerbation' group discontinued from the study, the magnitude of the difference between treatment groups are the same in the 'with exacerbation' group and the 'without exacerbation' group. In particular, the magnitude of the difference between treatment groups in the proportion that discontinued due to AEs is almost the same in the 'with exacerbation' group and the 'without exacerbation' group. Thus, additional analysis assigning patients who discontinued as 'with exacerbation' will most likely yield the same conclusion.

Table 7: Patient with at least one exacerbation by Disposition

	With Exacerbation		Without Exacerbation	
	Placebo N=2049	Tiotropium N=2001	Placebo N=957	Tiotropium N=985
Completed	1245 (61%)	1356 (68%)	403 (42%)	531 (54%)
Discontinued	**804 (39%)**	**645 (32%)**	**554 (58%)**	**454 (46%)**
AE	502 (25%)	421 (21%)	244 (26%)	206 (21%)
Lost to Follow-Up	26 (1%)	22 (1%)	50 (5%)	42 (4%)
Refused to Continue Medication	203 (10%)	149 (7%)	200 (21%)	151 (15%)
Other	73 (4%)	53 (3%)	60 (6%)	55 (6%)

Time to the first COPD exacerbation leading to hospitalization

The Kaplan-Meier estimates of the probability of no COPD exacerbation leading to hospitalization is presented in Figure 10. This includes a subset of patients with COPD exacerbation (i.e. patients that were hospitalized), thus the sample (numerator) is smaller. Similar to COPD exacerbation, although there is no treatment difference in the proportion of patients with at least one COPD exacerbation leading to hospitalization, there is some evidence that tiotropium reduced the risk of COPD exacerbation leading to hospitalization by 14% compared with placebo (Table 8). This is based on the estimated hazard ratio (using Cox model) of 0.86 [95% CI: (0.78, 0.95)] between tiotropium and placebo. Based on Kaplan-Meier estimates, the lower quartile time to first hospitalization due to COPD exacerbation in the tiotropium group is 35.9 months compared to 28.6 months in the placebo group. This implies a seven-month delay in the time to first exacerbation leading to hospitalization in the tiotropium-treated patients compared to placebo-treated patients.

A Poisson model with adjustment for overdispersion was used to estimate the mean number of exacerbation leading to hospitalization. Log-exposure was used in the model as the offset. The treatment difference measured by rate ratio, 0.94 [95% CI (0.82, 1.07)] for tiotropium vs. placebo, was not significant (p-value=0.3413).

Figure 10: Kaplan-Meier estimates of the probability of no COPD exacerbation leading to hospitalization – treated set

Source: Clinical Study Report, Figure 11.4.1.2.1:2, page 110, Table 15.2.6.1:2 page 444

Table 8: Analysis of COPD exacerbation leading to hospitalization

	Placebo N=3006 PY=8499.46	Tiotropium N=2986 PY=9222.31	Ratio or Difference 95% CI	p-value
Lower quartile time to first hospitalization due to exacerbation (months)	28.6	35.9	HR: 0.86 (0.78, 0.95)	0.0024
No. of patients with at least one exacerbation	811 (27%)	759 (25%)		0.1766
Estimated no. (rate) of COPD exacerbations leading to hospitalization per patient year	1379 (0.16)	1403 (0.15)	Ratio: 0.94 (0.82, 1.07)	0.3413

Source: Clinical Study Report Table 15.2.6.1:2 page 444, Table 14.2.6.2:3 page 448, Table 15.2.6.2:1 page 446

3.1.5 ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)

For SGRQ endpoints, an increase in scores indicated worsening of quality of life, while a decrease indicated improved quality of life.

Random effects model was used to estimate the rate of decline in SGRQ scores (Table 10). There was no treatment difference in SGRQ activity, impact and total scores. For symptom scores, tiotropium group showed a higher rate of increase (or worsening) than the placebo group did. According to the Applicant, this was due to the different change of symptom score between months 42 and 48, which can be attributed to higher dropout rate in the placebo group.

Table 9: Rate of increase in SGRQ scores from Month 6 until completion of treatment – treated set with at least 2 acceptable measurements

	Placebo		Tio 18 mcg		Difference (Tio 18 mcg - Placebo)		
Time point	N	Mean (SE) [per year]	N	Mean (SE) [per year]	Mean (SE) [per year]	95% CI	P-value
Activity	2362	1.51 (0.11)	2505	1.40 (0.11)	-0.11 (0.15)	(-0.4, 0.2)	0.4717
Impact	2362	1.18 (0.10)	2505	1.18 (0.10)	-0.00 (0.14)	(-0.3, 0.3)	0.9889
Symptom	2364	0.55 (0.14)	2512	1.00 (0.13)	0.45 (0.19)	(0.1, 0.8)	0.0171
Total	2362	1.21 (0.09)	2505	1.25 (0.09)	0.04 (0.13)	(-0.2, 0.3)	0.7840

Source data: Table 15.2.4: 2.

Source: Clinical Study Report Tabl 11 4 1 2 2:3 page 117

3.1.6 OTHER PULMONARY FUNCTION TESTING

Like the primary endpoint pre- and post-bronchodilator FEV_1, similar analyses are conducted to compare the yearly decline of pre- and post-bronchodilator Forced Vital Capacity (FVC) and pre- and post-bronchodilator Slow Vital Capacity (SVC) between tiotropium 18 mcg and placebo.

3.1.6.1 Forced Vital Capacity (FVC)

The results for the analyses of yearly rate of decline of pre- and post-bronchodilator FVC are summarized in Table 10. There were no significant treatment differences in the yearly rate of decline of pre- and post-bronchodilator FVC.

Table 10: Rate of decline in pre- or post-bronchodilator FVC

	Placebo		Tiotopium		Difference		
	N	Mean (SE) [ml/yr]	N	Mean (SE) [ml/yr]	Mean (SE) [ml/yr]	95% CI	p-value
Random Effects Model							
Pre-BD	**2413**	**-39 (3)**	**2557**	**-43 (3)**	**4 (4)**	**(-4, 12)**	**0.2990**
Post-BD	**2410**	**-61 (3)**	**2554**	**-61 (3)**	**1 (4)**	**(-7, 9)**	**0.8375**
Sensitivity #1							
Pre-BD	2863	-37 (3)	2906	-42 (3)	4 (4)	(-4, 12)	0.2463
Post-BD	2851	-59 (3)	2904	-61 (3)	1 (4)	(-7, 9)	0.7600
Sensitivity #2							
Pre-BD	1618	-12	1803	-10			0.2705
Post-BD	1613	-40	1805	-40			0.3060

Pre-BD: pre-bronchodilator FVC Post-PB: post-bronchodilator FVC
Primary: treated set with at least 3 measurement after (including) day 30 until completion of double-blind treatment
Sensitivity #1: analysis of primary endpoint based on treated set with at least 1 measurement after (including) day 30
Sensitivity #2: Rate of decline in FVC from Day 1 until end of trial using non-parametric approach Median scores are reported for the difference in FVC at last trial visit and on Day 1, divided by the duration between visits P-values were calculated based on Wilcoxon Rank Sum test
Source: Clinical Study Report, Table 11 4 1 2 2:2 (page 113), Table 15 2 2:4 (page 400), Table 15 2 2 : 3 (page 399)

3.1.6.2 Slow Vital Capacity

The results for the analyses of yearly rate of decline of pre- and post-bronchodilator SVC are summarized in Table 11. There were no significant treatment differences in the yearly rate of decline of pre- and post-bronchodilator SVC.

Table 11: Rate of decline in pre- or post-bronchodilator SVC

	Placebo		Tiotopium		Difference		
	N	Mean (SE) [ml/yr]	N	Mean (SE) [ml/yr]	Mean (SE) [ml/yr]	95% CI	p-value
Random Effects Model							
Pre-BD	**2374**	**-41 (3)**	**2531**	**-47 (3)**	**6 (4)**	**(-2, 14)**	**0.1143**
Post-BD	**2383**	**-65 (3)**	**2527**	**-66 (3)**	**1 (4)**	**(-7, 9)**	**0.7870**
Sensitivity #1							
Pre-BD	2851	-40 (3)	2895	-47 (3)	6 (4)	(-2, 14)	0.0928
Post-BD	2842	-64 (3)	2894	-65 (3)	1 (4)	(-7, 9)	0.8022
Sensitivity #2							
Pre-BD	1562	-17	1706	-17			0.8103
Post-BD	1540	-46	1711	-42			0.9814

Pre-BD: pre-bronchodilator SVC Post-PB: post-bronchodilator SVC
Primary: treated set with at least 3 measurement after (including) day 30 until completion of double-blind treatment
Sensitivity #1: analysis of primary endpoint based on treated set with at least 1 measurement after (including) day 30
Sensitivity #2: Rate of decline in SVC from Day 1 until end of trial using non-parametric approach Median scores are reported for the difference in SVC at last trial visit and on Day 1, divided by the duration between visits P-values were calculated based on Wilcoxon Rank Sum test
Source: Clinical Study Report, Table 11 4 1 2 2:2 (page 113), Table 15 2 3:4 (page 408), Table 15 2 3 : 3 (page 407)

3.1.7 EFFICACY CONCLUSION

After careful review of the UPLIFT Study, the following are the results from the analyses of the primary and secondary endpoints.

1. The two primary endpoints, rates of decline of pre- and post-bronchodilator FEV_1, did not achieve statistical significance when tiotropium was compared to placebo.

2. Additional analyses on the lung function FEV_1 produced the following results:

    a. When mean pre- or post-bronchodilator FEV_1 were estimated in the UPLIFT study, there is an initial increase of 105 and 71 ml, respectively, at Visit 3 (or Day 30) from baseline in the tiotropium group. Numerically, the treatment difference in mean pre- or post-bronchodilator FEV_1 was evident at Visit 3, and the difference was maintained throughout the trial. The overall mean treatment difference in mean pre-bronchodilator FEV_1 was 94 ml and 57 ml in mean post-bronchodilator FEV_1.
    b. Based on responder analysis, defined as 15% improvement in mean pre- or post-bronchodilator FEV_1 from baseline across all timepoints, 33% of patients treated with tiotropium achieved the level of response at Visit 3 (Day 30) in pre-bronchodilator FEV_1 compared to 16% in the placebo group (i.e. 17% treatment difference in the proportions of responder). At Month 48, there is roughly 7% difference in the proportions of responder between tiotropium (16%) and placebo (9%). For post-bronchodilator FEV1, the proportions of responder in both treatment groups are generally smaller compared to when pre-bronchodilator FEV1 measurements are used. However, the proportion of responder remains higher in the tiotropium group compared to the placebo group across all visits, particularly prior to Year 1 (or Month 12).

3. The following are results from the analyses of COPD exacerbation. Of note, the pre-specified multiplicity adjustment (i.e. hierarchical strategy) by the Applicant requires that the co-primary endpoints needs to achieve statistical significance prior to considering the 'key' secondary endpoints. Because the primary endpoints did not achieve statistical significance, caution needs to be exercised in making inferences for secondary endpoints. I will discuss this further in Section 5.1.

    a. There is no treatment difference in the proportion of patients with at least one COPD exacerbation. However when treatment exposure is taken into account, the estimated rate of COPD exacerbation per patient year is lower in the tiotropium group (rate=0.73) compared to the placebo group (rate=0.85). The rate ratio of 0.86 suggested a 14% reduction of COPD exacerbation events in the tiotropium group. In addition, there is evidence that tiotropium-treated patients experienced a delay in the time to first exacerbation compared to placebo-treated patients.

    b. There is no treatment difference in the proportion of patients with at least one COPD exacerbation leading to hospitalization. When treatment exposure is taken into account, the estimated rate of COPD exacerbation per patient year in the tiotropium group (rate=0.15) is not different to the placebo group (rate=0.16).

    c. In Table 12, I explored the exacerbation endpoints in the UPLIFT study following the exacerbation endpoints used in the VA study. At six months, the results from the UPLIFT study are similar to the VA study with the percentage of patients with a

COPD exacerbation meeting the protocol definition was lower for tiotropium compared to placebo, with an odds ratio of 0.84. The calculated hazard ratio in the VA study is also similar to the UPLIFT study at 0.83. Thus, at six months, there is a relative risk reduction of about 16% in the tiotropium group compared to the placebo group. The lower quartile time to first hospitalization due to COPD exacerbation in the tiotropium group is 5 months compared to 4 months in the placebo group.

4. There was no treatment difference in the rate of decline of SGRQ total score, yearly rate of decline of pre- and post-bronchodilator FVC, and yearly rate of decline of pre- and post-bronchodilator SVC.

Table 12: Analysis of COPD exacerbation – UPLIFT Study

	Placebo N=3006 PY=8499.46	Tiotropium N=2986 PY=9222.31	Ratio or Difference 95% CI	Unadjusted p-value
At Six Months				
No. of patients with at least one exacerbation	933 (31%)	821 (27%)	OR= 0.84	0.0026
No. of patients with at least one exacerbation meeting protocol definition	923 (31%)	810 (27%)	OR= 0.84	0.0023
No. of patients with at least one exacerbation leading to Hospitalization	192 (6%)	173 (6%)	OR= 0.90	0.3369
Lower quartile time to first exacerbation (months)	4.2	5.3	HR: 0.83 (0.76, 0.92)	0.0001
Median time to first exacerbation (months)*	N/A	N/A	HR: 0.87 (0.71, 1.07)	0.1987
At 48 Months				
No. of patients with at least one exacerbation	2049 (68%)	2001 (67%)		0.3481
No. of patients with at least one exacerbation leading to Hospitalization	811 (27%)	759 (25%)		0.1766
Estimated no. (rate) of COPD exacerbations per patient year ‡	7183 (0.85)	6691 (0.73)	Ratio: 0.86 (0.81, 0.91)	<0.0001
Estimated no. (rate) of COPD exacerbations per patient year leading to hospitalization‡	1379 (0.16)	1403 (0.15)	Ratio: 0.94 (0.82, 1.07)	0.3413

The following results are taken from the Clinical Review and Statistics Review of Study 266 (VA Study), serial number 024.

1. There were two primary (i.e. 'co-primary) endpoints, percentage of patients with a COPD exacerbation meeting the protocol definition and the percentage of patients with a hospitalization due to COPD exacerbation. Only one of the two 'co-primary' endpoints was met, that is, the percentage of patients with a COPD exacerbation meeting the protocol definition was significantly lower for tiotropium compared to placebo (p=0.04), with an odds ratio of 0.806 (Table 13).

2. One of the secondary endpoints the Applicant examined was the time-to-first COPD exacerbation. The Applicant reports that patients in the tiotropium group had a "significantly" longer time to event than patients in the placebo group with a hazard ratio of 0.834. The p-value of 0.04 was unadjusted. Similarly, patients in the tiotropium group had a longer time to first hospitalization due to COPD exacerbation compared to placebo, and the unadjusted p-value was 0.05.

3. The Applicant also explored the treatment effect in lung function. The following results are taken from Dr. Michele's review:

    a. When mean pre- or post-bronchodilator FEV_1 were estimated, the mean treatment difference in mean pre-bronchodilator FEV_1 was 100 ml and 160 ml in mean post-bronchodilator FEV_1 at 3 months.

    b. At 6 months, the mean treatment difference in mean pre-bronchodilator FEV_1 was 90 ml and 170 ml in mean post-bronchodilator FEV_1.

    c. Unlike the UPLIFT study, this study did not require administration of open-labeled inhaled salbutamol (albuterol) 400 mcg and ipratropium bromide 80 mcg in addition to study medication (tiotropium or placebo) to achieve optimal bronchodilation for post-bronchodilator lung function measurements; Thus, the mean difference in post-bronchodilator FEV_1 is higher compared to the mean difference in the UPLIFT study.

In Study 266 (VA study), sequential testing was conducted only on the 'co-primary' endpoints. Multiplicity correction was not pre-specified in the secondary endpoints, which includes time-to-first COPD exacerbation. This multiplicity issue was discussed in detail in Dr. Ruthanna Davi's review. In summary Dr. Davi wrote that

> Because of the expected and observed correlation between this secondary analysis and the primary analysis and because this analysis was a selection from one of a limited number of secondary efficacy endpoints, it is unlikely that these result of the time-to-first COPD exacerbation analysis is a spurious finding. Rather it is likely that the statistical significance observed in this comparison is a true representation of the treatment effect on this endpoint. In addition, this type of analysis may be considered more appropriate than the primary analysis in that subjects who dropped out of the study are censored.

The following is taken from the Clinical Review (VA Study) describing the efficacy conclusion:

> These results, while positive, are not sufficiently robust to allow approval on the basis of the single study submitted. A second placebo-controlled clinical trial demonstrating a reduction in COPD

exacerbations with Spiriva HandiHaler is required to confirm efficacy. The exact wording of the claim will need consideration as various aspects of exacerbation were measured in Protocol 205.266.

Table 13: Analysis of COPD exacerbation –VA Study

	Placebo N=915	Tiotropium N=914	Ratio or Difference 95% CI	p-value
Co-Primary Endpoints (at 6 months)				
No. of patients with at least one exacerbation meeting protocol definition	32%	28%	OR = 0.81	0.0368
No. of patients with at least one exacerbation leading to Hospitalization	10%	7%	OR= 0.72	0.0557
Secondary Endpoints				
Estimated no. (rate) of COPD exacerbations per patient year ‡	0.88	0.71	Ratio: 0.81	0.04
Estimated no. (rate) of COPD exacerbations per patient year leading to hospitalization‡	0.15	0.21	Ratio: 0.70	0.054

Source: Clinical Review and Statistical Review, SE8, S024

3.2 EVALUATION OF SAFETY

The Applicant proposed the inclusion of 'Survival and Respiratory Failure' in the Clinical Section of the SPIRIVA Handihaler label. They claimed that there was a 16% reduction in the risk of death while on treatment with SPIRIVA HandiHaler compared to placebo. The incidence rate of death was 4.10 per 100 patient years in the tiotropium group vs. 4.78 per 100 patient years in the placebo group [Hazard Ratio (tiotropium/placebo) = 0.84, 95% CI = 0.73, 0.97]. Treatment with tiotropium reduced the risk of respiratory failure by 19% (2.09 vs. 1.68 cases per 100 patient years [relative risk (tiotropium/placebo) = 0.81, 95% CI = 0.65, 1.00].

The following describes the Analysis Plan for the 'mortality' and 'respiratory failure' endpoints:

> Mortality events were analyzed for on-treatment death (onset of the fatal AE is between first drug intake and last drug intake + 30 days), and all deaths including post-discontinuation vital status collection. Causes of deaths were reported by investigator or via vital status collection, and the primary cause of death was also reported. The adjudication committee provided the adjudicated primary cause of death.
>
> Frequency and incidence density tables by SOC and PT for all deaths including vital status included all fatal events collected before 1470 days. Similar tables for on-treatment deaths included all the on-treatment fatal AEs without the 1470-day cut-off. Frequency and incidence density tables were prepared for adjudicated primary cause of death for all deaths including vital status, and on-treatment deaths, as well as for reported causes of on-treatment death.
>
> Time to death was defined as time to the end of a fatal AE. Analyses of time to death using the Kaplan-Meier estimates and Cox regression applied the cut-off Day of 1470 days (i.e., all patients after the planned trial period of 1470 days were censored for these analyses). The time to death analyses were carried out for both adjudicated primary cause of death for all deaths including vital status and on-treatment deaths. The mortality endpoints for these analyses included all cause, lower respiratory, cardiac disorders, stroke, and any fatal AE that occurred in more than 1% (or 60 cases) of the patients.
>
> Subgroup analysis for mortality data was carried out only for all-cause, lower respiratory, and cardiac death for adjudicated all deaths including vital status, and only for the time-to-death analysis. Cox regression with treatment, subgroup and treatment by subgroup interaction was used to assess consistency of treatment effect across subgroups.
>
> The statistical analyses for respiratory mortality were based on the adjudicated primary cause of death. Matching between adjudicated and investigator reported primary cause of death was explored using descriptive statistics. Respiratory mortality specified in the trial protocol was interpreted as lower respiratory mortality, as defined by the SPRIVA project rules.
>
> Analyses were added to investigate the risk of stroke in response to an FDA early communication. Kaplan-Meier estimates as well as Cox regression were carried out for stroke AE, serious AE, and fatal AEs.

In this review, I will focus on the 'mortality' claim. Please refer to Dr. Theresa Michele's review for a thorough discussion of these and other safety endpoints.

In the Study Report, fatal events are presented in two ways: 1) deaths on-treatment and 2) all deaths including post discontinuation vital status collection. Both 1 and 2 were analyzed with cut-off of 1440 days (4 years), 1470 days (4 years and 30 days) and with no cut-off.

Table 14 presents the summary of all-cause mortality. The total number of deaths from any cause during treatment (including the last day of study drug plus 30 days) was 792; 411

(14%) in the placebo group and 381 (13%) in the treatment group. Additional death information was collected from the post-discontinuation Vital Status (i.e. off-treatment) for 189 patients, totaling the number of deaths from any cause to 981; 514 (17%) in the placebo group and 467 (16%) in the tiotropium group. The hazard ratio for on-treatment death from any cause (tiotropium/placebo) was 0.84 [95% CI: 0.73, 0.97)], and 0.89 [95% CI: 0.78, 1.00)] for 'on-treatment and off-treatment' death. Of note, the confidence interval and p-value of the hazard ratio are unadjusted for multiplicity.

The Kaplan-Meier estimate of no all-cause mortality (on-treatment) by Day 1470 is presented in Figure 11. There is evidence that the two curves started to separate at Month 12 with the tiotropium curve on top of the placebo group, and the separation is maintained until Month 48.

Table 14: Fatal Adverse Event Summary – Treated Set

	Placebo	Tiotropium	ΔRates	Hazard Ratio Tiotropium vs. Placebo		
	N (%)	N (%)		HR	95% CI	P-value
On-Treatment (Day 1440)	400 (13.3)	361 (12.1)	1.2%	0.83	0.72, 0.95	0.010
On Treatment (Day 1470)	402 (13.4)	374 (12.5)	0.9%	0.85	0.74, 0.98	0.024
On-Treatment (all)	411 (13.7)	381 (12.8)	0.9%	0.84	0.73, 0.97	0.016
Vital Status (Day 1440)	491 (16.3)	430 (14.4)	1.9%	0.87	0.76, 0.99	0.034
Vital Status (Day 1470)	495 (16.5)	446 (14.9)	1.6%	0.89	0.79, 1.02	0.086
Vital Status (all)	514 (17.1)	467 (15.6)	1.5%	0.89	0.78, 1.00	0.058

Source data: Tables 15.3.3: 1 and 15.3.3: 2
Source: Clinical Study Report, Table 12 3:1, page 134; p-value is unadjusted

Figure 11: Kaplan-Meier estimates of the probability of no all-cause mortality – adjudicated; on-treatment deaths-treated set-censored at Day 1470

Source data: Figure 15.3.2.2.2: 1
Source: Clinical Study Report, Figure 12 3:1, page 135

Based on re-analysis of the 'raw' mortality data, all deaths were adjudicated. However it appears that 193 deaths were off-treatment (i.e. vital status information) and 788 deaths were on-treatment, as opposed to 189 and 792 deaths, respectively. Four subjects (tiotropium 2, placebo 2) were classified as off-treatment in the raw data (ID=10434, 15167, 21595, and 22955). This discrepancy did not alter the results described in Table 14.

Subgroup analyses were conducted for the on-treatment death with and without 1470 days cut-off. Although there were slight discrepancies in the 'days on treatment and days censored', these discrepancies did not alter the conclusion. The results are presented in Appendix 13 and Appendix 14 for the following subgroups: age (<55; 55-<65; 65-<75; ≥75 years), gender (male; female), smoking status (smoker; ex-smoker), baseline LABA use (yes; no), baseline ICS use, baseline use of ICS and LABA combination, baseline anticholinergic use, GOLD stage (I/II; III; IV), race (Asian; Black; White), region (Asia; Eastern Europe; Western Europe; Latin America; USA), reversibility, and BMI (<20; 20-<25; 25-<30; ≥30 kg/m^2).

Except for smoking status and BMI, there were no significant treatment-by-subgroup interactions detected in any subgroups on the mortality endpoints. Table 15 presents the subgroup analysis on on-treatment death (with 1470 cut-off) by smoking status and by BMI. There is some evidence of a qualitative interaction between treatment and smoking status, as well as between treatment and BMI in the proportion of death. There is numerically higher proportion of mortality in the placebo group among ex-smokers compared to tiotropium, while a numerically higher proportion of mortality is seen in the tiotropium group among current smokers compared to placebo. There is numerically higher proportion of mortality in the placebo group among patients with BMI between 25 and 30 kg/m^2 compared to tiotropium. These findings should be explored further in another study.

Table 15: Subgroup Analysis for on−treatment death (with 1470 cut-off) − treated set

	Placebo		Tiotropium			
	N	No. deaths (%)	N	No. deaths (%)	Hazard ratio (Tio vs. Placebo) 95% CI	Subgroup by treatment interaction p-value
Total treated with on-treatment fatal AE events	3006	402 (13.4)	2986	374 (12.5)	0.85 (0.74, 0.98)	
Smoking Status						0.0562
Ex-Smoker	2108	292 (13.9)	2112	252 (11.9)	0.78 (0.66, 0.92)	
Current Smoker	898	110 (12.2)	874	122 (14.0)	1.05 (0.81, 1.36)	
BMI						0.0562
<20	352	72 (20.5)	297	74 (24.9)	1.07 (0.77, 1.47)	
>=20, < 25	1024	128 (12.5)	1074	138 (12.8)	0.91 (0.72, 1.16)	
>=25, < 30	1033	141 (13.6)	1039	101 (9.7)	0.66 (0.51, 0.85)	
>=30	597	61 (10.2)	576	61 (10.6)	0.96 (0.67, 1.37)	0.0883

Table 16 and Table 17 present a summary of the most common causes of death (reported in >1% of patients in either treatment group) during study drug treatment as assessed by the adjudication committee, on-treatment death and on-treatment plus vital status, respectively. Like the subgroup analyses using Cox regression model in calculating the hazard ratio, there are also some discrepancies in the calculation of patient-year. However, this discrepancy did not alter the conclusion.

With the exception of pneumonia and sudden death, the incidence of fatal AE by selected preferred terms in the placebo group is higher or almost equal to the tiotropium group. The incidence of death caused by pneumonia and sudden death appears to be slightly higher (numerically) in the tiotropium group compared to the placebo group with a risk ratio that corresponds to a less favorable outcome in the tiotropium group. However, the confidence interval includes the null value and values that correspond to a more favorable outcome with tiotropium, so that the direction of the difference in risk, if any, is not known with much confidence. Similarly, the confidence interval across all other causes of death includes the null value, thus, the direction of the difference is not known with much confidence either.

Table 16: Incidence density of fatal AE by treatment, selected preferred terms − adjudicated primary cause; on−treatment death − treated set

	Placebo N=3006		Tiotropium N=2986		
	Pt-Year at risk	n (incidence)	Pt-Year at risk	n (incidence)	Risk Ratio (Tio vs. Placebo) 95% CI
Total treated with on-treatment fatal AE events	8575	411 (4.8)	9281	381 (4.1)	0.86 (0.75, 0.98)
COPD exacerbation	8702	121 (1.4)	9418	103 (1.1)	0.79 (0.60, 1.02)
Lung cancer	8718	66 (0.8)	9425	73 (0.8)	1.02 (0.73, 1.43)
Death (unknown cause)	8718	36 (0.4)	9452	29 (0.3)	0.74 (0.53, 1.07)
Sudden cardiac death	8742	23 (0.3)	9464	15 (0.2)	0.60 (0.31, 1.15)
Pneumonia	8740	18 (0.2)	9453	27 (0.3)	1.39 (0.76, 2.52)
Congestive heart failure	8740	14 (0.2)	9463	15 (0.2)	0.99 (0.48, 2.05)
Sudden death	8743	12 (0.1)	9466	14 (0.2)	1.08 (0.50, 2.33)
Cerebrovascular Accident (CVA) or Stroke	8740	13 (0.2)	9467	12 (0.1)	0.85 (0.39, 1.87)

Source: Clinical Study Report, Table 15.3.2.2.1.2:2 page 1046 - 1050

Table 17: Incidence density of fatal AE by treatment, selected preferred terms − adjudicated primary cause; on−treatment death including Vital Status (1470 cut-off) − treated set

	Placebo N=3006		Tiotropium N=2986		
	Pt-Year at risk	n (incidence)	Pt-Year at risk	n (incidence)	Risk Ratio (Tio vs. Placebo) 95% CI
Total treated with on-treatment fatal AE events	10718	495 (4.6)	10821	446 (4.1)	0.89 (0.79, 1.01)
COPD exacerbation	10950	150 (1.4)	11025	120 (1.1)	0.79 (0.62, 1.01)
Lung cancer	10984	70 (0.6)	11037	78 (0.7)	1.11 (0.80, 1.53)
Death (unknown cause)	10989	59 (0.5)	11092	56 (0.5)	0.94 (0.65, 1.36)
Sudden cardiac death	11052	25 (0.2)	11110	18 (0.2)	0.72 (0.39, 1.31)
Pneumonia	11039	21 (0.2)	11088	32 (0.3)	1.52 (0.87, 2.63)
Congestive heart failure	11044	17 (0.2)	11109	15 (0.1)	0.88 (0.44, 1.76)
Sudden death	11051	18 (0.2)	11114	15 (0.1)	0.8308 (0.42, 1.64)
Cerebrovascular Accident (CVA) or Stroke	11046	17 (0.2)	11112	14 (0.1)	0.82 (0.40, 1.66)

Source: Clinical Study Report, Table 15.3.2.2.1.1:2 page 1031 - 1044

The incidence of fatal death caused by pneumonia is further examined by evaluating the treatment effect in subgroup of patients with or without baseline ICS or LABA used. The results are presented in Table 18. Of note, when calculating the patient-year at risk, there is a slight difference in the result. However, this did not affect the overall conclusion.

There is some evidence of a qualitative interaction between treatment group and baseline ICS and/or LABA use. Numerically, there is slightly higher proportion of mortality due to pneumonia in patients with baseline ICS or LABA who are taking tiotropium compared to those taking placebo. In contrast, there is no difference in the proportion of mortality due to pneumonia in patients without baseline ICS or LABA. Because the number of events is small and the confidence interval for the risk ratio includes the null value, therefore the direction of the difference is not known with much confidence either.

Table 18: Subgroup Analyses of Pneumonia - on−treatment death − treated set

	Placebo		Tiotropium		
	N (Pt-Year at risk)	N (incidence)	Pt-Year at risk	N (incidence)	Risk Ratio (Tio vs. Placebo) 95% CI
Overall	3006 (8740)	18 (0.2)	2986 (9453)	27 (0.3)	1.39 (0.76, 2.52)
Baseline ICS: Yes	1860 (5335)	10 (0.2)	1840 (5797)	19 (0.3)	1.75 (0.81, 3.76)
No	1146 (3411)	8 (0.2)	1146 (3663)	8 (0.2)	0.93 (0.35, 2.48)
Baseline LABA: Yes	1808 (5214)	8 (0.2)	1796 (5695)	17 (0.3)	1.95 (0.84, 4.51)
No	1198 (3532)	10 (0.3)	1190 (3765)	10 (0.3)	0.94 (0.39, 2.25)
Baseline ICS/LABA: Yes	1462 (4197)	7 (0.2)	1464 (4610)	15 (0.3)	1.95 (0.80, 4.78)
No	1544 (4549)	11 (0.2)	1522 (4850)	12 (0.2)	1.02 (0.45, 2.32)

In conclusion, although there is some suggestion of a benefit of tiotropium for on-treatment mortality, this needs to be explored further. In particular, a different result was observed in a different SPIRIVA application using RESPIMAT delivery system. In that application, an increased number of deaths are observed in the Spiriva Respimat treatment groups compared to placebo for 1-year pivotal trials, resulting in a Complete Response action for the Spiriva Respimat NDA. On July 22, 2009, the Applicant amended the efficacy supplement to remove the mortality claim. According to the Applicant, there was no new Spiriva Handihaler data contributing to this decision.

Furthermore, according to the EMEA guidance

> If not defined as primary variables, clinically very important variables (e.g. mortality) need further study when significant benefits are observed, but the primary objective has not been achieved. Variables that have the potential of being indicative of a major clinical benefit or may in a different situation present an important safety issue (e.g. mortality) may be relegated to secondary variables because there is an *a priori* belief that the size of the planned trial is too small (and thus the power too low) to show a benefit. ***If, however, the observed beneficial effect is much higher than expected but the study fell short of achieving its primary objective, this would be a typical situation where information from further studies would be needed which can be used in support of the observed beneficial effect.***

4 FINDINGS IN SUBGROUPS AND SPECIAL POPULATIONS

On January 7, 2009, an information request was sent to the Applicant requesting subgroup analyses for the following endpoints:

- Time to first COPD exacerbation
- Time to first COPD exacerbation leading to hospitalization
- Number of COPD exacerbations per patient year
- Adverse events: individual, serious, cardiovascular events, stroke events

On February 17, 2009, the Applicant submitted their responses to the analyses request for the following subgroups (age, gender, smoking status, baseline concomitant medication use, COPD severity according to GOLD stages, race, region, reversibility, BMI). The results are presented in this Section. Of note, the Cox model was used for the time to first event analysis and the Poisson model adjusting for overdispersion was used to estimate the number of COPD exacerbations per patient year. Meanwhile, the incidence rate and rate ratio were reported for the adverse event analyses.

In addition to the four endpoints reported by the Applicant, I conducted additional subgroup analyses on the estimated mean pre- and post-bronchodilators FEV_1 scores at each visit. The repeated measures ANOVA model was used to conduct these analyses.

Because the two primary endpoints (i.e. the rates of decline of pre- and post-bronchodilator FEV_1) did not achieve statistical significance, I did not perform additional analyses other than what was conducted by the Applicant and summarized in Section 3.1.3.

Note that because these subgroup analyses are done post-hoc, these should be considered exploratory.

4.1 COPD EXACERBATION

The Applicant conducted subgroup analyses on the exacerbation endpoints. The subgroups were specified as follows: age (<55; 55-<65; 65-<75; ≥75 years), gender (male; female), smoking status (smoker; ex-smoker), baseline LABA use (yes; no), baseline ICS use, baseline use of ICS and LABA combination, baseline anticholinergic use, GOLD stage (I/II; III; IV), race (Asian; Black; White), region (Asia; Eastern Europe; Western Europe; Latin America; USA), reversibility, and BMI (<20; 20-<25; 25-<30; ≥30 kg/m^2).

The results from subgroup analyses of COPD exacerbation, COPD exacerbation leading to hospitalization, COPD exacerbation per patient year are summarized in Table 19, Table 20, and Table 21, respectively.

There were no significant treatment-by-subgroup interactions detected in any subgroups on the exacerbation endpoints.

Table 19: Analysis of COPD exacerbation – Number of Patients with Exacerbation (%) and Median Time to First Exacerbation (in months)

	Placebo	Tiotropium	Hazard Ratio 95% CI	p-value*
Overall	2049/3006 (68%) 13 months	2001/2986 (67%) 17 months	0.86 (0.81, 0.91)	
Sex: Female	539/784 (69%) 10 months	496/735 (68%) 15 months	0.83 (0.74, 0.94)	
Male	1510/2222 (68%) 13 months	1505/2251 (67%) 17 months	0.87 (0.81, 0.93)	0.5632
Gold Stage: I/II	883/1356 (65%) 17 months	824/1386 (60%) 23 months	0.82 (0.75, 0.90)	
III	942/1331 (71%) 10 months	944 /1304 (72%) 13 months	0.87 (0.79, 0.95)	
IV	188/271 (69%) 9 months	200/250 (80%) 10 months	0.99 (0.81, 1.21)	0.2341
Baseline Smoking Status Ex-Smoker	1458/2108 (69%) 12 months	1437/2112 (68%) 16 months	0.86 (0.80, 0.93)	
Smoker	591/898 (66%) 14 months	564/874 (65%) 18 months	0.85 (0.76, 0.95)	0.8680
Reversibility: Yes	1036/1513 (69%) 13 months	1021/1520 (67%) 17 months	0.86 (0.79, 0.94)	
No	946/1393 (68%) 12 months	913/1357 (67%) 16 months	0.86 (0.79, 0.94)	0.9854
Baseline ICS: Yes	1338/1860 (72%) 10 months	1302/1840 (71%) 13 months	0.85 (0.79, 0.92)	
No	711/1146 (62%) 18 months	699/1146 (61%) 23 months	0.86 (0.78, 0.96)	0.8068
Baseline LABA: Yes	1302/1808 (72%) 11 months	1275/1796 (71%) 13 months	0.85 (0.79, 0.92)	
No	747/1198 (62%) 17 months	726/1190 (61%) 22 months	0.87 (0.78, 0.96)	0.7171
Baseline ICS/LABA: Yes	1066/1462 (73%) 10 months	1052/1464 (72%) 12 months	0.86 (0.79, 0.93)	
No	983/1544 (64%) 17 months	949/1522 (62%) 21 months	0.86 (0.78, 0.94)	0.9146
Race: White	1845/2697 (68%) 12 months	1817/2691 (68%) 16 months	0.87 (0.81, 0.92)	
Black	36/53 (68%) 18 months	19/38 (50%) 41 months	0.48 (0.28, 0.85)	
Asian	118/185 (64%) 13 months	119/192 (62%) 18 months	0.81 (0.63, 1.05)	0.2310

	Placebo	Tiotropium	Hazard Ratio 95% CI	p-value*
Overall	2049/3006 (68%) 13 months	2001/2986 (67%) 17 months	0.86 (0.81, 0.91)	
Region: Asia	114/178 (64%) 13 months	113/184 (61%) 18 months	0.81 (0.62, 1.05)	
E. Europe	402/597 (67%) 20 months	367/590 (62%) 21 months	0.88 (0.76, 1.01)	
Latin America	163/207 (79%) 9 months	142/198 (72%) 15 months	0.78 (0.63, 0.98)	
USA	489/767 (64%) 12 months	477/767 (62%) 18 months	0.80 (0.71, 0.91)	
W. Europe	881/1257 (70%) 11 months	902/1247 (72%) 13 months	0.90 (0.82, 0.99)	0.5122
Age: <55	254/382 (67%) 12 months	248/384 (65%) 18 months	0.83 (0.70, 0.99)	
55 – 65	716/1055 (68%) 14 months	714/1054 (68%) 17 months	0.90 (0.81, 0.99)	
65 – 75	825/1198 (69%) 13 months	810/1208 (67%) 17 months	0.86 (0.78, 0.95)	
≥ 75	254/371 (69%) 9 months	229/340 (67%) 13 months	0.76 (0.64, 0.91)	0.4440
BMI: <20	263/352 (75%) 10 months	216/297 (73%) 13 months	0.76 (0.64, 0.91)	
20 – 25	673/1024 (66%) 12 months	709/1074 (66%) 16 months	0.86 (0.78, 0.96)	
25 – 30	704/1033 (68%) 14 months	705/1039 (68%) 17 months	0.91 (0.82, 1.01)	
≥ 30	407/597 (68%) 13 months	371/576 (64%) 19 months	0.82 (0.71, 0.94)	0.4118
Anticholinergic Use: Yes	922/1350 (68%) 11 months	950/1366 (70%) 14 months	0.87 (0.79, 0.95)	
No	1127/1656 (68%) 15 months	1051/1620 (65%) 18 months	0.85 (0.78, 0.92)	0.7960

Hazard ratio based on Cox model with treatment, baseline covariate and baseline covariate by treatment interaction;
* p-value was based on test of interaction.

Table 20: Analysis of COPD exacerbation leading to Hospitalization – Number of Patients with Exacerbation (%) and Lower Quartile Time to First Exacerbation (in months)

	Placebo	Tiotropium	Hazard Ratio 95% CI	p-value*
Overall	811/3006 (27%) 29 months	759/2986 (25%) 36 months	0.86 (0.78, 0.95)	0.0024
Sex: Female	199/784 (25%) 27 months	162/735 (22%) 43 months	0.77 (0.62, 0.94)	
Male	612/2222 (28%) 29 months	597/2251 (27%) 34 months	0.89 (0.79, 0.99)	0.2100
Gold Stage: I/II	265/1356 (20%) N/A months	211/1386 (15%) N/A months	0.74 (0.61, 0.88)	
III	413/1331 (31%) 23 months	421/1304 (32%) 25 months	0.93 (0.81, 1.06)	
IV	116/271 (43%) 11 months	112/250 (45%) 14 months	0.85 (0.66, 1.10)	0.1362
Baseline Smoking Status Ex-Smoker	570/2108 (27%) 29 months	530/2112 (25%) 37 months	0.84 (0.75, 0.95)	
Smoker	241/898 (27%) 29 months	229/874 (26%) 34 months	0.90 (0.75, 1.07)	0.5589
Reversibility: Yes	370/1513 (25%) 36 months	365/1520 (24%) 40 months	0.91 (0.78, 1.05)	
No	412/1393 (30%) 24 months	365/1357 (27%) 32 months	0.82 (0.71, 0.94)	0.2915
Baseline ICS: Yes	556/1860 (30%) 24 months	492/1840 (27%) 32 months	0.80 (0.71, 0.90)	
No	255/1146 (22%) 41 months	267/1146 (23%) 43 months	0.98 (0.83, 1.17)	0.0504
Baseline LABA: Yes	529/1808 (29%) 25 months	484/1796 (27%) 33 months	0.83 (0.73, 0.94)	
No	282/1198 (24%) 36 months	275/1190 (23%) 42 months	0.91 (0.77, 1.08)	0.3596
Baseline ICS/LABA: Yes	442/1462 (30%) 24 months	398/1464 (27%) 32 months	0.80 (0.70, 0.92)	
No	369/1544 (24%) 35 months	361/1522 (24%) 40 months	0.92 (0.79, 1.06)	0.1801
Race: White	709/2697 (26%) 30 months	664/2691 (25%) 37 months	0.85 (0.77, 0.95)	
Black	17/53 (32%) 18 months	11/38 (29%) 42 months	0.73 (0.34, 1.56)	
Asian	72/185 (39%) 15 months	68/192 (35%) 18 months	0.82 (0.59, 1.15)	0.9243

	Placebo	Tiotropium	Hazard Ratio 95% CI	p-value*
Overall	811/3006 (27%) 29 months	759/2986 (25%) 36 months	0.86 (0.78, 0.95)	0.0024
Region: Asia	69/178 (39%) 16 months	66/184 (36%) 18 months	0.85 (0.61, 1.19)	
E. Europe	159/597 (27%) 33 months	154/590 (26%) 35 months	0.97 (0.78, 1.22)	
Latin America	61/207 (30%) 25 months	49/198 (25%) 45 months	0.75 (0.52, 1.10)	
USA	173/767 (23%) 33 months	164/767 (21%) 38 months	0.84 (0.68, 1.04)	
W. Europe	349/1257 (28%) 28 months	326/1247 (26%) 36 months	0.83 (0.72, 0.97)	0.7561
Age: <55	78/382 (20%) N/A months	79/384 (21%) N/A months	0.93 (0.68, 1.27)	
55 – 65	273/1055 (26%) 32 months	251/1054 (24%) 43 months	0.85 (0.71, 1.01)	
65 – 75	343/1198 (29%) 27 months	323/1208 (27%) 32 months	0.87 (0.74, 1.01)	
≥ 75	117/371 (32%) 18 months	106/340 (31%) 27 months	0.81 (0.62, 1.05)	0.9337
BMI: <20	141/352 (40%) 17 months	119/297 (40%) 19 months	0.88 (0.69, 1.13)	
20 – 25	276/1024 (27%) 24 months	271/1074 (25%) 35 months	0.81 (0.68, 0.96)	
25 – 30	250/1033 (24%) 37 months	242/1039 (23%) 43 months	0.91 (0.77, 1.09)	
≥ 30	144/597 (24%) 37 months	127/576 (22%) 45 months	0.86 (0.68, 1.09)	0.8073
Anticholinergic Use: Yes	411/1350 (30%) 23 months	401/1366 (29%) 27 months	0.85 (0.74, 0.97)	
No	400/1656 (24%) 38 months	358/1620 (22%) 45 months	0.85 (0.74, 0.98)	0.9418

Hazard ratio based on Cox model with treatment, baseline covariate and baseline covariate by treatment interaction;
* p-value was based on test of interaction.

Table 21: Estimated Rate of Patients with Exacerbation per Patient-Year

	Placebo	Tiotropium	Ratio 95% CI	p-value*
Overall	0.85	0.73	0.86 (0.81, 0.91)	
Sex: Female	0.92	0.77	0.84 (0.74, 0.94)	
Male	0.82	0.71	0.87 (0.81, 0.93)	0.6084
Gold Stage: I/II	0.70	0.56	0.80 (0.72, 0.88)	
III	0.97	0.85	0.88 (0.80, 0.95)	
IV	1.15	1.05	0.92 (0.76, 1.12)	0.2462
Baseline Smoking Status				
Ex-Smoker	0.87	0.73	0.84 (0.78, 0.91)	
Smoker	0.79	0.71	0.90 (0.80, 1.01)	0.3930
Reversibility: Yes	0.82	0.69	0.85 (0.78, 0.92)	
No	0.87	0.76	0.87 (0.79, 0.95)	0.7430
Baseline ICS: Yes	0.96	0.82	0.85 (0.79, 0.92)	
No	0.67	0.57	0.86 (0.77, 0.96)	0.8834
Baseline LABA: Yes	0.96	0.81	0.84 (0.78, 0.91)	
No	0.68	0.60	0.89 (0.79, 0.99)	0.4690
Baseline ICS/LABA: Yes	1.00	0.85	0.85 (0.78, 0.92)	
No	0.71	0.61	0.86 (0.79, 0.95)	0.7915
Race: White	0.84	0.73	0.87 (0.81, 0.93)	
Black	0.62	0.39	0.63 (0.33, 1.19)	
Asian	0.92	0.66	0.72 (0.56, 0.93)	0.2324
Region: Asia	0.92	0.68	0.73 (0.57, 0.94)	
E. Europe	0.61	0.58	0.95 (0.82, 1.11)	
Latin America	1.09	0.82	0.82 (0.61, 0.92)	
USA	0.75	0.65	0.65 (0.75, 0.98)	
W. Europe	0.97	0.83	0.86 (0.79, 0.94)	0.2959
Age: <55	0.75	0.64	0.86 (0.72, 1.03)	
55 – 65	0.84	0.72	0.86 (0.77, 0.95)	
65 – 75	0.85	0.74	0.87 (0.79, 0.95)	
≥ 75	0.96	0.81	0.84 (0.70, 1.01)	0.9933
BMI: <20	1.12	0.88	0.78 (0.65, 0.93)	
20 – 25	0.83	0.73	0.88 (0.79, 0.98)	
25 – 30	0.79	0.72	0.90 (0.81, 1.00)	
≥ 30	0.81	0.66	0.81 (0.70, 0.93)	0.3807
Anticholinergic Use:				
Yes	0.93	0.81	0.88 (0.80, 0.96)	
No	0.79	0.65	0.83 (0.76, 0.91)	0.3745

Estimated mean and Ratio were calculated based on Poisson model with overdispersion adjusting for time at risk
* p-value was based on test of interaction.

4.2 PRE- AND POST-BRONCHODILATOR FEV_1

Additional subgroup analyses were conducted on the estimated mean pre- and post-bronchodilators FEV_1 scores at each visit. The results are summarized in Table 22 and Table 23, respectively. There appears to be a quantitative interaction between treatment and baseline ICS in the estimated mean pre- and post-bronchodilators FEV_1 scores. This implies that the treatment effect in each subgroup is in the same direction, but of 'slightly' different magnitude. The results from these subgroup analyses also were consistent with the overall treatment effect. Like baseline ICS, there is also a quantitative interaction between treatment and baseline anticholinergic in the estimated mean post-bronchodilators FEV_1 scores. The results from this subgroup analysis also were consistent with the overall treatment effect.

Table 22: Estimated* mean pre-bronchodilator FEV_1 from Day 30 until completion of double-blind treatment - Treated set with at least 3 measurements between Visits 3 – 19 (or Months 1 – 48)

	Treatment		Difference		
	Placebo Mean (SE)	Titropium Mean (SE)	Mean (SE) [ml/yr]	95% CI	p-value*
Pre-BD	**1.080 (0.004)**	**1.174 (0.004)**	**0.094**	**(0.084, 0.105)**	**<0.0001**
Sex: Female	0.875 (0.007)	0.955 (0.007)	0.080	(0.062, 0.099)	
Male	1.144 (0.005)	1.242 (0.004)	0.099	(0.087, 0.111)	0.1742
Gold Stage: I/II	1.293 (0.006)	1.403 (0.006)	0.110	(0.093, 0.126)	
III	0.903 (0.005)	0.991 (0.005)	0.088	(0.074, 0.103)	
IV	0.624 (0.010)	0.659 (0.010)	0.035	(0.008, 0.063)	0.2388
Baseline Smoking Status: Ex-Smoker	1.059 (0.004)	1.152 (0.004)	0.093	(0.081, 0.105)	
Smoker	1.131 (0.007)	1.228 (0.007)	0.097	(0.077, 0.117)	0.2833
Reversibility: Yes	1.113 (0.005)	1.221 (0.005)	0.108	(0.094, 0.122)	
No	1.040 (0.005)	1.120 (0.005)	0.080	(0.065, 0.095)	0.6380
Baseline ICS: Yes	1.064 (0.005)	1.153 (0.005)	0.089	(0.075, 0.102)	
No	1.104 (0.006)	1.207 (0.006)	0.103	(0.088, 0.119)	0.0319
Baseline LABA: Yes	1.052 (0.005)	1.120 (0.006)	0.093	(0.080, 0.106)	
No	1.146 (0.005)	1.216 (0.006)	0.096	(0.080, 0.113)	0.3031
Baseline ICS/LABA: Yes	1.045 (0.005)	1.143 (0.005)	0.098	(0.083, 0.113)	
No	1.111 (0.005)	1.202 (0.005)	0.091	(0.077, 0.106)	0.2051
Race: White	1.099 (0.004)	1.194 (0.004)	0.095	(0.084, 0.106)	
Black	0.941 (0.020)	1.026 (0.022)	0.085	(0.026, 0.144)	
Asian	0.823 (0.011)	0.917 (0.011)	0.094	(0.064, 0.125)	0.7327

	Treatment		Difference		
	Placebo Mean (SE)	Titropium Mean (SE)	Mean (SE) [ml/yr]	95% CI	p-value*
Pre-BD	**1.080 (0.004)**	**1.174 (0.004)**	**0.094**	**(0.084, 0.105)**	**<0.0001**
Region: Asia	0.815 (0.012)	0.910 (0.011)	0.095	(0.064, 0.127)	
E. Europe	1.168 (0.010)	1.245 (0.010)	0.077	(0.051, 0.104)	
Latin America	0.947 (0.012)	1.029 (0.012)	0.082	(0.049, 0.116)	
USA	1.062 (0.007)	1.155 (0.007)	0.094	(0.075, 0.113)	
W. Europe	1.106 (0.006)	1.212 (0.006)	0.106	(0.090, 0.122)	0.9936
Age: <55	1.217 (0.012)	1.320 (0.012)	0.104	(0.070, 0.138)	
55 – 65	1.106 (0.007)	1.199 (0.007)	0.093	(0.075, 0.111)	
65 – 75	1.039 (0.005)	1.135 (0.005)	0.096	(0.081, 0.111)	
≥ 75	0.958 (0.009)	1.043 (0.009)	0.085	(0.060, 0.110)	0.4898
BMI: <20	0.861 (0.010)	0.941 (0.010)	0.080	(0.053, 0.107)	
20 – 25	1.027 (0.006)	1.123 (0.006)	0.096	(0.077, 0.115)	
25 – 30	1.124 (0.007)	1.223 (0.006)	0.099	(0.081, 0.117)	
≥ 30	1.199 (0.009)	1.289 (0.009)	0.090	(0.066, 0.114)	0.1740
Anticholinergic:					
Yes	1.031 (0.006)	1.122 (0.006)	0.092	(0.076, 0.108)	
No	1.117 (0.005)	1.214 (0.005)	0.097	(0.083, 0.110)	0.0757

Estimated (least squares) means are based on repeated measures ANOVA model with visit as a discrete variable and baseline value as a covariate
*p-value based on test of interaction using repeated measures ANOVA with treatment, visit, subgroup, and treatment by subgroup interaction

Table 23: Estimated* mean post-bronchodilator FEV_1 from Day 30 until completion of double-blind treatment - Treated set with at least 3 measurements between Visits 3 – 19 (or Months 1 – 48)

	Treatment		Difference		
	Placebo Mean (SE)	Titropium Mean (SE)	Mean (SE) [ml/yr]	95% CI	p-value
Post-BD	**1.298 (0.004)**	**1.354 (0.004)**	**0.057**	**(0.046, 0.067)**	**<0.0001**
Sex: Female	1.053 (0.007)	1.106 (0.007)	0.053	(0.034, 0.071)	
Male	1.375 (0.005)	1.433 (0.004)	0.058	(0.045, 0.070)	0.4672
Gold Stage: I/II	1.544 (0.006)	1.613 (0.005)	0.069	(0.054, 0.084)	
III	1.098 (0.006)	1.148 (0.006)	0.050	(0.034, 0.065)	
IV	0.753 (0.012)	0.771 (0.011)	0.018	(-0.014, 0.049)	0.5848
Baseline Smoking Status: Ex-Smoker	1.276 (0.004)	1.326 (0.004)	0.050	(0.038, 0.062)	
Smoker	1.351 (0.008)	1.424 (0.007)	0.072	(0.052, 0.093)	0.4070
Reversibility: Yes	1.387 (0.005)	1.446 (0.005)	0.059	(0.045, 0.072)	
No	1.196 (0.006)	1.248 (0.006)	0.052	(0.036, 0.068)	0.4913

	Treatment		Difference		
	Placebo Mean (SE)	Titropium Mean (SE)	Mean (SE) [ml/yr]	95% CI	p-value
Post-BD	**1.298 (0.004)**	**1.354 (0.004)**	**0.057**	**(0.046, 0.067)**	**<0.0001**
Baseline ICS: Yes	1.278 (0.005)	1.329 (0.005)	0.051	(0.038, 0.065)	
No	1.329 (0.006)	1.394 (0.006)	0.065	(0.049, 0.080)	0.0467
Baseline LABA: Yes	1.268 (0.005)	1.326 (0.005)	0.058	(0.045, 0.072)	
No	1.342 (0.006)	1.396 (0.006)	0.054	(0.038, 0.070)	0.7631
Baseline ICS/LABA:					
Yes	1.260 (0.006)	1.322 (0.005)	0.062	(0.047, 0.078)	
No	1.333 (0.005)	1.384 (0.005)	0.051	(0.037, 0.065)	0.4761
Race: White	1.321 (0.004)	1.379 (0.004)	0.057	(0.046, 0.069)	
Black	1.137 (0.018)	1.151 (0.021)	0.013	(-0.041, 0.068)	
Asian	1.004 (0.012)	1.062 (0.011)	0.058	(0.026, 0.090)	0.5805
Region: Asia	0.998 (0.012)	1.056 (0.011)	0.057	(0.025, 0.089)	
E. Europe	1.373 (0.010)	1.429 (0.011)	0.056	(0.029, 0.084)	
Latin America	1.171 (0.013)	1.202 (0.013)	0.032	(-0.003, 0.067)	
USA	1.295 (0.007)	1.344 (0.006)	0.049	(0.031, 0.066)	
W. Europe	1.327 (0.006)	1.394 (0.006)	0.066	(0.050, 0.082)	0.9726
Age: <55	1.456 (0.013)	1.537 (0.012)	0.081	(0.046, 0.116)	
55 – 65	1.332 (0.007)	1.391 (0.006)	0.060	(0.041, 0.078)	
65 – 75	1.252 (0.005)	1.300 (0.005)	0.048	(0.033, 0.063)	
≥ 75	1.140 (0.009)	1.189 (0.009)	0.050	(0.025, 0.075)	0.3673*
BMI: <20	1.044 (0.009)	1.100 (0.010)	0.056	(0.030, 0.081)	
20 – 25	1.238 (0.006)	1.302 (0.006)	0.064	(0.047, 0.081)	
25 – 30	1.352 (0.007)	1.406 (0.006)	0.054	(0.036, 0.072)	
≥ 30	1.426 (0.009)	1.475 (0.009)	0.048	(0.024, 0.073)	0.3165
Anticholinergic:					
Yes	1.248 (0.006)	1.296 (0.006)	0.049	(0.032, 0.065)	
No	1.336 (0.005)	1.399 (0.005)	0.063	(0.049, 0.076)	0.0225

By-subgroup estimated (least squares) means are based on repeated measures ANOVA model with visit as a discrete variable and baseline value as a covariate
*p-value based on test of interaction using repeated measures ANOVA with treatment, visit, subgroup, and treatment by subgroup interaction

5 SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

The Applicant proposed to add 'Long-Term Effect of Lung Function', 'Exacerbation' and 'Survival and Respiratory Failure' in the Clinical Section of the SPIRIVA Handihaler label.

On January 11, 2008, the Applicant submitted the results of a six-month clinical trial with Spiriva HandiHaler (Study 266 or VA study) as pivotal evidence to support inclusion of the 'exacerbation' language in the labeling of Spiriva Handihaler. After careful review of the application, the Division concluded that the submitted data failed to provide substantial evidence of efficacy to support labeling claim for reduction of exacerbation in patients with COPD. In the Action Letter, it stated the following deficiency that precludes approval of the application.

> The submitted data do not provide substantial evidence of efficacy to support the labeling claim for reduction of exacerbation in COPD patients. Replicate findings from two adequate and well controlled studies are necessary to support a COPD exacerbation labeling claim. The results from combined analysis of clinical studies 205.254 and 205.255 are not acceptable for replication because these studies were conducted with Spiriva Respimat, which is a distinct product in terms of efficacy. To support the proposed claim of reduction of COPD exacerbation, provide data from an adequate and well controlled clinical study that shows statistically significant reduction in COPD exacerbation with Spiriva HandiHaler compared to placebo.

The Division Director's Memo summarized the results from Study 266

> The submitted data failed to show substantial evidence to support a reduction of COPD exacerbation claim for Spiriva HandiHaler. Results of the co-primary efficacy variables for study 266 are shown in Table 13. One of the two co-primary efficacy variables was met in this study and the other efficacy variable showed positive trend. Secondary efficacy variable generally trended in the right direction, but the results were not consistent (additional data not shown in this review). This study, while it may be considered positive, is not sufficiently robust to support approval of the labeling claim.

On January 30, 2009, the Applicant submitted a Complete Response to the FDA November 13, 2008 Complete Response letter for NDA 21-395 Serial No. 024. In this submission, they referred to the data and summaries from the UPLIFT clinical trial (Serial No. 029) to address the Division's comments regarding the reduction in COPD exacerbations, as well as stroke. In the UPLIFT Study Report, the Applicant claimed the following:

> Tiotropium did result in significant improvement in lung functions (i.e. FEV_1, FVC, and SVC, and this improvement was maintained over the four years of the trial. They also claimed that tiotropium reduced the risk of the first COPD exacerbation and the risk of the first COPD exacerbation leading to hospitalization by 14% each. Tiotropium significantly reduced the number of COPD exacerbations by 14%, and reduced the number of exacerbation days by 11%. The two treatment groups had comparable numbers of COPD exacerbations leading to hospitalization and comparable numbers of hospitalization days.

In the UPLIFT study, the co-primary endpoints directly relate to the study objective and these were the focus of the design and power of the study. However, statistical significance was not achieved in favor of tiotropium for these co-primary endpoints in order to continue testing the 'key' secondary endpoints (i.e. time to the first COPD exacerbation and time to the first COPD exacerbation leading to hospitalization) and 'other' endpoints (i.e. estimated mean pre- and post-bronchodilators FEV_1 by visit), based on a pre-specified multiplicity adjustment strategy. In the strictest sense of alpha spending, all the alpha has been spent by the primary efficacy analyses. Furthermore, evaluating the secondary endpoints (i.e. COPD exacerbation) is "to provide additional clinical characterization of

the treatment effect". Although the observed results (i.e. reduction in risk of COPD exacerbation) were in favor of tiotropium, the evidence from this study is insufficient to support the result from the VA study and to warrant a claim 'for reduction of exacerbation in patients with COPD'.

In the VA study, only one of the two 'co-primary' endpoints achieved statistical significance. Similar to the UPLIFT Study, the secondary endpoint (i.e. time-to-first COPD exacerbation) is the basis of the labeling claim 'for reduction of exacerbation in patients with COPD'. Like the UPLIFT study, multiplicity is a problem in interpreting the result of the secondary endpoint analysis because not all primary endpoints achieved statistical significance. However, as Dr. Davi pointed out in her review, there is a correlation between the primary analysis and secondary analysis of the same outcome (i.e. COPD exacerbation) such that it is unlikely the result of the time-to-first COPD exacerbation analysis is a spurious finding. Nevertheless, the overall conclusion by the Division was that the evidence is insufficient to warrant a claim from the VA study.

Therefore the statistical evidence taken collectively from the VA Study and the UPLIFT study, in particular because of the multiplicity issue in the UPLIFT study, does not support labeling claim for reduction of exacerbation in patients with COPD.

Aside from 'COPD exacerbation', the Applicant proposed to add the long-term effect in lung function (FEV_1) in the Clinical Section of the label. They claimed that "SPIRIVA HandiHaler maintained improvements in pulmonary function throughout 4 years. Specifically, SPIRIVA HandiHaler sustained improvements in trough (pre-dose) FEV_1 (adjusted means over time: 87 – 103 mL) throughout the 4 years of the study." Like COPD exacerbation, multiplicity is a problem in interpreting the results of these secondary analyses (i.e. estimated mean pre- or post-bronchodilator FEV_1). Furthermore, 'maintenance' and 'sustainability' are hard to quantify when group means are used instead of individual response. In other words, there are no pre-defined criteria that would allow us to determine 'maintenance' of effect.

Nonetheless, the current approved label indicated that

> SPIRIVA HandiHaler, administered once-daily in the morning, provided improvement in lung function (forced expiratory volume in one second, FEV_1), with peak effect occurring within 3 hours following the first dose.

In addition, the label described the results from the one-year and the six-month placebo controlled studies. It stated that there is evidence that improvement of lung function was maintained for 24 hours after a single dose and consistently maintained over the 1-year and the 6-month treatment period, respectively.

The result from UPLIFT study was consistent with the one-year and six-month studies when the mean trough FEV_1 scores were calculated throughout the 4-year period. When continuous responder analyses were performed for each Visit until Month 48, there is evidence that a higher proportion of patients treated with tiotropium responded better compared to the placebo as early as Month 1. Visually, the difference was maintained until Month 48 for the pre-bronchodilator FEV_1, and until at least until Month 24 for the post-bronchodilator FEV_1. Therefore the evidence from the UPLIFT study does support labeling claim for long-term effect in lung function.

The Applicant also proposed to include the following result in the Clinical Section of the label:

> Improvement in symptom scores was also seen in patients treated with SPIRIVA HandiHaler compared to placebo.

Based on statistical review of the UPLIFT study, the evidence that there is improvement in symptom score is insufficient to warrant inclusion in the Clinical Section of the Label.

Lastly, the Applicant proposed to add mortality and respiratory failure claims in the Clinical Section of the label. The following is the proposed language:

> In the 4-year multicenter trial, there was a 16% reduction in the risk of death while on treatment with SPIRIVA HandiHaler compared to placebo. The incidence rate of death was 4.10 per 100 patient years in the tiotropium group vs. 4.78 per 100 patient years in the placebo group [Hazard Ratio (tiotropium/placebo) = 0.84, 95% CI = 0.73, 0.97]. Treatment with tiotropium reduced the risk of respiratory failure by 19% (2.09 vs. 1.68 cases per 100 patient years [relative risk (tiotropium/placebo) = 0.81, 95% CI = 0.65, 1.00].

Like COPD exacerbation and long-term effect in lung function, mortality and respiratory failure are classified as secondary endpoints. However, unlike COPD exacerbation and lung function, the general consensus is that mortality can reach the status of a primary endpoint, if analyzed properly and supported by other study. In papers written by Dr. D'Agostino Sr.[3] and Dr. O'Neill[4] and several other researchers, they have alluded that a statistical significant finding on mortality has clinical impact. They also stated that the usual reason for designating mortality as a secondary endpoint is that the trialist believes *a priori* that there is little chance a treatment effect will be observed, given the sample sizes and the power to detect a clinically important effect on mortality.

In the UPLIFT Study, there is evidence of a benefit of tiotropium on on-treatment mortality. However, because a different result was observed in another SPIRIVA application using RESPIMAT delivery system, the result from UPLIFT needs to be explored further. Of note, in the RESPIMAT application, an increased number of deaths were observed in the Spiriva Respimat treatment groups compared to placebo for 1-year pivotal trials, resulting in a Complete Response action for the Spiriva Respimat NDA. Although there is evidence of a benefit of tiotropium on on-treatment mortality, a different result was observed in another SPIRIVA application using the RESPIMAT delivery system which complicates the mortality claim. On July 22, 2009, the Applicant amended the efficacy supplement to remove the mortality claim. According to the Applicant, there was no new Spiriva Handihaler data contributing to this decision.

The following is from Dr. Michele's review about the 'respiratory failure claim.

> Based on the SAE data, the applicant is requesting a claim for reduction in respiratory failure. BI proposes the following language for the clinical studies section of the label: "In the 4-year multicenter trial….Treatment with tiotropium reduced the risk of respiratory failure by 19% (2.09 vs. 1.68 cases per 100 patient years [relative risk (tiotropium/placebo) = 0.81, 95% CI 0.65, 1.00]."
> While the incidence of SAEs of respiratory failure is reduced in the tio HH18 group, the difference is marginally significant and there are multiple related preferred terms that have been analyzed separately. Unlike mortality, which is a hard endpoint and was pre-specified in the protocol as an event of interest (including vital status collection and an independent adjudication committee), the term "respiratory failure" is undefined and subject to investigator interpretation. Inclusion of the term respiratory failure may be appropriate as part of adverse event reporting for the study; however, there is insufficient evidence to justify a specific claim that Spiriva HandiHaler reduces respiratory failure.

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[3] Ralph D'Agostino Sr., "Controlling alpha in a clinical trial: the case for secondary endpoints", Statistics in Medicine, 2000 19: 763-766

[4] Robert T. O'Neill, "Secondary Endpoints Cannot be Validly Analyzed if the Primary Endpoint Does Not Demonstrate Clear Statistical Significance", Controlled Clinical Trials, 1997 18: 550-556

5.2 CONCLUSIONS AND RECOMMENDATIONS

Spiriva HandiHaler (tiotropium bromide inhalation powder) was approved on January 30, 2004 for long-term maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema.

The primary objective of the clinical program is to supplement the Clinical Studies section of the product information with additional information to prescribers concerning the long-term (4 year) efficacy and safety of tiotropium in the treatment of patients with COPD, based on the results from the UPLIFT study. The requested efficacy claims are: 1) description of the long-term effects on lung function, 2) reduction in exacerbations, 3) reduction in mortality, and 4) reduction in respiratory failure.

From a statistical perspective, because of multiplicity issue in the UPLIFT study, there is insufficient evidence that tiotropium 18 mcg is effective in reducing risk of COPD exacerbation and delaying the onset of COPD exacerbation. On the other hand, there is evidence from the UPLIFT study supporting the labeling claim for long-term effect on lung function. As noted in the clinical review, reduction in respiratory failure is not supported because the improvement is marginally significant and is not predefined.

A Pulmonary and Allergy Drug Advisory Committee meeting is scheduled on November 19, 2009. The Division plans to discuss the results from the UPLIFT study along with the RESPIMAT data.

6 LABELING

The following are the proposed changes and comments to the label.

1 INDICATIONS AND USAGE

SPIRIVA HandiHaler (tiotropium bromide inhalation powder) is indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

14 CLINICAL STUDIES

The SPIRIVA HandiHaler clinical development program consisted of six Phase 3 studies in 2,663 patients with COPD (1,308 receiving SPIRIVA HandiHaler): two 1-year, placebo-controlled studies, two 6-month, placebo-controlled studies and two 1-year, ipratropium-controlled studies. These studies enrolled patients who had a clinical diagnosis of COPD, were 40 years of age or older, had a history of smoking greater than 10 pack-years, had an FEV_1 less than or equal to 60 or 65% of predicted, and a ratio of FEV_1/FVC of less than or equal to 0.7.

In these studies, SPIRIVA HandiHaler, administered once-daily in the morning, provided improvement in lung function (forced expiratory volume in one second, FEV_1), with peak effect occurring within 3 hours following the first dose.

Two additional trials evaluated exacerbations: a 6-month, randomized, double-blind, placebo-controlled, multicenter clinical trial of 1,829 COPD patients in a US Veterans Affairs setting and a 4-year, randomized, double-blind, placebo-controlled, multicenter, clinical trial of 5,993 COPD patients. Long-term effects on lung function and other outcomes were also evaluated in the 4 year multicenter trial. **[Reviewer: These sentences in red are new and are acceptable]**

Lung Function

In the 1-year, placebo-controlled trials, the mean improvement in FEV_1 at 30 minutes was 0.13 liters (13%) with a peak improvement of 0.24 liters (24%) relative to baseline after the first dose (Day 1). Further improvements in FEV_1 and FVC were observed with pharmacodynamic steady state reached by Day 8 with once-daily treatment. The mean peak improvement in FEV_1, relative to baseline, was 0.28 to 0.31 liters (28% to 31%), after 1 week (Day 8) of once-daily treatment. Improvement of lung function was maintained for 24 hours after a single dose and consistently maintained over the 1-year treatment period with no evidence of tolerance.

In the two 6-month, placebo-controlled trials, serial spirometric evaluations were performed throughout daytime hours in Trial A (12 hours) and limited to 3 hours in Trial B. The serial FEV_1 values over 12 hours (Trial A) are displayed in Figure 1. These trials further support the improvement in pulmonary function (FEV_1) with SPIRIVA HandiHaler, which persisted over the spirometric observational period. Effectiveness was maintained for 24 hours after administration over the 6-month treatment period.

Figure 1 Mean FEV_1 Over Time (prior to and after administration of study drug) on Days 1 and 169 for Trial A (a Six-Month Placebo-Controlled Study)*

Day 1 Day 169

*Means adjusted for center, treatment, and baseline effect. On Day 169, a total of 183 and 149 patients in the SPIRIVA HandiHaler and placebo groups, respectively, completed the trial. The data for the remaining patients were imputed using last observation or least favorable observation carried forward.

Results of each of the one-year ipratropium-controlled trials were similar to the results of the one-year placebo-controlled trials. The results of one of these trials are shown in Figure 2.

Figure 2 Mean FEV_1 Over Time (0 to 6 hours post-dose) on Days 1 and 92, respectively for one of the two Ipratropium-Controlled Studies*

Day 1 Day 92

*Means adjusted for center, treatment, and baseline effect. On Day 92 (primary endpoint), a total of 151 and 69 patients in the SPIRIVA HandiHaler and ipratropium groups, respectively, completed through three months of observation. The data for the remaining patients were imputed using last observation or least favorable observation carried forward.

A randomized, placebo-controlled clinical study in 105 patients with COPD demonstrated that bronchodilation was maintained throughout the 24-hour dosing interval in comparison to placebo, regardless of whether SPIRIVA HandiHaler was administered in the morning or in the evening.

Throughout each week of the one-year treatment period in the two placebo-controlled trials, patients taking SPIRIVA HandiHaler had a reduced requirement for the use of rescue short-acting $beta_2$-agonists. Reduction in the use of rescue short-acting $beta_2$-agonists, as compared to placebo, was demonstrated in one of the two 6-month studies.

Long-Term Effects on Lung Function

A 4-year, randomized, double-blind, placebo-controlled, multicenter clinical trial involving 5,993 COPD patients was conducted to evaluate the long-term effects of SPIRIVA HandiHaler. Patients were permitted to use all respiratory medications (including short-acting and long-acting beta-agonists, inhaled and systemic steroids, and theophyllines) other than inhaled anticholinergics. The patients were 40 to 88 years of age with a diagnosis of COPD and a post-bronchodilator $FEV_1 \leq 70\%$ of predicted at study entry. The co-primary efficacy endpoints, yearly rate of decline in pre- and post-bronchodilator FEV_1, were not significantly different between the two groups. [SPIRIVA HandiHaler maintained improvements in pulmonary function throughout 4 years.-] [Reviewer: I suggest deleting the previous sentence because (1) it is not clear what improvement means and what criterion was maintained; and (2) it seems redundant with the next sentence. In fact, the next sentence gave a better description of what 'improvement' means.] Specifically, SPIRIVA HandiHaler sustained improvements in trough (pre-dose) FEV_1 (adjusted means over time: 87-103 mL) throughout the 4 years of the study. (Figure 3)

Figure 3 Trough FEV_1 - Mean values at each time point

*P<0.0001 vs. placebo. [I suggest removing the p-values]]Repeated measure ANOVA was used to estimate means. Means are adjusted for baseline measurements. Baseline trough FEV_1 (observed mean) = 1.116. Patients with ≥3 acceptable PFTs after day 30 and non-missing baseline value were included in the analysis.

Exacerbations
In a 6-month clinical trial of COPD patients in a Veterans Affairs setting, SPIRIVA HandiHaler significantly reduced the proportion of COPD patients who experienced exacerbations compared to placebo and significantly delayed the time to first exacerbation. These findings are supported by a pre-specified combined analysis of two one-year clinical trials using SPIRIVA RESPIMAT.

Exacerbations were evaluated as a secondary outcome in the 4-year multicenter trial. In this trial, COPD exacerbations were defined as an increase or new onset of more than one of the following respiratory symptoms (cough, sputum, sputum purulence, wheezing, dyspnea) with a duration of three or more days requiring treatment with antibiotics and/or systemic (oral, intramuscular or intravenous) steroids. SPIRIVA HandiHaler reduced the risk of an exacerbation by 14% (Hazard Ratio 0.86, 95% CI = 0.81, 0.91, p<0.001) and exacerbation-related hospitalization by 14% (Hazard Ratio 0.86, 95% CI = 0.78, 0.95, p<0.002) compared to placebo. [I recommend removing this paragraph because there is insufficient evidence that tiotropium 18 mcg reduces the risk of COPD exacerbation, from a statistical perspective] Improvement in symptom scores was also seen in patients treated with SPIRIVA HandiHaler compared to placebo. [The last sentence should be removed because there is no statistical basis for this claim i.e. improvement in symptom scores]

Survival and Respiratory Failure
In the 4-year multicenter trial, there was a 16% reduction in the risk of death while on treatment with SPIRIVA HandiHaler compared to placebo. The incidence rate of death was 4.10 per 100 patient years in the tiotropium group vs. 4.78 per 100 patient years in the placebo group [Hazard Ratio (tiotropium/placebo) = 0.84, 95% CI = 0.73, 0.97]. Treatment with tiotropium reduced the risk of respiratory failure by 19% (2.09 vs. 1.68 cases per 100 patient years [relative risk (tiotropium/placebo) = 0.81, 95% CI = 0.65, 1.00]. [The claim of respiratory failure should be removed because as noted in the clinical review, reduction in respiratory failure is not supported. The improvement is marginally significant and is not predefined.]

7 APPENDIX

Appendix 1: Changes in Planned Analyses

- The co-primary endpoints, yearly rate of decline in trough FEV1 and yearly rate of decline in FEV1 90 minutes post-bronchodilators were tested at the 0.049 overall significance level (two-sided), adjusted for all interim evaluations, for the final trial analysis.

- In the protocol, it was stated that the yearly rate of decline in FEV1, FVC, and SVC pre- and post-bronchodilator from Day 1 until completion of the trial (30 days post-study drug treatment) would be compared using ANOVA, or equivalently a two-sample t-test. For robustness, the test was changed to a Wilcoxon rank sum test.

- Based on comments from the FDA (29 May 2008), the individual rate of decline from Day 30 until completion of double blinded treatment was calculated for trough (pre-bronchodilator) and post-bronchodilator FEV1 by taking the difference between the last on-treatment visit and visit 3 (Day 30) divided by the time difference. Treatment groups were compared using Wilcoxon rank sum test.

- Two secondary endpoints, time to the first exacerbation and time to the first COPD exacerbation leading to hospitalization, were identified as key secondary endpoints. In addition, a gate-keeping strategy for statistical hypothesis testing was established to test the co-primary endpoints, number of hospitalizations due to an exacerbation of COPD, and the two key secondary endpoints and the TSAP. P-value adjustment for interim analyses was planned for the number of hospitalizations due to an exacerbation of COPD and the co-primary endpoints.

- Based on comments from the FDA (29 May 2008), all the exacerbation endpoints were analyzed using the exacerbation data with seven days between distinct events. This data allowed for clear distinction between events. Number of COPD exacerbations and number of COPD exacerbations leading to hospitalization based on the Poisson model were also analyzed using an exacerbation data with 1 day between events as sensitivity analysis.

- For the number of COPD exacerbations and the number of COPD exacerbations leading to hospitalization, Poisson regression adjusted for overdispersion and exposure to treatment was performed in addition to the protocol-specified Wilcoxon rank-sum test.

- For the number of COPD exacerbation days and number of days hospitalized due to COPD exacerbation, Poisson regression adjusted for overdispersion was performed in addition to the protocol-specified Wilcoxon rank sum test.

- For the analysis of COPD exacerbations, the following endpoints were added: time to the first COPD exacerbation treated with steroids, number of exacerbations treated with steroids per patient year, time to the first COPD exacerbation treated using antibiotics, and number of exacerbations treated with antibiotics per patient year.

- The number of days between exacerbations was included as a secondary endpoint in the protocol. However, for the first and the last exacerbations, it was impossible to accurately estimate the number of days from the previous exacerbation to the first event during the trial, and from the last exacerbations in the trial to the next post-trial event. Consequently, if calculated, this endpoint would have been highly biased, especially for those patients with 0 or 1 exacerbation, thus this endpoint was not analyzed.

- The statistical analyses for respiratory mortality were based on the adjudicated primary cause of death. Matching between adjudicated and investigator reported primary cause of death was explored using descriptive statistics. Respiratory mortality specified in the trial protocol was interpreted as lower respiratory mortality, as defined by the SPRIVA® project rules.

- Analyses were added to investigate the risk of stroke in response to an FDA early communication. Kaplan-Meier estimates as well as Cox regression were carried out for stroke AE, serious AE, and fatal AEs.

- In addition to SGRQ total scores, the declines in SGRQ impact, symptom, and activity scores were analyzed.

- All the exacerbation endpoints were analyzed using the exacerbation data with seven days between distinct events. This data would allow for clear distinction between events. Number of exacerbation and number of exacerbations leading to hospitalization based on the Poisson model were also analyzed using exacerbation data with 1 day between events as sensitivity analysis.

- Individual rate of decline from Day 30 until completion of double-blinded treatment was calculated for trough and peak FEV1 by taking the difference between the last on-treatment visit and visit 3 (Day 30) divided by the time difference. Treatment groups were compared using Wilcoxon rank sum test.

- Post-unblinding analyses:

    - Assuming a patient had one rate of decline of FEV1 while on LABA or ICS (either monoproduct or combination), and another rate of decline when he/she was off LABA or ICS (not on either), a random-effects model was used to estimate treatment difference for the on- and off-LABA/ICS periods.

    - A random-effects model was used to compare treatment difference of the rate of decline of FEV1 in patients not treated with either LABA or ICS (monoproduct or combination) at baseline.
    - A random-effects model was used to compare treatment difference of the rate of decline of FEV1 in completers and in non-completers

    - To explore the sensitivity of the hazard ratio and p-values to cut-off days, different cut-off days and no cut-off were used in the Cox-regression of on-treatment deaths and all deaths including vital status. In particular, Day 1440 was planned in accordance with the designed length of the vital status collection.

- Subgroup analyses were conducted for on-treatment deaths using Cox regression with 1440-day and 1470-day cut-offs, or without any cut-off day.

- Responder analysis of SGRQ total scores was included after unblinding. A patient was considered a responder if there was a decrease of at least 4 units in SGRQ total score from the baseline. A logistic regression was used to calculate the odds ratio of responder between treatment groups at years 1, 2, 3 and 4 while adjusting for baseline covariates. The frequency table was provided for the portion of responders at these time points. Similarly, a deteriorator was defined as someone with an increase of at least 4 units in SGRQ total score from the baseline. Similar analyses of proportion of deteriorator were carried out at years 1, 2, 3, and 4.

Appendix 2: Treatment exposure – Treated Set

	Placebo	Tio 18 mcg	Total
Total treated	3006(100.0)	2986(100.0)	5992(100.0)
Exposure [Months]			
>=1	2867(95.4)	2915(97.6)	5782(96.5)
>=3	2740(91.2)	2816(94.3)	5556(92.7)
>=6	2618(87.1)	2726(91.3)	5344(89.2)
>=9	2513(83.6)	2634(88.2)	5147(85.9)
>=12	2418(80.4)	2565(85.9)	4983(83.2)
>=15	2344(78.0)	2496(83.6)	4840(80.8)
>=18	2249(74.8)	2432(81.4)	4681(78.1)
>=21	2161(71.9)	2363(79.1)	4524(75.5)
>=24	2090(69.5)	2293(76.8)	4383(73.1)
>=27	2013(67.0)	2236(74.9)	4249(70.9)
>=30	1947(64.8)	2177(72.9)	4124(68.8)
>=33	1891(62.9)	2117(70.9)	4008(66.9)
>=36	1831(60.9)	2060(69.0)	3891(64.9)
>=39	1779(59.2)	2001(67.0)	3780(63.1)
>=42	1723(57.3)	1970(66.0)	3693(61.6)
>=45	1665(55.4)	1904(63.8)	3569(59.6)
Treatment Exposure [days]			
Mean	1032.7	1128.1	1080.3
Min	1	1	1
Max	1550	1655	1655
SD	533.0	486.5	512.5

Source: Clinical Study Report, Table 15 3 1 1:1 page 463

Appendix 3: Unblinded Patients – Treated Set

Country	Site Number	Patient Number	Treatment Allocation (tiotropium or placebo)	Adverse Event
Argentina	0107	10181	tiotropium	Interstitial lung disease
Brazil	0514	10591	placebo	Fecal impaction
Denmark	0801	17543	placebo	Acute laryngitis
Germany	1110	18852	tiotropium	COPD exacerbation
Greece	1201	19016	placebo	Dysphonia, pharyngeal disorder
Hungary	1304	16123	placebo	COPD exacerbation
Italy	1629	19800	tiotropium	Pneumonia
Mexico	2002	10680	tiotropium	Hyperplasia of prostate, Bladder neck obstruction
Netherlands	2109	20602	tiotropium	Shortness of breath, COPD exacerbation
New Zealand	0212	23831	placebo	Increased shortness of breath on exertion, Wheeze, Sub-acute exacerbation of COPD with asthmatic component
Singapore	1906	27043	placebo	COPD exacerbation
Spain	3027	21600	placebo	COPD exacerbation
Switzerland	3203	24308	tiotropium	Ventricular fibrillation
Thailand	3404	26645	placebo	Chest tightness, Sudden death
Thailand	3404	26639	tiotropium	Acute myocardial infarction
Turkey	3512	22812	placebo	COPD exacerbation
Turkey	3512	22815	placebo	Type 2 respiratory failure, COPD exacerbation
United States	3787	13557	placebo	Atrial flutter
United States	3788	13581	tiotropium	Atrial flutter
United States	3789	13606	placebo	Prolonged ileus
United States	3789	13615	tiotropium	Sudden death, presumably arrhythmic
United States	3789	13685	placebo	Atrial fibrillation

Source data: Patients were unblinded via IVRS. Data on file in BI Drug Safety Database.

Source: Study Report, Table 10 1 2, page 97

Appendix 4: Protocol Violations – Treated Set

	Placebo N (%)	Tio 18 mcg N (%)	Total N (%)
Treated patients	3006 (100.0)	2986 (100.0)	5992 (100.0)
Total with important PV[1]	217 (7.2)	223 (7.5)	440 (7.3)
PV Category[1]			
Known active tuberculosis	0 (0.0)	1 (0.0)	1 (0.0)
History of excluded pulmonary disease	10 (0.3)	7 (0.2)	17 (0.3)
History of thoracotomy with resection	1 (0.0)	4 (0.1)	5 (0.1)
Respiratory infection/COPD exacerbation	26 (0.9)	29 (1.0)	55 (0.9)
Unstable respiratory medication use	7 (0.2)	10 (0.3)	17 (0.3)
Known narrow-angle glaucoma	1 (0.0)	3 (0.1)	4 (0.1)
Sympomatic prostatic hyperplasia/bladder-neck obstruction	0 (0.0)	1 (0.0)	1 (0.0)
Malignancy treated in the last 5 years	5 (0.2)	2 (0.1)	7 (0.1)
Anticholinergic drug hypersensitivity	0 (0.0)	1 (0.0)	1 (0.0)
Involved in other trials	0 (0.0)	1 (0.0)	1 (0.0)
FEV_1 >70% of predicted or FEV_1 >70% of FVC	28 (0.9)	32 (1.1)	60 (1.0)
Informed consent signed late	2 (0.1)	2 (0.1)	4 (0.1)
Incorrect trial medication taken	1 (0.0)	0 (0.0)	1 (0.0)
Improper medication washout	39 (1.3)	43 (1.4)	82 (1.4)
Anticholinergic use for at least two consecutive visits	115 (3.8)	112 (3.8)	227 (3.8)

Source data: Table 15.1.2: 1

[1] Percentages are based on treated patients

Source: Clinical Study Report, Table 10 2:1 page 98

Appendix 5: Summary of demographic characteristics – Treated Set

	Placebo		Tio 18 mcg		Total	
	N (%)	Mean (SD)	N (%)	Mean (SD)	N (%)	Mean (SD)
Total treated	3006 (100)		2986 (100)		5992 (100)	
Sex [N (%)]						
Male	2222 (73.9)		2251 (75.4)		4473 (74.6)	
Female	784 (26.1)		735 (24.6)		1519 (25.4)	
Race [N (%)]						
White	2697 (89.7)		2691 (90.1)		5388 (89.9)	
Black	53 (1.8)		38 (1.3)		91 (1.5)	
Asian	185 (6.2)		192 (6.4)		377 (6.3)	
Missing	71 (2.4)		65 (2.2)		136 (2.3)	
GOLD stage [N(%)]						
Stage I	1 (0.0)		2 (0.1)		3 (0.1)	
Stage II	1355 (45.1)		1384 (46.3)		2739 (45.7)	
Stage III	1331 (44.3)		1304 (43.7)		2635 (44.0)	
Stage IV	271 (9.0)		250 (8.4)		521 (8.7)	
Missing	48 (1.6)		46 (1.5)		94 (1.6)	
Age [years]	3006	64.5 (8.5)	2986	64.5 (8.4)	5992	64.5 (8.5)
Height [cm]	3006	169.1 (8.7)	2986	169.3 (8.6)	5992	169.2 (8.7)
Weight [kg]	3006	74.4 (17)	2986	74.9 (17.2)	5992	74.7 (17.1)
BMI	3006	25.9 (5.1)	2986	26.0 (5.1)	5992	26 (5.1)
Smoking history [N(%)]						
Ex-Smoker	2108 (70.1)		2112 (70.7)		4220 (70.4)	
Smoker	898 (29.9)		874 (29.3)		1772 (29.6)	
Smoking history [pack years]	3006	48.4 (27.9)	2986	49 (28.0)	5992	48.7 (27.9)
COPD duration [years]	3006	9.7 (7.4)	2986	9.9 (7.6)	5992	9.8 (7.5)

Source data: Table 15.1.4.1: 1

Source: Clinical Study Report, Table 11 2:1, page 102

Appendix 6: Summary of baseline disease characteristics – Treated Set

	Pre-bronchodilator			Post-bronchodilator		
	Placebo	Tio 18 mcg	Total	Placebo	Tio 18mcg	Total
Total Treated	3006	2986	5992	3006	2986	5992
FEV_1 [liters]						
N	2937	2908	5845	2958	2940	5898
Mean	1.092	1.101	1.096	1.315	1.328	1.322
SD	0.4	0.403	0.401	0.441	0.438	0.44
FEV_1 increase [%]*						
N	-	-	-	2906	2877	5783
Mean	-	-	-	23.4	23.4	23.4
SD	-	-	-	18	18	18
%Predicted FEV_1						
N	2937	2908	5845	2958	2940	5898
Mean	39.3	39.5	39.4	47.4	47.7	47.6
SD	11.9	12	12	12.6	12.7	12.7
FEV_1/FVC [%]						
N	2937	2908	5845	2958	2940	5898
Mean	42.1	42.4	42.3	43.3	43.6	43.4
SD	10.5	10.5	10.5	10.7	10.8	10.7
FVC [liters]						
N	2937	2908	5845	2958	2940	5898
Mean	2.626	2.625	2.625	3.09	3.09	3.09
SD	0.83	0.807	0.819	0.902	0.863	0.882
%Predicted FVC						
N	2937	2908	5845	2958	2940	5898
Mean	74.9	74.7	74.8	88.3	88.1	88.2
SD	18	18.1	18.1	18.8	18.7	18.7
SVC [liters]						
N	2925	2882	5807	2930	2909	5839
Mean	2.798	2.802	2.8	3.195	3.213	3.204
SD	0.827	0.817	0.822	0.902	0.88	0.891

Source: Table 15.1.4.1:2
* FEV_1 increase refers to % increase in FEV_1 following maximal brochodilation, i.e., 100*(post-BD - pre-BD)/pre-BD.

Source: Clinical Study Report, Table 11 2:2, page 103

Appendix 7: Summary of baseline SGRQ scores – Treated Set

	Placebo		Tio 18 mcg		Total	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Total treated	3006		2986		5992	
Activity score*	2909	61.64 (19.3)	2888	61.44 (19.67)	5797	61.54 (19.48)
Impact score*	2909	35.68 (19.55)	2888	35.37 (18.89)	5797	35.53 (19.22)
Symptom score*	2941	50.49 (22.45)	2920	49.9 (22.64)	5861	50.2 (22.55)
Total score*	2909	46.03(17.22)	2888	45.7 (17)	5797	45.87 (17.11)

Source data: Table 15.1.4.1: 6
* Excluding Turkish patients
Source: Clinical Study Report, Table 11 2:3, page 104

Appendix 8: Summary of pulmonary medication use at baseline – Treated Set

	Placebo	Tio 18 mcg	Total
	N (%)	N (%)	N (%)
Total treated	3006 (100.0)	2986 (100.0)	5992 (100.0)
Total taking pulmonary medication	2800 (93.1)	2788 (93.4)	5588 (93.3)
Anticholinergic (Long-Acting/Inhaled)	49 (1.6)	60 (2.0)	109 (1.8)
Anticholinergic (Short-Acting/Inhaled)	1325 (44.1)	1342 (44.9)	2667 (44.5)
Beta Adrenergics (Long-Acting/Inhaled)	1808 (60.1)	1796 (60.1)	3604 (60.1)
Beta Adrenergics (Oral/Short-Acting/Inhaled)	2047 (68.1)	2044 (68.5)	4091 (68.3)
Leukotriene Receptor Antagonists	94 (3.1)	98 (3.3)	192 (3.2)
Mucolytics	208 (6.9)	222 (7.4)	430 (7.2)
Oxygen	57 (1.9)	68 (2.3)	125 (2.1)
Steroids(Inhaled)	1860 (61.9)	1840 (61.6)	3700 (61.7)
Steroids(Other)	251 (8.3)	251 (8.4)	502 (8.4)
Xanthines	858 (28.5)	848 (28.4)	1706 (28.5)
Xanthines/Beta Adrenergics Combination	1 (0.0)	2 (0.1)	3 (0.1)

Source data: Table 15.1.4.1: 4

Source: Clinical Study Report, Table 11 2:4, page 105

Appendix 9: Subgroup Analyses for the mean slope of FEV_1 from day 30 until completion of treatment – Treated Set

	Subgroup		N	Placebo Mean (SE) [ml/year]	N	Tio 18 mcg Mean (SE) [ml/year]	Subgroup by treatment interaction p-value	Difference (Tio 18 mcg - Placebo) Mean (SE) [ml/year]	P-value
Pre-BD	Age						0.5125		
		< 55	322	-41(4)	340	-40(3)		1(5)	0.8302
		>= 55, <65	861	-36(2)	908	-34(2)		2(3)	0.4669
		>= 65, <75	976	-24(2)	1029	-27(2)		-3(3)	0.2678
		>= 75	254	-21(4)	280	-17(4)		4(6)	0.4800
	Gender						0.8017		
		Male	1815	-31(2)	1946	-31(1)		0(2)	0.8549
		Female	598	-27(3)	611	-27(3)		-1(4)	0.8530
	Smoking status						0.1924		
		Ex-smoker	1706	-25(2)	1818	-26(1)		-2(2)	0.4775
		Currently smokes	707	-43(2)	739	-40(2)		4(3)	0.2743
	LABA use						0.6718		
		No	969	-33(2)	1021	-32(2)		1(3)	0.7207
		Yes	1444	-28(2)	1536	-29(2)		-1(2)	0.8163
	ICS use						0.5782		
		No	942	-36(2)	989	-35(2)		1(3)	0.6451
		Yes	1471	-26(2)	1568	-27(2)		-1(2)	0.7533
	LABA/ICS						0.4968		
		No	1254	-32(2)	1310	-34(2)		-1(3)	0.6553
		Yes	1159	-28(2)	1247	-26(2)		1(3)	0.6077
	Antichol inergics						0.5303		
		No	1382	-32(2)	1409	-31(2)		1(2)	0.6692
		Yes	1031	-28(2)	1148	-29(2)		-1(3)	0.6453
	GOLD stage						0.1913		
		I/II	1159	-37(2)	1221	-35(2)		2(3)	0.3794
		III	1033	-26(2)	1107	-27(2)		-1(3)	0.6233
		IV	185	-9(5)	193	-20(5)		-11(7)	0.1293

Random effects model is used: treatment, subgroup and treatment by subgroup interaction for slope and intercept.

	Subgroup		N	Placebo Mean (SE) [ml/year]	N	Tio 18 mcg Mean (SE) [ml/year]	Subgroup by treatment interaction p-value	Difference (Tio 18 mcg - Placebo) Mean (SE) [ml/year]	P-value
Pre-BD	Race						0.4419		
		White	2158	-31(1)	2304	-30(1)		1(2)	0.6643
		Black	46	-22(10)	34	-39(10)		-17(14)	0.2415
		Asian	153	-18(5)	165	-21(5)		-2(7)	0.7443
	Region						0.7695		
		Asia	147	-18(5)	158	-20(5)		-2(7)	0.8346
		E. Europe	530	-33(3)	521	-35(3)		-2(4)	0.5323
		Latin America	180	-32(5)	180	-25(5)		6(7)	0.3446
		USA	565	-25(3)	621	-26(3)		-2(4)	0.6438
		W. Europe	991	-33(2)	1077	-32(2)		1(3)	0.5993
	Reversibility						0.9956		
		No	1084	-31(2)	1150	-32(2)		-0(3)	0.9666
		Yes	1255	-29(2)	1319	-29(2)		-0(3)	0.9696
	BMI						0.3721		
		<20	280	-36(4)	245	-39(4)		-2(6)	0.6917
		>=20,<25	784	-37(2)	915	-33(2)		4(3)	0.1798
		>=25,<30	852	-27(2)	904	-27(2)		-0(3)	0.9260
		>=30	497	-22(3)	493	-26(3)		-4(4)	0.2782
Post-BD	Age						0.5718		
		< 55	322	-54(4)	340	-47(3)		6(5)	0.2083
		>= 55, <65	860	-48(2)	909	-45(2)		3(3)	0.2877
		>= 65, <75	971	-35(2)	1027	-36(2)		-1(3)	0.8391
		>= 75	257	-35(4)	278	-29(4)		6(6)	0.3509
	Gender						0.6289		
		Male	1812	-43(2)	1945	-41(1)		2(2)	0.3782
		Female	598	-39(3)	609	-35(3)		4(4)	0.2945
	Smoking status						0.9011		
		Ex-smoker	1700	-38(2)	1815	-36(2)		2(2)	0.3432
		Currently smokes	710	-52(3)	739	-50(2)		3(4)	0.4515

Random effects model is used: treatment, subgroup and treatment by subgroup interaction for slope and intercept.

	Subgroup		N	Placebo Mean (SE) [ml/year]	N	Tio 18 mcg Mean (SE) [ml/year]	Subgroup by treatment interaction p-value	_Difference (Tio 18 mcg - Placebo)_ Mean (SE) [ml/year]	P-value
Post-BD	LABA use						0.5703		
		No	968	-44(2)	1018	-40(2)		4(3)	0.2165
		Yes	1442	-41(2)	1536	-39(2)		2(2)	0.5421
	ICS use						0.6762		
		No	940	-45(2)	988	-42(2)		3(3)	0.2676
		Yes	1470	-40(2)	1566	-38(2)		2(2)	0.4734
	LABA/ICS						0.7128		
		No	1252	-43(2)	1307	-42(2)		2(3)	0.5201
		Yes	1158	-41(2)	1247	-38(2)		3(3)	0.2583
	Antichol inergics						0.6861		
		No	1383	-42(2)	1405	-39(2)		3(3)	0.2208
		Yes	1027	-42(2)	1149	-41(2)		2(3)	0.6007
	GOLD stage						0.0787		
		I/II	1158	-49(2)	1218	-43(2)		6(3)	0.0235
		III	1031	-38(2)	1104	-39(2)		-0(3)	0.8667
		IV	185	-23(5)	194	-32(5)		-9(7)	0.2406
	Race						0.7543		
		White	2154	-43(1)	2301	-40(1)		3(2)	0.1880
		Black	46	-36(10)	34	-44(11)		-8(15)	0.5905
		Asian	153	-31(6)	165	-27(5)		4(8)	0.5591
							0.7543		
		White	2154	-43(1)	2301	-40(1)		3(2)	0.1880
		Black	46	-36(10)	34	-44(11)		-8(15)	0.5905
		Asian	153	-31(6)	165	-27(5)		4(8)	0.5591
							0.7543		
		White	2154	-43(1)	2301	-40(1)		3(2)	0.1880
		Black	46	-36(10)	34	-44(11)		-8(15)	0.5905
		Asian	153	-31(6)	165	-27(5)		4(8)	0.5591
	BMI						0.7736		

Random effects model is used: treatment, subgroup and treatment by subgroup interaction for slope and intercept.

	Subgroup		N	Placebo Mean (SE) [ml/year]	N	Tio 18 mcg Mean (SE) [ml/year]	Subgroup by treatment interaction p-value	_Difference (Tio 18 mcg - Placebo)_ Mean (SE) [ml/year]	P-value
Post-BD	BMI	<20	280	-55(4)	242	-53(4)		1(6)	0.8456
		>=20,<25	782	-49(2)	915	-44(2)		5(3)	0.1209
		>=25,<30	853	-37(2)	903	-36(2)		2(3)	0.5882
		>=30	495	-34(3)	494	-34(3)		-0(4)	0.9763

Source: Clinical Study Report , Table 15 2 1:4, page 380 – 382

Appendix 10: Estimate mean FEV1 using repeated measure ANOVA from day 30 to completion of treatment − treated set with baseline and at least 3 measurements after (including) day 30

	Time point	Placebo Mean (SE) [L]	Tio 18 mcg Mean (SE) [L]	Difference (Tio 18 mcg - Placebo) Mean (CI)	P-value
Day 1	Pre-BD	1.116	1.116		
	Post-BD	1.347	1.347		
Month 1	Pre-BD	1.134(0.004)	1.221(0.004)	0.087(0.077, 0.098)	<.0001
	Post-BD	1.372(0.004)	1.418(0.004)	0.047(0.037, 0.057)	<.0001
Month 6	Pre-BD	1.126(0.004)	1.225(0.004)	0.099(0.087, 0.110)	<.0001
	Post-BD	1.365(0.004)	1.423(0.004)	0.058(0.047, 0.069)	<.0001
Month 12	Pre-BD	1.111(0.004)	1.213(0.004)	0.103(0.091, 0.115)	<.0001
	Post-BD	1.345(0.004)	1.398(0.004)	0.054(0.042, 0.065)	<.0001
Month 18	Pre-BD	1.101(0.005)	1.192(0.005)	0.091(0.078, 0.104)	<.0001
	Post-BD	1.326(0.005)	1.379(0.005)	0.053(0.040, 0.066)	<.0001
Month 24	Pre-BD	1.079(0.005)	1.173(0.005)	0.094(0.081, 0.107)	<.0001
	Post-BD	1.294(0.005)	1.356(0.005)	0.062(0.049, 0.075)	<.0001
Month 30	Pre-BD	1.061(0.005)	1.156(0.005)	0.095(0.081, 0.109)	<.0001
	Post-BD	1.274(0.005)	1.335(0.005)	0.061(0.047, 0.075)	<.0001
Month 36	Pre-BD	1.045(0.005)	1.144(0.005)	0.099(0.085, 0.114)	<.0001
	Post-BD	1.250(0.005)	1.315(0.005)	0.065(0.051, 0.080)	<.0001
Month 42	Pre-BD	1.034(0.005)	1.129(0.005)	0.095(0.080, 0.110)	<.0001
	Post-BD	1.236(0.006)	1.297(0.005)	0.061(0.045, 0.076)	<.0001
Month 48	Pre-BD	1.024(0.006)	1.112(0.005)	0.088(0.073, 0.103)	<.0001
	Post-BD	1.219(0.006)	1.268(0.006)	0.049(0.033, 0.065)	<.0001
Overall mean	Pre-BD	1.080(0.004)	1.174(0.004)	0.094(0.084, 0.105)	<.0001
	Post-BD	1.298(0.004)	1.354(0.004)	0.057(0.046, 0.067)	<.0001

Pre-BD: before bronchodilator on test day 1; before bronchodilator and study medication on other test days
Post-BD: after bronchodilator on test day 1; after bronchodilator and study medication on other test days
For pre-BD, N = 2363 and 2494 for treatment Placebo and Tio 18 mcg respectively
For post-BD, N = 2374 and 2516 for treatment Placebo and Tio 18 mcg respectively
The mean, standard error and 95% confidence interval are estimated using repeated measure ANOVA model
Model adjusted for baseline measurement. Day 1 (baseline) values are observed overall mean value, not estimated from the mixed model

Source: Clinical Study Report, Table 15.2.1:12 page 391

Appendix 11: Proportion of Responders* (≥ 15% improvement) in mean pre- or post-bronchodilator FEV_1 at each Visit from Baseline - Treated set with at least 3 measurements between Visits 3 – 19 (or Months 1 – 48) and have baseline score

	Pre-Bronchodilator		Post-Bronchodilator	
Month	Placebo N=2363	Titropium N=2494	Placebo N=2374	Titropium N=2516
1	16%	33%	11%	17%
6	18%	35%	13%	21%
12	17%	33%	12%	17%
18	16%	29%	11%	16%
24	13%	25%	9%	13%
30	11%	23%	8%	12%
36	10%	21%	7%	11%
42	9%	19%	7%	9%
48	8%	16%	6%	9%

* Dropouts are considered non-responder. Last observed value carried forward to missed visit/values.

Appendix 12: Proportion of Responders* (≥ 15% improvement) in mean pre- or post-bronchodilator FEV_1 at each Visit from Baseline - Treated set with at least 3 measurements between Visits 3 – 19 (or Months 1 – 48) and have baseline score

	Pre-Bronchodilator		Post-Bronchodilator	
Month	Placebo N=2363	Titropium N=2494	Placebo N=2374	Titropium N=2516
1	16%	33%	11%	17%
6	18%	35%	13%	21%
12	17%	33%	12%	17%
18	16%	29%	11%	16%
24	13%	25%	9%	13%
30	11%	23%	8%	12%
36	10%	21%	7%	10%
42	9%	19%	6%	9%
48	8%	16%	6%	8%

* All Missing Data are considered non-responders.

Appendix 13: Subgroup Analysis for On-treatment Death (no cut-off), Cox-Regression – Treated Set

	Placebo N	Placebo Number of deaths	Tio 18 mcg N	Tio 18 mcg Number of deaths	Subgroup by treatment interaction p-value	Within subgroup Tio 18 mcg vs. Placebo Hazard ratio (95% CI)	P-value
Age					0.3348		
< 55	382	26	384	24		0.82 (0.47, 1.43)	0.4873
>= 55, <65	1055	108	1054	96		0.79 (0.60, 1.04)	0.0966
>= 65, <75	1198	191	1208	194		0.95 (0.78, 1.17)	0.6507
>= 75	371	86	340	67		0.69 (0.50, 0.95)	0.0237
Gender					0.8610		
Male	2222	335	2251	310		0.84 (0.72, 0.98)	0.0253
Female	784	76	735	71		0.84 (0.61, 1.16)	0.2946
Smoking status					0.0613		
Ex-smoker	2108	299	2112	256		0.77 (0.65, 0.91)	0.0024
Currently smokes	898	112	874	125		1.04 (0.80, 1.34)	0.7847
LABA use					0.7252		
No	1198	178	1190	168		0.87 (0.70, 1.08)	0.2003
Yes	1808	233	1796	213		0.82 (0.68, 0.99)	0.0403
ICS use					0.7180		
No	1146	169	1146	158		0.87 (0.70, 1.08)	0.2151
Yes	1860	242	1840	223		0.83 (0.69, 0.99)	0.0399
LABA/ICS					0.9098		
No	1544	233	1522	211		0.84 (0.70, 1.01)	0.0640
Yes	1462	178	1464	170		0.85 (0.69, 1.05)	0.1323
Anticholinergics					0.6823		
No	2957	404	2926	375		0.85 (0.73, 0.97)	0.0194
Yes	49	7	60	6		0.71 (0.24, 2.13)	0.5428
GOLD stage					0.8363		
I/II	1356	134	1386	119		0.83 (0.65, 1.07)	0.1525
III	1331	204	1304	200		0.86 (0.71, 1.05)	0.1333
IV	271	66	250	57		0.76 (0.53, 1.09)	0.1325
Race					0.3248		
White	2697	353	2691	339		0.87 (0.75, 1.01)	0.0686
Black	53	5	38	2		0.42 (0.08, 2.19)	0.3068
Asian	185	42	192	30		0.63 (0.40, 1.01)	0.0545
Region					0.3975		
Asia	178	39	184	29		0.66 (0.41, 1.07)	0.0950
E. Europe	597	86	590	86		0.96 (0.71, 1.30)	0.7872
Latin America	207	52	198	35		0.66 (0.43, 1.02)	0.0594
USA	767	86	767	93		0.97 (0.72, 1.30)	0.8264
W. Europe	1257	148	1247	138		0.83 (0.65, 1.04)	0.1060
Reversibility					0.9145		
No	1393	227	1357	210		0.84 (0.70, 1.01)	0.0666
Yes	1513	171	1520	157		0.84 (0.68, 1.05)	0.1270
BMI					0.0782		
<20	352	72	297	75		1.06 (0.77, 1.47)	0.7111
>=20,<25	1024	131	1074	140		0.90 (0.71, 1.14)	0.3714
>=25,<30	1033	145	1039	103		0.65 (0.51, 0.84)	0.0009
>=30	597	63	576	63		0.95 (0.67, 1.35)	0.7866

P-value and hazard ratio are based on Cox regression with treatment,subgroup and treatment by subgroup interaction as covariates.
Time to death is actual death date, not the onset of fatal AE

Source: Clinical Study Report, Table 15 3 3:3, page 111

Appendix 14: Subgroup Analysis for On-treatment Death (1470 days cut-off), Cox-Regression – Treated Set

	Placebo N	Placebo Number of deaths	Tio 18 mcg N	Tio 18 mcg Number of deaths	Subgroup by treatment interaction p-value	Within subgroup Tio 18 mcg Hazard ratio (95% CI)	vs. Placebo P-value
Age					0.4051		
< 55	382	26	384	24		0.82 (0.47, 1.43)	0.4873
>= 55, <65	1055	106	1054	92		0.80 (0.61, 1.06)	0.1261
>= 65, <75	1198	185	1208	192		0.95 (0.78, 1.17)	0.6498
>= 75	371	85	340	66		0.70 (0.51, 0.96)	0.0289
Gender					0.9081		
Male	2222	327	2251	305		0.85 (0.72, 0.99)	0.0365
Female	784	75	735	69		0.85 (0.62, 1.18)	0.3453
Smoking status					0.0562		
Ex-smoker	2108	292	2112	252		0.78 (0.66, 0.92)	0.0034
Currently smokes	898	110	874	122		1.05 (0.81, 1.36)	0.7051
LABA use					0.8871		
No	1198	178	1190	164		0.86 (0.70, 1.07)	0.1694
Yes	1808	224	1796	210		0.84 (0.70, 1.02)	0.0762
ICS use					0.9274		
No	1146	166	1146	154		0.86 (0.69, 1.07)	0.1737
Yes	1860	236	1840	220		0.84 (0.70, 1.01)	0.0707
LABA/ICS					0.7397		
No	1544	230	1522	206		0.84 (0.69, 1.01)	0.0605
Yes	1462	172	1464	168		0.87 (0.71, 1.08)	0.2105
Anticholinergics					0.8617		
No	2957	396	2926	368		0.85 (0.74, 0.98)	0.0271
Yes	49	6	60	6		0.78 (0.25, 2.41)	0.6607
GOLD stage					0.8196		
I/II	1356	130	1386	117		0.85 (0.66, 1.09)	0.1970
III	1331	199	1304	195		0.86 (0.71, 1.05)	0.1474
IV	271	66	250	57		0.76 (0.53, 1.09)	0.1325
Race					0.3115		
White	2697	344	2691	332		0.88 (0.76, 1.02)	0.0922
Black	53	5	38	2		0.42 (0.08, 2.19)	0.3068
Asian	185	42	192	30		0.63 (0.40, 1.01)	0.0545
Region					0.4282		
Asia	178	39	184	29		0.66 (0.41, 1.07)	0.0950
E. Europe	597	86	590	84		0.96 (0.71, 1.30)	0.8091
Latin America	207	51	198	34		0.65 (0.42, 1.00)	0.0517
USA	767	85	767	91		0.96 (0.71, 1.29)	0.7738
W. Europe	1257	141	1247	136		0.85 (0.67, 1.08)	0.1854
Reversibility					0.8981		
No	1393	225	1357	208		0.84 (0.70, 1.02)	0.0725
Yes	1513	164	1520	152		0.86 (0.69, 1.07)	0.1668
BMI					0.0883		
<20	352	72	297	74		1.07 (0.77, 1.47)	0.7035
>=20,<25	1024	128	1074	138		0.91 (0.72, 1.16)	0.4637
>=25,<30	1033	141	1039	101		0.66 (0.51, 0.85)	0.0015
>=30	597	61	576	61		0.96 (0.67, 1.37)	0.8111

P-value and hazard ratio are based on Cox regression with treatment,subgroup and treatment by subgroup interaction as covariates.
Time to death is actual death date, not the onset of fatal AE

Source: Clinical Study Report, Table 15 3 3:5, page 1116

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21395	SUPPL-29	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	SPIRIVA HANDIHALER

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/s/

JOAN K BUENCONSEJO
11/30/2009

QIAN H LI
12/01/2009
Different views in interpreting evidence are covered in the secondary statistical review.

THOMAS J PERMUTT
12/04/2009
I concur with Dr. Buenconsejo. I do not concur with the secondary review by Dr. Li. See my tertiary review.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-395/S029

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA:	21-395 (SE-029)
Generic Name:	Tiotropium Bromide Inhalation Powder
Proprietary Drug Name:	**Spiriva® HandiHaler®**
Indication:	long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.
Dosage Form:	Inhalation powder
Strengths:	18 μg
Route of Administration:	Oral inhalation
Applicant:	Boehringer Ingelheim
Clinical Division:	DPAP (HFD-570)
Type of Submission:	NDA (Efficacy Supplement)
Submission Date:	November 18, 2008
Reviewer:	Yun Xu, M.D., Ph.D.
Team Leader (acting):	Partha Roy, Ph. D.

1. EXECUTIVE SUMMARY

The present NDA submission is a safety and efficacy supplement for Spiriva® HandiHaler (tiotropium bromide) dry powder inhaler. The supplement describes clinical efficacy and safety information in a 4-year, multi-center trial (UPLIFT study) in support of the addition of language to the clinical section of the PLR label.

Spiriva® HandiHaler® consists of a capsule dosage form containing a dry powder formulation of Spiriva intended for oral inhalation only with the HandiHaler inhalation device. Spiriva® HandiHaler® was approved by the Agency on 01/30/2004 under NDA 21-395 for long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema . The recommended dose of Spiriva® HandiHaler® is the inhalation of the contents of one SPIRIVA capsule (18 mcg), once-daily, with the HandiHaler inhalation device.

There is no new clinical pharmacology information included in the present submission. However, the label was revised to comply with the PLR format. The label is revised partly based on the original review for NDA 21-395 on 09/18/2002 by Dr. Shinja Kim, and the review for S024 on 10/21/2008 by Dr. Sandra Suarez-Sharp.

1.1 Recommendation

The Office of Clinical Pharmacology/ Division of Clinical Pharmacology II (OCP / DCP-II) has reviewed the efficacy and safety supplement (S029) submitted to NDA 21-395 and found it acceptable from an OCP standpoint provided that agreement on the labeling recommendations was reached with the sponsor.

1.2 Phase IV Commitments

None.

2 Label recommedation

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

17 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21395	SUPPL-29	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	SPIRIVA HANDIHALER

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/s/

YUN XU
12/01/2009

PARTHA ROY
12/01/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-395/S029

OTHER REVIEW(S)

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology

Date:	December 11, 2009
To:	Badrul Chowdhury, M.D., Director **Division of Pulmonary and Allergy Products (DPAP)**
Through:	Mary Willy, Ph.D., Deputy Director **Division of Risk Management (DRISK)** LaShawn Griffiths, MSHS-PH, BSN, RN Senior Patient Product Information Reviewer, Acting Team Leader **Division of Risk Management**
From:	Robin Duer, MBA, BSN, RN Patient Product Information Reviewer **Division of Risk Management**
Subject:	DRISK Review of Patient Labeling (Patient Package Insert and Patient Instructions for Use)
Drug Name(s):	Spiriva Handihaler (tiotropium bromide inhalation powder)
Application Type/Number:	NDA 21-395/S-029, (b) (4)
Applicant/sponsor:	Pfizer, Inc.
OSE RCM #s:	2009-1441 and 2009-1920

1 INTRODUCTION AND BACKGROUND

This review is written in response to a request by the Division of Pulmonary and Allergy Products (DPAP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Spiriva Handihaler (tiotropium bromide inhalation powder) Patient Package Insert (PPI) and Patient Instructions for Use (IFU) submitted on January 30, 2009 for Supplement 029 and (b) (4) for Supplement (b) (4)

The January 30, 2009 submission provided for a complete response to DPAP's November 13, 2008 complete response (CR) letter for S-024. Supplement 024 provided for the addition of reduction in COPD excacerbation information to the Spiriva HandiHaler labeling. Supplement 029 provides for the information requested by DPAP for S-024 and also proposes new language to reflect the primary positive outcomes of the Spiriva Handihaler pivotal trial. The July 28, 2009 submission includes the patient labeling submitted on January 30, 2009, but added two graphics with associated text at the beginning of the PPI and IFU to clarify that the Spiriva capsule should not be swallowed but instead should be inhaled using the Handihaler device. Additionally, a graphic was added to the IFU (Figure C) to illustrate to patients that a small amount of powder is present in the Spiriva capsule.

DRISK had previously reviewed the Spiriva Handihaler (tiotropium bromide inhalation powder) Patient Package Insert and Patient Instructions for Use for S-014 on October 6, 2008, and had recommended extensive labeling changes for the patient labeling at that time.

2 MATERIALS REVIEWED

- Draft Spiriva Handihaler (tiotropium bromide inhalation powder) Prescribing Information (PI) submitted July 28, 2009
- Draft Spiriva Handihaler (tiotropium bromide inhalation powder) Patient Package Insert and Patient Instructions for Use submitted July 28, 2009
- DRISK review of Spiriva Handihaler (tiotropium bromide inhalation powder) Patient Package Insert and Patient Instructions for Use for S-014 dated October 6, 2008

3 RESULTS OF REVIEW

In our review of the PPI and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the PI
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Our annotated PPI and IFU are appended to this memo. Any additional revisions to the PI should be reflected in the PPI and IFU.

Please let us know if you have any questions.

33 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21395	SUPPL-29	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	SPIRIVA HANDIHALER

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/s/

ROBIN E DUER
12/11/2009

MARY E WILLY
12/11/2009
I concur

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

Date: November 2, 2009

To: Miranda Raggio -- Regulatory Project Manager
Division of Pulmonary and Allergy Products (DPAP)

From: Robyn Tyler, Regulatory Review Officer
Samuel M. Skariah, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: NDA #21-395
DDMAC labeling comments for Spiriva® HandiHaler® (tiotropium bromide inhalation powder)

DDMAC has reviewed the proposed product labeling (PI) and patient information for Spiriva® HandiHaler® (tiotropium bromide inhalation powder) (Spiriva) submitted for consult on November 21, 2008.

DDMAC offers the following comments.

General Comment

While this is an efficacy supplement, DDMAC has reviewed the entire label (version submitted on November 17, 2008 with NDA 21-395/S-029 dated November 2008) and thus may be commenting on sections of the label that are already approved. DDMAC has provided comments on the Patient Information, which is now part of the approved product labeling (PI) (March 3, 2009).

PI

HIGHLIGHTS OF PRESCRIBING INFORMATION

WARNINGS AND PRECAUTIONS

- Should the following information from section 5.4 of the Warnings and Precautions be added to the proposed label?: "As a predominanty renally excreted drug, patients with moderate to severe renal impairment (creatinine clearance of ≤ 50 mL/min) treated with SPIRIVA HandiHaler should be monitored closely for anticholinergic side effects."

- (b) (4)

  We recommend adding the phrase "SPIRIVA Handihaler may potentially worsen symptoms and signs associated with. . ." from section 5.4 of the Warnings and Precautions, to this statement. This will help clarify why caution should be used with these patients.

ADVERSE REACTIONS

- Please consider revising this section to include additional adverse reactions listed in section 6 of the PI (i.e., Table 1 from the PI).

Full PI

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

- "The most commonly reported adverse drug reaction was dry mouth. Dry mouth was **usually mild and often resolved during continued treatment**" (emphasis added).

  Is this description accurate and necessary to include? If not, we recommend deleting this phrase from the PI because it has promotional implications.

8 USE IN SPECIFIC POPULATIONS

8.7 Patients with Hepatic Impairment

- "The effects of hepatic impairment on the pharmacokinetics of tiotropium were not studied. However, **hepatic insufficiency is not expected to have relevant influence on tiotropium pharmacokinetics**. . ." (emphasis added).

  Is this assumption supported by evidence? If not, please consider deleting it as it may be used promotionally to minimize the importance of this information.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

- Would it be possible to provide context to the phrase “long-acting”?

12.2 Pharmacodynamics

- Would it be possible to provide context to the phrase “lasted longer than 24 hours”?

12.3 Pharmacokinetics

Distribution

- “At steady state, peak tiotropium plasma levels in COPD patients were 17-19 pg/mL. . .and **decreased rapidly** in a multi-compartmental manner” (emphasis added).

  Would it be possible to provide context for the phrase “decreased rapidly”?

14 CLINICAL STUDIES

- “In a 6-month clinical trial of COPD patients in a Veterans Affairs setting. SPIRIVA Handihaler **significantly reduced the proportion of COPD patients who experienced exacerbations compared to placebo and significantly delayed the time to first exacerbation**. These findings are supported by a pre-specified combined analysis of two one-year clinical trials using SPIRIVA RESPIMAT” (emphasis added).

  If these claims are indeed supported by substantial evidence, we recommend presenting the results/data for context.

- “In the 4-year multicenter trial, there was 16% reduction in the risk of death while on treatment with SPIRIVA HandiHaler compared to placebo.”

  Is this statement supported by substantial evidence? If not, we recommend that it be deleted because it has strong promotional implications.

Patient Information:

What should I tell my healthcare provider before using SPIRIVA HandiHaler?

For consistency with the Warnings and Precautions section of the proposed PI, DDMAC recommends including risk information on paradoxical bronchospasm.

What are the possible side effects of SPIRIVA HandiHaler?

DDMAC recommends revising the side effects in this section to be consistent with the most common side effects listed in the highlights section.

Patient's Instructions for Use

DDMAC has reviewed the Patient's Instruction for use and have no comments at this time.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21395	SUPPL-29	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	SPIRIVA HANDIHALER

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/s/

SAMUEL M SKARIAH
11/02/2009

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	October 19, 2009
To:	Badrul A. Chowdhury Director, Division of Pulmonary and Allergy Products Office of New Drugs
Through:	Solomon Iyasu, MD, MPH Director, Division of Epidemiology Office of Surveillance and Epidemiology
From:	Simone P. Pinheiro, ScD MSc Epidemiologist Office of Surveillance and Epidemiology
Subject:	Review of ERASMUS observational study on safety of tiotropium bromide
Drug Name(s):	Tiotropium bromide (marketed as Spiriva)
Submission Number:	S029
Application Type/Number:	NDA # 021-395
Applicant/sponsor:	Boehinger Ingelheim
OSE RCM #:	2009-1598

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CONTENTS

EXECUTIVE SUMMARY 1
1 BACKGROUND/HISTORY 1
2 REVIEW METHODS AND MATERIALS 3
2.1 Materials Reviewed 3
3 RESULTS OF REVIEW 3
3.1 Proposed Objectives/Actual Objectives 3
3.2 Actual Design 4
3.3 Informed Consent 4
3.4 Data Source 4
3.5 Study Time Period(s) 5
3.6 Population 6
3.7 Exposure 7
3.8 Disease Outcome of Interest 8
3.9 Analyses and/or Study Results 11
4 SUMMARY AND RECOMMENDATIONS 17
5 REFERENCEs 19

EXECUTIVE SUMMARY

Inhaled anticholinergics have been considered both effective and safe for the management of chronic obstructive pulmonary disease (COPD). However, a few recent publications and reports raised concerns about the safety of inhaled anticholinergics, including tiotropium bromide (TB) and ipratropium bromide (IB). These reports were recently reviewed by the Office of Surveillance and Epidemiology (OSE) (DARRTS Communication PK # 2663713, Communication Date 08/04/2009). In this review, the OSE concluded that the data implicating inhaled anticholinergics in increasing risk of cardiovascular outcomes and death was not compelling due to substantial limitations of these studies. Additionally, the findings of these reports did not agree with the findings of previously published meta-analyses of randomized clinical trials, nor do they agree with the findings of a large 4-year placebo-controlled randomized clinical trial (UPLIFT), none of which suggested an association between anticholinergics and increased risk of cardiovascular events or mortality.

An epidemiology study report concerning the safety of tiotropium bromide, conducted by Erasmus Medical Center (Rotterdam, The Netherlands), was recently submitted by Boehringer Ingelheim. The Division of Division of Pulmonary and Allergy Products (DPAP) within the Office of New Drugs consulted the Division of Epidemiology (DEPI) within the Office of Surveillance and Epidemiology (OSE) to review the methodology and results of this study.

In summary, the study conducted by Erasmus Medical Center is a population-based case-control study nested within a cohort of COPD patients over the age of 40 years, participating in the IPCI - a longitudinal observational database that contains data from computer-based patient records of a selected group of GPs in The Netherlands. The primary objective of this study was to evaluate the safety profile of tiotropium compared to both non-users of anticholinergics drugs as well as to users of LABA. The main limitation of this study is the potentially inadequate statistical power to detect associations between safety outcomes including cardiovascular adverse events and mortality between tiotropium users vs. non users or LABA users. However, confidence limits were relatively narrow, and the upper bound confidence interval for cardiovascular/cerebrovascular events of current users vs. non users of anticholinergics (95% CI of 0.64 -1.27) and for current user of tiotropium *vs.* LABA [(95% CI (0.50, 1.41)] were lower than the increase in risk reported in the only meta-analysis of randomized trials that suggested an increase in risk in cardiovascular events [RR (tiotropium vs. conrols) =1.49, 95% CI (0.98, 2.26); RR (anticholinergics vs. controls) = 1.60 (1.22, 2.10)] [3, correction in JAMA 2009]. The results of this study, in combination with most of the epidemiologic evidence noted in the OSE's previous review (DARRTS communication PK # 2663713, Communication Date 08/04/2009) failed to provide evidence for an association between tiotropium and increased risk of cardiovascular events, mortality or stroke.

1 BACKGROUND/HISTORY

Tiotropium bromide is a long acting anticholinergic with specificity for muscarinic receptors approved as Spiriva HandiHaler (Spiriva® Boehringer Ingelheim). This product is a dry powder capsule formulation approved on January 30, 2004 (NDA # 21-395) for the long-term, once daily management of bronchospasm associated with chronic obstructive pulmonary disease (COPD).

On November 16 of 2007, Boehringer Ingelheim (BI) submitted an NDA (NDA # 021-936) application for a novel inhalation device, the Respimat Inhalation Spray, to deliver tiotropium bromide (TB) for oral inhalation. During the development program, several safety issues surfaced.

On November 2005, prior to submitting the NDA, BI informed the Division of Pulmonary and Allergy Products (DPAP) about an imbalance in fatal adverse events favoring the placebo group in two of the Respimat 1-year clinical trials. Because DPAP was concerned about the impact of this signal on the approved product Spiriva HandiHaler, DPAP presented the preliminary mortality data to the Drug Safety Oversight Board (DSOB) on June of 2006. The DSOB noted the mortality signal to be weak. However, the DSOB recommended that BI obtain vital status follow up data on 100% of patients who dropped out of the trials as there was substantial differential discontinuation between the placebo and TB treatment groups. The mortality issue was reviewed again in an internal Regulatory Briefing meeting held on July 18, 2008 once complete follow-up data for the above mentioned trials were submitted as part of the NDA 21-936. The committee concluded that while a portion of the mortality signal could be explained by differential follow-up, additional data are required to determine if the potential signal represents a true safety issue.

In November of 2007, BI submitted preliminary results of a routine pooled safety analysis of 29 clinical trials with Spiriva HandiHaler (n=25 studies) and Respimat (n=4 studies) (unpublished report). In this analysis, BI noted an increase in risk of stroke in patients treated with TB *vs.* placebo [RR and 95% CI of 1.37 (0.73, 1.56)]. While this analysis did not adjust for multiplicity and the association between TB and stroke was not statistically significant, the Agency released an Early Communication on March of 2008 describing potential risk of stroke associated with tiotropium [12].

The results of a recently published meta-analysis of 17 randomized clinical trials raised questions about the safety of inhaled anticholinergic agents, particularly in regards to the risk of cardiovascular outcomes [3,13]. In this analysis, TB was associated with a non-significant 49% increase in risk of cardiovascular outcomes [RR and 95% CI: 1.49 (0.98 - 2.26)] compared to comparator groups, which included both placebo and active controls. Moreover, a few other recent observational studies raised concerns about the safety of ipratropium bromide (IB), another inhaled anticholinergic agent. These studies included two large nested case-control studies, which suggested that IB increased the risk of death [4] and of certain cardiovascular events [5]; and a large cohort study by Ogale and colleagues [6], which suggested that IB may increase the risk of cardiovascular events.

These reports were recently reviewed by the Office of Surveillance and Epidemiology (OSE) (DARRTS Communication PK # 2663713, Communication Date 08/04/2009). In this review, OSE concluded that, due to the limitations of these studies, including biased selection of studies, lack of information on participants who discontinued trial, failure to use person-time data [3], and failure to adjust for important confounders [4-6], these studies did not provide substantial and convincing data to implicate inhaled anticholinergics in increasing risk of cardiovascular outcomes. Furthermore, the findings of these reports did not agree with findings of previously published meta-analyses [7-10], nor did they agree with the recently published findings from a 4-year large randomized, placebo-controlled clinical trial [11], none of which suggested an association between anticholinergics and cardiovascular events or mortality. Based on the currently available data, while the Agency will continue to monitor the safety of anticholinergics, OSE did not recommend the pursuit of further studies by the Agency or by the sponsor to assess the safety of inhaled anticholinergics.

An epidemiology study report concerning the safety of TB, conducted by Erasmus Medical Center (Rotterdam, The Netherlands), was submitted by the BI (by Erasmus Medical Center, report dated 20 May 2009). The Division of Pulmonary and Allergy Products (DPAP) within the Office of New Drugs consulted the Division of Epidemiology (DEPI) within OSE to review the methodology and results of this study. The review focuses on the results related to the safety of tiotropium bromide.

2 REVIEW METHODS AND MATERIALS

2.1 MATERIALS REVIEWED

- Epidemiology Study Report entitled "Cardiovascular, cerebrovascular, and respiratory events in association with long-acting bronchodilators: a comparative study in persons with COPD." (by Erasmus Medical Center, report dated 20 May 2009).

3 RESULTS OF REVIEW

3.1 PROPOSED OBJECTIVES/ACTUAL OBJECTIVES

3.1.1 Actual Objective

This study had several objectives. These are described below.

***Objective 1*:** To describe use of tiotropium bromide in the source population and to assess indication of first use of tiotropium in the source population.

Objectives 2:
To explore the safety of tiotropium bromide in comparison to a long acting β_2 agonist (i.e. salmeterol or formoterol) on several safety enpoints (e.g. cardiovascular and cerebrovascular endpoints, mortality, diabetes mellitus (DM), renal failure) and on a few effectiveness endpoints (e.g. COPD-related hospitalization and exacerbation rates).

Objective 3: To assess event rates in the cohort of incident COPD patients

Objective 4: To describe and compare the baseline characteristics of persons starting with different respiratory drugs in incident COPD patients.

3.1.2 OSE Comments on Actual Objectives

We concur with the objectives of this study. Objective # 2 is the most relevant objective to evaluate the safety of tiotropium bromide.

3.2 ACTUAL DESIGN

3.2.1 Actual Design

The study designs differed according to each study objective and they are outlined below:

Objective 1
Retrospective cohort study

Objective 2
Several case-control studies nested in a cohort

Objective 3
Retrospective cohort study

Objective 4
Cross-sectional study

3.2.2 OSE Comments on Actual Design

The study designs were appropriate to evaluate the objectives of this study.

3.3 INFORMED CONSENT

3.3.1 Proposed/Actual Informed Consent

Patient identification information, notes, prescriptions, physician linked indications for therapy, physical findings, and laboratory values are entered into the database directly by the GPs. This information was anonymized by the database gatekeeper.

3.3.2 OSE Comments on Actual Informed Consent

Not applicable

3.4 DATA SOURCE

3.4.1 Data Source

The IPCI is a longitudinal observational database that contains data from computer based patients records of a selected group of general practitioners (GPs) throughout the Netherlands, who voluntarily chose to supply data to the database. GPs receive a minimal reimbursement for their data and completely control usage of their data through

the Steering Committee and through the possibility to withdraw data for specific studies. Collaborating practices are spread throughout the Netherlands and collaborating GPs are comparable to other GPs regarding age and gender. As of Sept of 2007, there were more than 400 GP practices that have provided data to the database. The IPCI database contains information on more than 1 million patients (including any patient who was ever registered). Turnover occurs as patients move and transfer to new practices. The database contains identification information (age, sex, patient identification, GP registration information), notes, prescriptions, physician-linked indications for therapy, physical findings, and laboratory values, all directly entered by the GPs.

3.4.2 OSE Comments on Actual Data Sources

Data comparing IPCI participants against residents of the Netherlands (*e.g.* distribution of age, gender, region) would be helpful to assess whether source population is representative of the general country population. Additionally, it would be also helpful to have information on participating practices (*e.g.* location/region, rural/urban, number of patients, type of practice).

The turnover and the mean length of follow-up time in the database are not described. In the IPCI, patients exit the database if they transfer to a new practice. Therefore, case ascertainment is likely to be incomplete if patients who develop certain outcomes seek new practices.

3.5 STUDY TIME PERIOD(S)

3.5.1 Study Time Period(s)

Objective 1
Patients entered the study on January 1st of 2000 or after one year of valid history (whichever came latest) and were followed up until death, latest availability of data or end of study (1st of July 2007).

Objective 2
Patients entered the study on January 1st of 2000, after one year of valid history, or at diagnosis of COPD (whichever came latest) and were followed up until the earliest of the following events: death, latest availability of data, transfer to nursing home, occurrence of outcome, or end of study (1st of July 2007).

Objective 3
Patients entered the study upon diagnosis of incident COPD and were followed up until the earliest of the following events: death, latest availability of data, transfer out of GP practice, occurrence of outcome, or end of study (1st of July 2007).

Objective 4
Patients entered the study upon diagnosis of incident COPD. Only baseline characteristics were assessed for this objective; therefore, patients were not followed up over time.

3.5.2 OSE Comments on Actual Study Time Period(s)

Length of study time period seems appropriate to allow for the occurrence of the safety outcomes of interest (*e.g.* cardiovascular and cerebrovascular outcomes, death, DM, renal failure) among COPD patients as well as for the occurrence of effectiveness outcomes of interest after exposure to respiratory medications.

3.6 POPULATION

3.6.1 Population

Objective 1

A total of 185,325 patients in the IPCI-PHARMO GP database, all of whom had 365 days of history available in the database and were at least 40 years of age at start of follow-up.

Objective 2

Incident cases of diseases and matched control-moments nested in a cohort of patients in the IPCI-PHARMO GP database (01/01/2000-07/01/2007) who had at least 365 days of history available in the database, who were diagnosed with COPD (prevalent and incident COPD) and who were at least 40 years of age at study entry were selected.
For each endpoint, a separate case-control study including incident cases of the particular disease and a maximum number of control moments matched to cases on *index date, gender, and year of birth* was created. These ten case-control studies include:

- Myocardial Infarction Case-Control Study included 155 cases of MI and 6,799 matched control moments
- Ventricular Arrythmia Case-Control Study included 17 cases and 833 matched control moments
- Cardiac Heart Failure Case-Control Study included 466 cases and 16,039 matched control moments
- Stroke/Transient Ischemic Attack Case-Control Study included 357 cases and 13,909 matched control moments
- Cardiovascular/Cerebrovascular events Case-Control Study included 784 cases and 25,899 matched control moments
- Mortality Case-Control Study included 1032 cases and 40,615 matched control moments
- Diabetes Mellitus Case-Control Study included 295 cases and 10,428 matched control moments
- Renal failure Case-Control Study included 83 cases and 3,975 matched control moments
- COPD-related hospitalization Case-Control Study included 357 cases and 13,909 matched control moments
- COPD exacerbation Case-Control Study included 3,439 cases and 88,724 matched control moments

Objective 3

Retrospective cohort study including all patients in the IPCI-PHARMO GP database (from 1st of January 2000 to 1st of July 2007) who had at least 365 days of history available in the database and who had a diagnosis of COPD dated after cohort entry (*incident* COPD)

Objective 4
Cross-sectional study describing baseline characteristics of all patients in the IPCI-PHARMO GP database (from 1st of January 2000 to 1st of July 2007) who had at least 365 days of history available in the database and who had a diagnosis of COPD dated after cohort entry (incident COPD).

In *objectives* 2 through 4 (described in session 3.1.1 of this report), patients with either *definite* or *probable* COPD diagnosis were included in the analyses. Diagnosis of COPD was assessed via review of medical files searching on ICPC codes ICPC-R95, ICPD_R91, as well as spirometry and free text searching including "COPD" or "chronic bronchitis" or "emphysema" or "exacerbation." Diagnosis of *definite* COPD was made based on *either* records of COPD diagnosis, confirmed by a specialist *or* COPD diagnosed by a GP only and confirmed by spirometry (a single record was sufficient). A diagnosis of *probable* COPD was made based on COPD diagnosis by a GP only and a subsequent at least 2 records of COPD (free text, ICPC coding or prescription of bronchodilator drugs) within 1 year of first record of COPD.

3.6.2 OSE Comments on Actual Population

The definition of *control-moments* is not clearly stated in the study report for Objective #2. OSE reviewer assumed control moments referred to person-years.

3.7 EXPOSURE

3.7.1 Exposure

Information on usage of drugs given for treatment of COPD was retrieved from the prescription records of both cases and controls. The National Database of drugs, maintained by the Royal Dutch Association for Advancement of Pharmacy, enables coding of prescriptions according to the Anatomical Therapeutic Chemical (ATC) classification scheme recommended by the WHO.

In the case-control studies (*objective 2*), treatment exposure was categorized by type of drug, timing and dose. Drug exposure was defined as, *current* (last prescription covered the index date or ended less than 30 days prior to the index date), *recent* (last prescription ended 30 days < 6 months prior to index date), *distant* (last prescription ended > 6 months prior to index date), or *none*. Some analyses used *none* use of the study drug as the reference categories while other analyses used *use of another class of drug* as the reference category. Tiotropium was the main exposure of interest. Other drugs considered in this study included short acting anticholinergic agents, single-ingredient LABA, single-ingredient SABA, inhaled corticosteroids, theophyllines, fixed combination therapies (e.g. LABA + inhaled corsticosteroids, anticholinergic agents +

SABA), oral β_2-agonists, leukotriene receptor antagonists. In the main analyses of objective 2 (nested case-control studies), tiotropium was compared to *no anticholinergics*, *LABA* and *SABA*.

In some analyses, mutually exclusive categorization of current use of bronchodilators was created (*i.e*. only tiotropium, only other short acting anticholinergics, only LABA, only SABA, only xanthines). Patients who used multiple products were classified as multiple drug combinations. ICS was not used for categorization but instead adjusted for. In analyses of class effects of drugs, short and long-acting anticholinergics (called *anticholinergics*), short and long-acting β_2- agonists (called *beta-agonists*), and xanthines were combined.

For current users of the primary study drugs (i.e. short acting anticholinergics drugs and tiotropium), the dose effect was assessed with daily dose in daily recommended average dosage (DDD) and categorized as *low*, *medium*, or *high*. Recency of starting (first 2 weeks of index date), route of administration (nebulizer, aerosol, power) and cumulative effect of duration were assessed.

To assess drug specific event rates, exposure cohorts were created based on the actual exposure at each day. Patients contributed person-time to a specific exposure category during current use of that drug without carry-over (objective 3). In objective 4, exposure cohorts were defined according to first drug use of the various respiratory medications. Patients were classified as exposed to a particular drug at the moment they used one of the drugs for the first time. Therefore, one person was allowed to contribute to multiple cohorts upon switching of therapy.

3.7.2 OSE Comments on Actual Exposure

Medication prescription was used as surrogate for drug exposure, which requires the assumption that participants used the drugs as prescribed. This type of misclassification, however, is unlikely to have differed between those who subsequently developed the outcomes of interest and those who did not. This non-differential misclassification would tend to make the comparison groups more similar to one another in respect to the exposure of interest, ultimately attenuating the association between tiotropium use and risk of the outcomes of interest.

3.8 DISEASE OUTCOME OF INTEREST

3.8.1 Disease Outcome of Interest

The International Classification of Primary Care (ICPC) is the coding system for patient complaints and diagnosis; these can be mapped to ICD-9 codes. Additionally, diagnoses and complaints can be entered as free text. Safety endpoints were searched in the database and reviewed by 2 medical doctors blinded to patients' exposure status as described below for each outcome.

Safety endpoints

Mortality : Deaths were reviewed by a broad search in the database on ICPC code A96 (death), a free text search on death related terms, and death as reason for end of follow-up. For patients who died, the complete electronic record file, including referral and discharge letters, were reviewed and deaths were classified according to respiratory, cardiovascular or other reasons. The cause of death was adjudicated by the Physician reviewers. A sample of the adjudicated deaths was sent for GPs for validation. The positive predictive value was 90%.

Stroke (overall and hemorrhagic/ischemic, fatal and non-fatal stroke) and transient ischemic attack (TIA): Cases of stroke and TIA were searched in the database according to ICPC codes and free text search. The medical records of all potential stroke/TIA cases were manually reviewed by 2 medical doctors blinded to the patients' exposure status. A patient was considered a case if a CT scan was done or a neurologist diagnosis or discharge letter was available. For those not hospitalized, a GP diagnosis was required and the clinical symptoms needed to be consistent. All doubtful cases and a sample of the definite cases were reviewed by an expert neurologist. Stroke and TIA were combined as endpoints in primary analyses.

Myocardial Infarction (fatal and non-fatal): MI cases were identified via automatic search on ICPC codes for myocardial infarction as well as through search of free text, ECG and cardiac enzyme results. All potential cases of MI were manually reviewed by 2 medical doctors blinded to the patients' exposure status. Only MI confirmed by a specialist (via discharge letters) or MI diagnosed by the GP in the presence of typical symptoms in combination with ECG findings and/or elevation of cardiac enzymes were considered valid.

Heart failure: Cases of CHF were identified via search on ICPC codes for heart failure as well as via searches in the free text and medication codes from prescription dataset in IPCI. All potential cases of CHF were manually reviewed by 2 medical doctors blinded to the patients' exposure status. Cases were classified as *definite* or *possible* heart failure. *Definite* cases were patients with heart failure confirmed by a specialist by means of an echocardiography. *Possible* cases were patients diagnosed by a GP as having symptoms of heart failure and receiving cardiovascular treatment with heart failure as indication.

Ventricular arrhythmia: Cases of ventricular arrhythmia were identified via search on ICPC codes as well as via searches in the free text. All potential cases of Ventricular arrhythmias were manually reviewed by 2 medical doctors blinded to the patients' exposure status. Only VA cases confirmed by a cardiologist or on ECG were considered as cases.

Renal failure: Cases of renal failure were identified via search on ICPC codes as well as via searches in the free text. Chronic renal failure was defined as patients requiring dialysis or those indicating renal failure based on age adjusted clearance formulas for at least 3 months apart. All potential cases of renal failure were manually reviewed by 2 medical doctors blinded to the patients' exposure status.

Diabetes mellitus: Cases of diabetes mellitus were identified via search on ICPC codes as well as via searches in the free text and glucose levels. A patient was considered as having DM upon specialist diagnosis (hospital discharge letter) or upon diagnosis by the GP (ICPC code/free text) in combination with an increased blood glucose or need to anti-diabetic drug. All potential cases of DM were manually reviewed by 2 medical doctors blinded to the patients' exposure status

Combined cardiovascular endpoint (including MI, stroke, heart failure, and ventricular arrhythmias): Identification and validation of these events as described above.

Effectiveness endpoint

COPD exacerbations (hospitalized and non hospitalized): defined as hospitalizations due to COPD (identified via manual search through free text of discharge summaries and referral letters from GPs) or short course (i.e. < 4 weeks) of oral corticosteroids/antibiotics for COPD exacerbations.

3.8.2 OSE Comments on Actual Disease Outcome of Interest

In the IPCI, patients exit the database if they transfer to a new practice. Therefore, case ascertainment is likely to be incomplete if patients who develop certain outcomes seek new practices. This type of misclassification/under-ascertaiment is unlikely to differ between those exposed and not exposed to tiotropium. In the case-control studies (objective 2), this is unlikely to play important role as cases and controls were matched on index dates.

3.8.3 Sample Size

The source population consisted of 185,325 persons. Prevalence of tiotropium at baseline was 0/1000 person-years (product marketed in 2002 in The Netherlands) and peaked in 2006, reported as 17 users/1,000 person-years (please refer to report figure 5.1.1. below). The sample size for each case-control is as follows:

- Myocardial Infarction Case-Control Study included 155 cases of MI and 6,799 matched control moments
- Ventricular Arrhythmia Case-Control Study included 17 cases and 833 matched control moments
- Cardiac Heart Failure Case-Control Study included 466 cases and 16,039 matched control moments
- Stroke/Transient Ischemic Attack Case-Control Study included 357 cases and 13,909 matched control moments
- Cardiovascular/Cerebrovascular events Case-Control Study included 784 cases and 25,899 matched control moments
- Mortality Case-Control Study included 1032 cases and 40,615 matched control moments
- Diabetes Mellitus Case-Control Study included 295 cases and 10,428 matched control moments

- Renal failure Case-Control Study included 83 cases and 3,975 matched control moments
- COPD-related hospitalization Case-Control Study included 357 cases and 13,909 matched control moments
- COPD exacerbation Case-Control Study included 3,439 cases and 88,724 matched control moments

Figure 5.1.1 prevalence of tiotropium use in the population by calendar year

3.8.4 OSE Comments on Actual Sample Size

Because tiotropium was only marketed in the Netherlands in 2002, there would be no cases and controls exposed to tiotropium before 2002. This time period represents 25% of the study follow-up period, which could translate in substantial decrease in statististical power to detect an association between tiotropium and adverse events. Information on the number of cases and controls identified during this time period (not provided in the current report) would be informative.

Additionally, due to the limited number of cases in some of the case-control studies, this study had limited power to detect differences in incidence of ventricular arrhythmia (n=17 cases) and renal failure (n=83 cases) associated with use of tiotropium. Additionally, analyses restricted to incident COPD patients as well as analyses of effect modification by various variables were limited in statistical power due to low number of cases.

3.9 ANALYSES AND/OR STUDY RESULTS

3.9.1 Analyses and Study Results

Analyses

Use of tiotropium in the source population was described as the number of users and number of prescriptions over time. To study channeling in prescribing behavior, the cardiovascular risk profile at the time of first prescription of LABA *vs.* tiotropium was compared.

Within the incident cohort, event rates associated with each exposure (alone) were calculated. Use of multiple drugs during the same duration of time was classified as 'combination of drugs' in these analyses.

Within the COPD cohort (incident and prevalent), conditional logistic regression analysis was used to assess the matched unadjusted and adjusted risk estimates for the association between tiotropium and the different outcomes. Several covariates were considered in these analyses. COPD severity was assessed longitudinally on the basis of available spirometry data and severity classification schemes according to the GOLD criteria (if spirometry was available). In cases were spirometry was not available, COPD severity was categorized using data from GP or health care databases, which include a combination of recency of diagnosis, treatment with bronchodilators, xhanthines or combination therapy, COPD-related hospitalization with antibiotic for treatment of respiratory infections, systemic corticosteroids for the treatment of COPD exacerbations, and/or diagnosis of pneumonia, and use of oxygen therapy. Other covariates were also assessed, including smoking history, drug use, (central nervous system drugs, anticholinergic drugs, drugs affecting cerebrovascular and cardiovascular disease, other respiratory drugs), use of resources (i.e. number of GP office visits and home visits in the year preceding the index date), and co-morbidities (e.g. myocardial infarction, angina pectoris, other fatal and non-fatal ischemic heart diseases, stroke or TIA, peripheral arterial disease, heart failure, arrhythmia, hypertension, lipid disorder, diabetes, renal insufficiency, migraine, other diseases, malignancies). In adjusted analyses, all covariates which were individually associated with the outcome ($p<0.10$) were included in the models. Risk factors that changed the estimates by more than 5% were included in models. COPD severity (primary analyses adjusted for severity as measured one year prior to index date), duration and smoking were always included in the models.

Effect modification by several factors (i.e. gender, calendar year, smoking staus, and severity of COPD, incident/prevalent COPD at baseline) was examined through stratified analyses as well as through the inclusion of interaction terms in logistic regression models. Presence of effect modification was determined if interaction terms between the potential effect modifier and tiotropium were statistically significant at the 0.05 level.

Results

The source population consisted of 185,325 persons, 48% of them were male. The mean age for males and females were 55.4 and 57.7 years, respectively. Prevalence of tiotropium peaked in 2006 and it was reported as 17 users per 1000 person years. Incidence of tiotropium peaked in 2003-2004 at the rate of 6 new users per 1000 person years and decreasing from 2005 onwards. The main indication for tiotropium use is COPD, followed by asthma.

Among patients newly diagnosed with COPD, new users of tiotropium were more likely to have *moderate* COPD while new users of LABA were more likely to have *mild* COPD. LABA users were more likely to have a history of asthma, stroke or TIA, and pneumonia, while less likely to have lipid disorders compared to tiotropium users. The prevalence of other co-morbidities (*e.g.* history of MI, peripheral arterial disease, heart failure, hypertension, diabetes, malignancy, depressive disorders) were similar between new users of tiotropium and LABA.

Of the 6,788 COPD patients, 5,230 (77%) were prevalent COPD. Compared to prevalent COPD patients, incident COPD patients were slightly younger, more likely to be *past* or *current* smokers (and more likely to have a non missing smoking history), more likely to have *mild* COPD, while slightly less likely to have a history of heart failure.

Unadjusted event rates associated with various respiratory medications (in mutually exclusive categories) were estimated among patients newly diagnosed with COPD. No cases of MI occurred among tiotropium users. Unadjusted incident rates (IR) of MI for ipratropium vs. LABA users were 15.9 *vs.* 10.1 cases/1,000 p-years, respectively. IR of heart failure for tiotropium, ipratropium, and LABA users were 19.0, 41.6, and 19.5 cases per 1,000 person-years, respectively. The IR of stroke/TIA for tiotropium, ipratropium and LABA users were 34.3, 28.1, and 10.2 per 1,000 p-years, respectively. For all cardiovascular and cerebrovascular events combined, the IR associated with tiotropium, ipratropium and LABA were 38.9, 66.9, and 35.5 cases per 1,000 p-years, respectively. The IR of death for tiotropium, ipratropium and LABA users were 33.8, 39.0, and 32.1 per 1,000 p-years, respectively. The IR of diabetes mellitus for tiotropium, ipratropium and LABA users were 27.3, 13.3, and 21.7 per 1,000 p-years, respectively. The IR of renal failure for ipratropium was 4.1 per 1,000 p-years, respectively. No new cases of renal failure were observed among exclusive users of tiotropium or LABA among incident COPD users. The IR of hospital admissions for tiotropium, ipratropium and LABA users were 23.1, 35.9, and 18.5 per 1,000 p-years and those associated with COPD exacerbation were 249.7, 329.9, and 215.6 per 1,000 p-years, respectively.

Within the COPD cohort (incident and prevalent COPD), 784 new cases of combined cardiovascular and cerebrovascular events (which included new cases of MI, heart failure, ventricular arrhythmias, stroke and TIA) and 25,899 matched control moments were identified. Patients with a history of heart failure were excluded from these analyses. Current use of tiotropium or ipratropium was not associated with increased risk of cardiovascular and cerebrovascular events when compared to non users of anticholinergics (multivariate OR and 95% CI were 0.90 (0.64, 1.27) and 1.19 (0.99, 1.45), respectively). Multivariate models accounted for age, gender, index date, COPD severity 1 year prior to index date, duration of COPD, and smoking. Current use of either product independent of ICS and SABA were unchanged. Compared to non-use of anticholinergics, use of tiotropium of duration ≥ 365 days was associated with a decrease in risk of combined endpoints (multivariate OR and 95% CI was 0.43 (0.20, 0.93), although these estimates were based on only 7 exposed cases. Compared to non use of anticholinergics, ipratropium use at doses ≤ 0.5 DDD, as well as recent start, aerosol

formulation, and duration of use >30 days were associated with increased risk of cardiovascular and cerebrovascular events (multivariate OR and 95% CI were 1.50 (1.12, 2.01), 3.59 (1.74, 7.43), 1.49 (1.19, 1.87), and 2.46 (1.33, 4.57), respectively). The risk of cardiovascular and cerebrovascular events did not differ between current users of tiotropium *vs.* LABA, tiotropium *vs.* SABA, or ipratropium *vs*. LABA (independently of ICS).

Association between respiratory drugs and individual cardiovascular and cerebrovascular events were also examined. In a case-control including 155 new cases of MI and 6,799 matched control moments, no significant associations were observed between use, dose, duration and recency of use of tiotropium or ipratropium and risk of MI. Risk of MI associated with current use of either of these agents independently of ICS use did not differ from that associated with current use of LABA (multivariate OR and 95% CI for current use of tiotropium *vs.* LABA and ipratropium *vs.* LABA were 0.82 (0.55, 1.23) and 1.30 (0.79, 2.14), respectively). Due to the limited number of participants in the ventricular arrhythmia case-control (N=17 cases and 883 matched control moments), the association between respiratory drug use (including tiotropium and ipratropium) and risk of ventricular arrhythmias were not obtained in this study. In a case-control including 446 new cases of heart failure and 16,039 matched controls, current and recent use of anticholinergics were associated with an increase in risk of heart failure compared to non-use of anticholinergics (multivariate OR and 95% CI were 1.35 (1.05, 1.72) and 1.39 (1.00, 1.93), respectively). Tiotropium use, recency of first use, and duration were unassociated with risk of heart failure compared to non users of anticholinergics (multivariate OR and 95% CI were 1.26 (0.81, 1.95), 1.28 (0.82, 2.00), and 0.46 (0.14, 1.50) for use, non-recent first use, and duration length of >=365 days, respectively). However, ipratropium use was associated with an increase in risk (multivariate OR and 95% CI was 1.33 (1.03, 1.72)). Low doses (≤ 0.5 DDD), recent first use, aerosol formulation, and short duration of use (< 30days) of ipratropium were also associated with increased risk of heart failure compared to non use (multivariate OR and 95% CI were 5.18 (2.40, 11.2), 1.74 (1.29, 2.35), and 2.95 (1.41, 6.15), respectively). RR of heart failure independently from ICS use were similar for current use of tiotropium *vs.* LABA (multivariate OR and 95% CI 1.06 (0.53, 2.10)) as well as for current use of ipratropium *vs.* LABA (multivariate OR and 95% CI 1.22 (0.85, 1.74)). Finally, no significant associations were observed between use of tiotropium and risk of stroke in a case-control including 357 new cases of stroke/TIA and matched 13,909 control moments except for an increase in risk among recent starters of ipratropium (multivariate OR and 95% CI 1.61 (1.08, 2.39). Risk of stroke/TIA (independently of ICS use) was similar between current users of tiotropium vs. LABA (multivariate OR and 95% CI 0.89 (0.45, 1.76)) and between current users of ipratropium vs. LABA (multivariate OR and 95% CI 1.07 (0.73, 1.55)).

Compared to non users of anticholinergics, current use of tiotropium or ipratropium was not associated with an increase in risk of death in a case-control study including 1032 new cases of death and 40,615 matched control moments (multivariate OR and 95% CI were 0.89 (0.65, 1.21) and 1.09 (0.90, 1.32), respectively). However, recent past use of tiotropium and both recent and distant past use of ipratropium were associated with an

increase in risk of death (multivariate OR and 95% CI were 1.69 (1.17, 2.44), 1.32 (1.05, 1.67) and 1.23 (1.02, 1.49), respectively). Risk of death was similar between current use of tiotropium *vs.* LABA (multivariate OR and 95% CI 0.79 (0.49, 1.28)), tiotropium *vs.* SABA multivariate OR and 95% CI 0.67 (0.38, 1.18)), and (between current use of ipratropium *vs.* LABA (multivariate OR and 95% CI 1.17 (0.91, 1.49)).

Risk of diabetes mellitus and renal failure were also examined in this study. In a case-control of 295 new DM cases and matched 10,428 control moments, neither tiotropium nor ipratropium were associated with risk of diabetes. Patients with a history of DM prior to cohort entry were excluded from these analyses. The risk of DM also did not differ between current use of tiotropium *vs*. LABA (multivariate OR and 95% CI 0.71 (0.31, 1.61)), between current use of tiotropium *vs*. SABA (multivariate OR and 95% CI 0.92 (0.35, 2.40)), or between current use of ipratropium *vs.* LABA (multivariate OR and 95% CI 0.92 (0.59, 1.41)), independently of ICS use. Similarly, these respiratory medications were also unassociated with risk of renal failure. In a case-control study including 83 new cases of renal failure and 3,975 matched control moments, tiotropium and ipratropium were not associated with risk of renal failure. Patients with a history of renal failure prior to cohort entry were excluded from these analyses. Risk also did not differ between current users of ipratropium *vs.* LABA (multivariate OR and 95% CI 1.18 (0.39, 3.56); estimates comparing current user of tiotropium *vs*. LABA or SABA were not provided due to limited number of cases available in these analyses.

Additionally, two case-control studies were constructed to examine effectiveness endpoints. In a case-control study including 619 new COPD-related hospital admissions and 24,820 matched controls, current use of tiotropium and of ipratropium was unassociated with increased risk of COPD-related hospitalization compared to users of LABA (multivariate OR and 95% were 0.51 (0.24, 1.06) and 1.17 (0.85, 1.61) for tiotropium *vs.* LABA and ipratropium *vs.* LABA, respectively). The association between these drugs and COPD exacerbation requiring oral steroids or antibiotics was also examined. In a case-control study including 3,439 new COPD exacerbations and 88,725 controls, rate of exacerbation was similar between current users of tiotropium and current users of LABA (multivariate OR and 95% was 0.93 (0.70, 1.23). Current use of ipratropium was associated with an increased risk of exacerbations compared to current use of LABA (multivariate OR and 95% was 1.26 (1.10, 1.44)).

No compelling evidence for effect modification by factors including gender, calendar time, incident *vs*. prevalent COPD, certainty of COPD diagnosis, COPD severity and smoking were provided.

3.9.2 OSE Comments on Proposed/Actual Analyses and/or Study Results

The results of this study do not provide evidence for an association between tiotropium and increased risk of cardiovascular events, mortality, or stroke. The current study also fails to suggest an association between tiotropium and increased risk of renal failure and of diabetes mellitus.

Objective 1

Indication for tiotropium use was missing in large proportions of new users of tiotropium, ranging from 23.4% (in 2003) and 50% (in 2007). Additionally, the date of data extraction for some of the practices fell before 2006. Thus, analyses on indication of use are based on information on a relatively small number of participants (i.e. N=268 in 2002, N=535 in 2003, N=482 in 2004, N=322 in 2005, N=105 in 2006, and N=3 in 2007) and may not appropriately represent the utilization in the source population.

Objective 2:

The large majority of COPD patients (77%) were diagnosed prior to cohort entry (prevalent COPD). These patients are therefore likely to have used respiratory medications prior to cohort entry. Inclusion of prevalent drug users in observational studies makes adjustment for certain covariates challenging because these variables may be affected by use of study drug itself (intermediate variables). For instance, adjustment for COPD severity among prevalent users of tiotropium may not be appropriate as COPD symptoms/severity may be affected by use of respiratory medications. Adjustment for variables affected by drug exposure typically attenuate the association between tiotropium and outcomes of interest. This problem may have been alleviated as COPD severity as measured 1 year prior to index date was used in primary analyses. It would be helpful to compare new vs. prevalent drug users in this study particularly in relation to age, COPD severity, and co-morbidities. Additionally, it would be helpful to restrict case-control analyses to incident COPD patients, although these analyses would probably lack statistical power due to the small number of incident COPD patients in the dataset.

Information on smoking is missing for approximately 46% of the patients (32% and 50% of incident and prevalent COPD patients, respectively). Therefore, residual confounding by smoking is likely in this study. However, this type of confounding would tend to over-estimate the association between tiotropium and study outcome; and, is therefore unlikely to explain the null associations observed in this study.

Additionally, information on spirometry values is missing for 69% of COPD patients. For these patients, COPD severity was classified according to data from GP or health care databases, which included a combination of recency of diagnosis, treatment with bronchodilators, xanthines or combination therapy, COPD-related hospitalization with antibiotic for treatment of respiratory infections, systemic corticosteroids for the treatment of COPD exacerbations, and/or diagnosis of pneumonia, and use of oxygen therapy. Thus, residual confounding by COPD severity cannot be ruled out this study. If tiotropium users tend to have more severe COPD (and more co-morbidities), confounding by COPD severity would attend to over-estimate the association between tiotropium and the outcomes of interest, and, is therefore unlikely to explain the null associations observed in this study.

Moreover, in many of the nested case-control studies, the final models did not adjust for several factors associated with the outcome, probably because these may not have been associated with the outcome at the $p<0.10$. For instance, previous history of diabetes, hyperlipidemia, and arrhythmia (among other factors) increased risk of cardiovascular

and cerebrovascular events (matched OR and 95% CI were 2.71 (1.99, 3.69), 1.20 (1.03, 1.41, and 1.69 (1.36, 2.09), respectively)) but were not included in the final models. Therefore, it may be advisable to adjust for factors associated with the outcome at the $p<0.05$ level. Confounding by these factors would likely to lead to an over-estimation of the RR and is therefore unlikely to explain the lack of association between TB and cardiovascular and cerebral events observed in this study.

While current use of tiotroprium was not associated with increased risk of cardiovascular or cerebrovascular events; low doses, recent use, short duration and aerosol formulation of ipratropium were associated with a moderate increase in risk of cardiovascular or cerebrovascular events when compared to non users of anticholinergics. These findings were mostly driven by cases of heart failure. Due to the early symptoms of heart failure, which may include coughing and dyspnea, these patients may have been prescribed ipratropium for relief of COPD exacerbation (*i.e.* protopathic bias), explaining the association with low dose, recent use and short duration of ipratropium and risk of heart failure.

While current use of tiotropium was not associated with an increased risk of death, an increase in risk was suggested with recent past use of anticholinergics (i.e. prescriptions ending >30 days and < 6 months prior to index) [RR (95% CI) =1.31 (1.03, 1.66)] and with distant past use of anticholinergics (i.e. prescriptions ending 6+ months prior to index) [RR (95% CI) =1.21(0.98, 1.48)]. However, this increase in risk among recent past users may reflect worsening of COPD and/or potential switching of medications as patients near death (i.e. confounding by disease severity). Similarly, the not statistically significant increase in risk with distant past use is also difficult to interpret as these patients may have been using other respiratory medications (i.e. confounding by medication use).

Objective 3:
Analyses yielding unadjusted event rates per respiratory medication may not be informative in determining the safety profile of tiotropium because (i) they are based on small number of cases (only incident COPD included) and because (*ii)* they are likely to be confounded by several factors, including age, gender, smoking, COPD severity, among other important risk factors for the outcomes of interest.

4 SUMMARY AND RECOMMENDATIONS

This is a review of the results of a population-based case-control study nested within a cohort of COPD patients over the age of 40 years conducted by Erasmus Medical Center by the Sponsor. This review focuses on the results related to the safety of tiotropium bromide.

This study has several strengths, including its population-based nature and the large amount of information, including identification information (age, sex, patient identification, GP registration information), notes, prescriptions, physician-linked indications for therapy, physical findings, laboratory values (all directly entered by the

GPs), in addition to medication prescription information, including use, dose, duration and timing of drug exposure is also available.

Limitations were also noted. Limitations that could potentially bias the results towards the null value (i.e. attenuate the associations) and explain the results of this study are described below.

Misclassification of exposure: Medication prescription was used as surrogate for drug exposure, which requires the assumption that participants used the drugs as prescribed. This type of misclassification, however, is unlikely to have differed between those who subsequently developed the outcomes of interest and those who did not. This non-differential misclassification would tend to make the comparison groups more similar to one another in respect to the exposure of interest and may attenuate the association between tiotropium use and risk of the outcomes of interest.

Inclusion of prevalent drug users: the large majority of COPD patients (77%) were diagnosed prior to cohort entry (prevalent COPD). These patients are therefore likely to have used respiratory medications prior to cohort entry. Inclusion of prevalent drug users in observational studies makes adjustment for covariates that may be affected by drug use very difficult. For instance, adjustment for COPD severity among prevalent users of tiotropium may not be appropriate as COPD symptoms/severity may be affected by use of respiratory medications. Adjustment for variables affected by drug exposure may attenuate the association between tiotropium and outcomes of interest. This problem may have been alleviated as COPD severity as measured 1 year prior to index date was used in primary analyses.

Low statistical power: Tiotropium was only marketed in the Netherlands in 2002; therefore, cases and controls exposed to tiotropium before 2002 (potentially 25% of the total number of cases and controls) are necessarily unexposed. Information on the number of cases and controls identified during this time period (not provided in the current report) would be informative. Additionally, this study may not have had sufficient statistical power to examine the association between TB use and certain outcomes including renal failure and ventricular arrhythmias. Additionally, this study lacked statistical power to examine risk of mortality according to cause of death. Finally, this study had limited statistical power to examine effect modification by various factors.

In summary, this is a population-based case-control study nested within a cohort of COPD patients over the age of 40 years, participating in the IPCI - a longitudinal observational database that contains data from computer-based patient records of a selected group of GPs in The Netherlands. The primary objective of this study was to evaluate the safety profile of tiotropium compared to both non-users of anticholinergics drugs as well as to users of LABA. The main limitation of this study is potentially inadequate statistical power to detect associations between safety outcomes including cardiovascular events and mortality between tiotropium users vs. non users or LABA users due to the fact that a proportion of cases and controls could not contribute exposed person-time before 2002 (when tiotropium was marketed in the Netherlands).

Nonetheless, it is worth noting that confidence limits were relatively narrow; the upper bound confidence interval for cardiovascular/cerebravascular events of current tiotropium users vs. non users of anticholinergics (95% CI of 0.64 -1.27) and for current user of tiotropium *vs.* LABA [(95% CI (0.50, 1.41)] is lower than the increase in risk reported by the only meta-analysis of randomized trials [3] which suggested an increase in risk in cardiovascular events [RR (tiotropium vs. controls) =1.49, 95% CI (0.98, 2.26); RR (anticholinergics vs. controls) = 1.60 (1.22, 2.10)] [3]. The results of this study, in combination with most of the epidemiologic evidence noted in the OSE's previous review (DARRTS communication PK # 2663713, Communication Date 08/04/2009) failed to provide evidence for an association between tiotropium and increased risk of cardiovascular events, mortality or stroke.

5 REFERENCES

[1] Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. American Thoracic Society. Am J Respir Crit Care Med 1995; 152(5 Pt 2): S77-121.

[2] Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. Am J Respir Crit Care Med 2001; 163(5): 1256-76.

[3] Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. JAMA 2008; 300(12): 1439-50.

[4] Lee TA, Pickard AS, Au DH, Bartle B, Weiss KB. Risk for death associated with medications for recently diagnosed chronic obstructive pulmonary disease. Ann Intern Med 2008; 149(6): 380-90.

[5] Macie C, Wooldrage K, Manfreda J, Anthonisen N. Cardiovascular morbidity and the use of inhaled bronchodilators. Int J Chron Obstruct Pulmon Dis 2008; 3(1): 163-9.

[6] Ogale SS, Lee TA, Au DH, Boudreau DM, Sullivan SD. Cardiovascular Events Associated With Ipratropium Bromide in COPD. Chest 2009.

[7] Kesten S, Jara M, Wentworth C, Lanes S. Pooled clinical trial analysis of tiotropium safety. Chest 2006; 130(6): 1695-703.

[8] Barr RG, Bourbeau J, Camargo CA, Ram FS. Tiotropium for stable chronic obstructive pulmonary disease: A meta-analysis. Thorax 2006; 61(10): 854-62.

[9] Salpeter SR, Buckley NS. Systematic review of clinical outcomes in chronic obstructive pulmonary disease: beta-agonist use compared with anticholinergics and inhaled corticosteroids. Clin Rev Allergy Immunol 2006; 31(2-3): 219-30.

[10] Wilt TJ, Niewoehner D, MacDonald R, Kane RL. Management of stable chronic obstructive pulmonary disease: a systematic review for a clinical practice guideline. Ann Intern Med 2007; 147(9): 639-53.

[11] Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, Decramer M. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med 2008; 359(15): 1543-54.

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SIMONE P PINHEIRO
10/29/2009

SOLOMON IYASU
10/29/2009
By Dr. Tarek Hammad, Associate Director, DEPI peformed the secondary review and concurred with the Primary Reviewer's conclusions. My signature indicates concurrence with both reviewers.

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: September 11, 2009

TO: Miranda Raggio, MSN, Regulatory Project Manager
Theresa Michele, MD, Medical Officer
Division of Pulmonary and Allergy Products

FROM: John Lee, MD, Medical Officer
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, MD
Branch Chief, Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspection

SUBMISSION: NDA 21-395 S-029

APPLICANT: Boehringer Ingelheim Pharmaceuticals, Inc.

DRUG: Tiotropium Bromide (Spiriva HandiHaler)

NME: No

THERAPEUTIC CLASSIFICATION: Standard

INDICATION (product labeling change, clinical studies section): reduction in COPD exacerbations, mortality, and respiratory failure

CONSULTATION REQUEST DATE: January 30, 2009

DIVISION ACTION GOAL DATE: September 3, 2009

PDUFA DATE: September 17, 2009

I. BACKGROUND

Tiotropium bromide (Spiriva) is a long-acting anticholinergic bronchodilator which permits once-daily long-term maintenance management of chronic obstructive pulmonary disease (COPD), currently either as an alternative or in addition to other bronchodilators (ipratropium, salmeterol, albuterol). Tiotropium is increasingly used as a first-line agent, owing to its convenience of once-daily dosing and increased patient compliance.

The UPLIFT Study (Protocol 205.235)

This is a key study of tiotropium bromide therapy in managing COPD, owing to its large study scope involving nearly 6000 patients over a four-year period in five world regions (United States, Western Europe, Eastern Europe, Latin America, and Asia), 37 countries, and 490 study sites. The study was conducted as a randomized, double-blind, placebo-controlled, parallel-group study to evaluate the rate of lung function decline over 4 years (co-primary endpoints) and clinical outcome (major secondary endpoints).

A total of 5993 patients with moderate to severe COPD (post-bronchodilator $FEV_1 \leq 70\%$ of predicted, $FEV_1 \leq 70\%$ of FVC) and on stable respiratory medication were randomized in equal ratio to receive either tiotropium 18 mcg (2986 subjects) or placebo (3006 subjects) by inhalation once daily using HandiHaler. The co-primary efficacy endpoints were the yearly rate of decline in FEV_1 before and after bronchodilator therapy. Major secondary endpoints included time to first COPD exacerbation and time to first COPD exacerbation leading to hospitalization.

There was no difference between the two groups in the rate of decline in FEV_1 (pre-bronchodilator or post-bronchodilator). However, unblinded subgroup analysis suggested that tiotropium therapy significantly reduced the rate of decline in post-bronchodilator FEV_1 (by 10 ml/year, in comparison with placebo) in subjects not receiving a long-acting beta-agonist or inhaled corticosteroid. Further, in comparison with placebo, significantly favorable FEV_1, FVC, and SVC were noted with tiotropium, which were sustained over the four-year study period.

Time to first COPD exacerbation (including exacerbations leading to hospitalization) were significantly longer for the treatment group, and COPD exacerbations were fewer (0.85 vs. 0.73 per patient-year, $p < 0.0001$) and briefer (13.6 vs. 12.1 days per patient-year, $p = 0.001$) in the active group. Safety outcome was similar for the two groups with the exception of mortality rate during treatment, which appeared to be lower for the treatment group (odds ratio = 0.84, 95% CI = 0.73-0.97, mortality rate for study = 16.4%). The overall study results supported a favorable risk-benefit profile of tiotropium in the treatment of COPD.

Safety Outcome in UPLIFT

Three safety endpoints are important to CDER review of this NDA supplement: mortality, stroke, and cardiovascular events. The concern for these potential adverse outcomes is based on the following observations:

- In a previous pivotal study of tiotropium bromide (Spiriva Respimat), on-study mortality was higher in the treatment group than in the placebo group.
- The sponsor's recent (November 2007) IND information amendment suggests that the incidence of stroke increases with tiotropium bromide therapy, based on a pooled analysis of 29 studies involving both the HandiHaler and Respimat devices.
- Two recent publications report an increased risk of cardiovascular events (including deaths) in patients who received tiotropium.

The safety outcome in the UPLIFT study is important not only for evaluating this NDA efficacy supplement, but also for (b) (5) the safety of tiotropium bromide. As a large, long-term international study, the safety findings of UPLIFT (b) (5)

(b) (5). Based on UPLIFT study results, the sponsor maintains that the use of tiotropium in COPD does not increase the incidence of stroke or cardiovascular events. The sponsor's proposed labeling claim includes mortality reduction, a safety outcome, among other efficacy claims.

Proposed Labeling Claim

In this NDA efficacy supplement, BI seeks the following claim for Spiriva HandiHaler, under the clinical studies section of the product label: improvement in lung function (trough FEV_1) and reduction in COPD exacerbations, respiratory failure, and mortality.

II. CLINICAL INSPECTIONS

Inspection Planning

The pivotal study for this NDA supplement (the UPLIFT study) involved nearly 6000 patients at 487 clinical sites worldwide. Given this scope of the UPLIFT study, the inspectional review of this NDA supplement included a statistical analysis (performed at DSI) to determine how many clinical sites should be inspected in order to confidently confirm, for the entire UPLIFT study, acceptable compliance with Good Clinical Practice (GCP) regulations and standards. The statistical analysis indicated that if unacceptable GCP were not found at any of 7 sites, the GCP compliance rate could be determined to be $\geq$ 80% (sites with unacceptable GCP < 20% of all sites) with 80% confidence. If the 7 clinical sites are well-selected and the FDA's inspectional findings are also supported by the sponsor's site monitoring results and other compliance-related information provided by the sponsor in the NDA supplement, negative finding at all 7 inspections would support a GCP compliance rate well above 80%. If a positive (serious) concern were to be noted at any of the 7 inspections, additional inspections would be needed to determine the adequacy of the GCP compliance status for the UPLIFT study as a whole.

The 7 clinical sites for cycle 1 inspections, selected jointly by the review division and DSI at CDER, consisted of 4 domestic and 3 foreign sites. The 4 domestic sites were selected based primarily on subject enrollment ($\geq$ 20 subjects) and the following secondary risk attributes:

- Previous inspection status: Sites 3741 (Greenwald), 3812 (Chetty/Mahutte), and 3708 (Bailey) have not been inspected previously by the FDA.
- Primary efficacy outcome: Sites with large contributions to the efficacy outcome of the study (apparent efficacy outliers, based on co-primary endpoints) were included. Site 3812 (Chetty/Mahutte) was a negative efficacy outlier, but was included based on other risk attributes, to include highest protocol deviation reporting rate.
- Mortality rates (> 20%) and Serious Adverse Events (SAE): All four sites had morality rates > 20%, with Site 3741 (Greenwald) having the highest mortality rate of 35% among US sites.
- Protocol deviation rate (> 10%): All four sites had reporting rates > 10 %, with Site 3812 (Chetty/Mahutte) having the highest reporting rate of 31%, an apparent outlier among the 487 sites worldwide.
- Financial disclosure: (b) (4)

Inspection Results

No serious GCP deficiencies were identified at the 7 selected clinical sites. The overall inspectional outcome is shown in **Table 1**, followed by a discussion of each inspection.

Table 1: Inspectional Outcome

	Clinical Investigator and Site	Site Number Subjects	Inspection Dates	Classification	
				Field	CDER
1	Donald Tashkin, MD UCLA Geffen School of Medicine 10833 Le Conte Ave, Room 37-156 Los Angeles, CA 90095	Site 3800 146 subjects	May 11 - July 8 2009	NAI	NAI
2	Gary Greenwald, MD Advances in Medicine 42362 Bob Hope Drive, Rancho Mirage, CA 92270	Site 3741 25 subjects	June 15 - June 26 2009	VAI	VAI
3	Kota Chetty, MD Long Beach VAMC, 03-119 5901 East 7th Street Long Beach, CA 90822	Site 3812 25 subjects	June 1 - June 9 2009	VAI	VAI
4	William Bailey, MD University of Alabama, Birmingham 1808 7th Ave South, Building 356 Birmingham, AL 35249	Site 3708 70 subjects	July 21 - July 23 2009	NAI	NAI
5	Jiri Erban, MD SPLIN s r.o. Čimická 37/446 182 00 Praha 8; Czech Republic	Site 0707 27 subjects	July 7 - July 10 2009	NAI	NAI
6	Rodolfo Posadas-Valay, MD Ceprep Hospital Universitario Av. Madero Y Gonzalitos S/N Monterrey, Nuevo Leon, Mexico	Site 2004 27 subjects	July 20 - July 24 2009	VAI	VAI
7	Wanchai Dejsomritrutai, MD Dept of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University Bangkoknoi, Bangkok 10700, Thailand	Site 3404 20 subjects	July 13 - July 17 2009	VAI	VAI

NAI: No action indicated (no deviations from regulations)
VAI: Voluntary action indicated (no significant deviations from regulations)
OAI: Official action indicated (significant deviations from regulations)

1. **Donald Tashkin, MD (Site 3800)**

   UCLA Geffen School of Medicine
   10833 Le Conte Ave, Room 37-156
   Los Angeles, CA 90095

   a. What was inspected:

      - Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring, IRB oversight, adverse event reporting, and adherence to protocol and applicable regulations
      - Data verification: primary efficacy endpoint data, adverse event data and reporting, concomitant medication use, protocol deviations, and subject discontinuation
      - Subjects: 146 subjects were screened to enroll 99 subjects into the study. Records were reviewed for 40 subjects.

   b. General observations and commentary:

      Dr. Tashkin was the principal investigator for the entire UPLIFT study. All primary efficacy endpoint data were verified to be accurate. No unreported adverse events were noted. Study monitoring oversight appeared to be adequate. No significant GCP deficiencies were observed and a Form FDA 483 was not issued.

   c. How FDA inspectional findings compare with sponsor's site monitoring results:

      - Sponsor's monitoring of this site consisted of 43 site visits by a single study monitor. Each visit typically required 2 days to complete a comprehensive review of informed consent, safety information, and selected subject case histories. CRFs for 39 subjects (~40% of subjects) were completely reviewed by end of study. Given the high enrollment at this site, the scope of the sponsor's monitoring was increased to assure adequate GCP at this site.
      - Findings: No significant deficiencies were identified. Good adherence to the protocol reflected close oversight by the sub-investigator (Dr. Kleerup), in the absence of the principal investigator (Dr. Tashkin). Safety procedures were consistently followed and CRF data were well-supported by source documentation. Minor deficiencies were readily corrected.
      - Comparison: The sponsor's findings while the study was on-going at this site are consistent with FDA's inspectional findings.

   d. Assessment of data integrity: The data from this study site appear to be reliable.

2. **Gary Greenwald, MD (Site 3741)**

   Advances in Medicine
   42362 Bob Hope Drive,
   Rancho Mirage, CA 92270

   a. What was inspected:

      - Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring, IRB oversight, adverse event reporting, and adherence to protocol and applicable regulations
      - Data verification: primary efficacy endpoint data, adverse event data and reporting, concomitant medication use, protocol deviations, and subject discontinuation

- Subjects: 36 subjects were screened to enroll 25 subjects into the study. Complete records were reviewed for 10 subjects.

b. General observations and commentary:

All primary efficacy endpoint data were verified to be accurate. No unreported adverse events were noted. IRB oversight and study monitoring appeared to be adequate. A Form FDA 483 was issued for the following GCP deficiencies:

- Informed consent: The signature of Subject 12404 (dated June 5, 2003; screening visit) on the informed consent document (ICD) did not match the subject's signature (dated January 15, 2004; Visit 5) on a revised ICD. A note to file (dated 6/24/09) provided an explanation as to why the signatures did not match, that as it required "some effort for this particular subject to sign, the wife signed for the subject."
- Adherence to the investigational plan:
  - Pulmonary function tests (PFT) were frequently performed at time points outside the protocol-specified time window of 5 minutes following a 90 minute delay between bronchodilator dosing and post-bronchodilator PFT. For example:
    - Subject 11604: On January 29, 2004, the study drug was administered at 09:43 and the PFT was to be performed between 11:13 and 11:18, but the PFT was actually performed at 11:23, 5 minutes after the latest time point permitted by the study protocol.
    - Subject 12390: On March 11, 2004, the study drug was administered at 09:33 and the PFT was to be performed between 11:03 and 11:08, but the PFT was actually performed at 11:14, 6 minutes after the latest time point permitted by the study protocol.
  - Records for Subject 12398 (Visit 3, December 23, 2003) indicated that the subject was treated with doxycyclin for 10 days, but this concomitant medication use was not reported to the sponsor as specified in the study protocol.
- Study drug disposition: Source records for Subject 14345 indicated that no study medication was dispensed to the subject on May 15, 2007 (Visit 18). The information on the Study Drug Dispensing and Return Log (reference to Kit 871473, 120 capsules) for this subject visit was inconsistent with the source record and appeared to be inaccurate.

c. How FDA inspectional findings compare with sponsor's site monitoring results:

- Sponsor's monitoring of this site consisted of 23 site visits over 5 years by 2 different monitors. About half of the visits required two or more days to complete a comprehensive review of informed consent, safety information, and selected subject case histories. CRFs for 30 subjects were completely reviewed by end of study.
- Findings: No significant persistent issues were identified. Adherence to the protocol was considered to be adequate, safety procedures were consistently followed, and CRF data were well-supported by source documentation. Minor deficiencies were found but were readily corrected with the assistance from the study monitors.
- Comparison: The sponsor's findings while the study was on-going at this site appear to be consistent with FDA's inspectional findings. FDA findings suggest that the sponsor's monitoring and intervention were important in maintaining this site at an acceptable level of GCP compliance.

d. Assessment of data integrity:

These GCP deficiencies noted at FDA inspection are not expected to importantly affect the study outcome. The data from this study site appear to be reliable.

3. **Kota Chetty, MD (Site 3812)**

Long Beach VAMC, 03-119
5901 East 7th Street
Long Beach, CA 90822

a. What was inspected:

- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring, IRB oversight, adverse event reporting, and adherence to protocol and applicable regulations
- Data verification: primary efficacy endpoint data, adverse event data and reporting, concomitant medication use, protocol deviations, and subject discontinuation
- Subjects: 36 subjects were screened, 26 enrolled, and 17 completed the study. Subject records were reviewed for all enrolled subjects, including complete record review for 10 subjects.

b. General observations and commentary:

All primary efficacy endpoint data were verified to be accurate. No unreported adverse events were noted. IRB oversight appeared to be adequate. A Form FDA 483 was issued for the following GCP deficiencies (not adhering to the study protocol):

- Several subjects (at least three) were treated with tiotropium during the study period, in deviation from the study protocol which prohibited the use of tiotropium or other long-acting anticholinergic medications for at least one month prior to Visit 2 and throughout the study, including the follow up period. For example:
  - Subject 14597, Visit 13: Tiotropium was given to treat COPD exacerbation considered to be a serious adverse event.
  - Subject 14601, End of Therapy Visit: Tiotropium was given to treat COPD (not listed as an adverse event).
  - Subject 14612, Visit 13: Tiotropium was given in managing respiratory symptoms associated with a right lower lung abscess.
- Many subjects were treated with Atrovent or Combivent to manage COPD exacerbations, in deviation from the study protocol which prohibited the use Atrovent, Combivent, or other inhaled anticholinergic medications. For example:
  - Subject 13807 (Visit 12): Atrovent (via nebulizer) was given to manage a non-serious COPD exacerbation.
  - Subject 14601 (Visits 14, 17, 18, 19): Atrovent (via nebulizer) and Combivent were given to manage serious and non-serious COPD exacerbations (apparent complications of pneumonia).
  - Subject 14612 (Visit 6): Atrovent (via nebulizer) and Combivent were given to manage a serious COPD exacerbation.

These deviations from the study protocol were observed in a significant fraction of the subjects (30-50%) at this clinical site. However, for any given subject, the protocol deviations appeared to have occurred at a limited number of study visits (fewer than 5) over the four-year treatment period, and the deviations were considered unlikely to have importantly affected the major study endpoints that measure long-term treatment effects (yearly rate of decline in pulmonary function; chronic susceptibility to complications of COPD).

c. How FDA inspectional findings compare with sponsor's site monitoring results:

- Sponsor's monitoring of this site consisted of 19 site visits by two study monitors, one of whom was newly trained. Each visit typically required 2 days to complete a review of informed consent, safety information, and selected subject case histories. CRFs for all subjects were completely reviewed by end of study.
- Findings: No significant deficiencies were identified. Adherence to the protocol was considered to be adequate, safety procedures were consistently followed, and CRF data were considered to be well-supported by source documentation. Minor deficiencies were readily corrected.
- Comparison: Unlike the 6 other clinical sites inspected in support of this NDA supplement review, the sponsor's findings for this site do not appear to be consistent with FDA's inspectional findings. FDA findings (prohibited medication use) do not appear to have been previously identified by the sponsor's study monitors, possibly because the sponsor's monitor was newly (inadequately) trained.
- In view of the apparent/potential inadequacy of the sponsor's monitoring, the review division may consider the information presented below in **Table 2** in interpreting the study data from this site. **Table 2** compares site-specific information (study results and audit findings) with the equivalent information for the entire study (all other sites).

Table 2: Comparison of Site-Specific Data (Site 3812) with Overall Study Data

	Subjects Enrolled	Yearly Decline in Post-Bronchodilator FEV_1 (mL/year)		Fraction of Subjects with SAE	Sponsor's Monitoring	FDA's Inspectional Findings
		Spiriva	**Placebo**			
Site 3812	n = 26	47 mL	18 mL	73%	may be inadequate	use of prohibited medication in managing COPD exacerbations
All Sites	N = 5992	40 mL	42 mL	51%	acceptable	GCP compliant (by extrapolation)

The summary data indicate that, in comparison with the overall study population, the subjects at Site 3812 experienced SAEs more frequently, which were often COPD exacerbations. In managing COPD exacerbations, prohibited medications (including long-acting anticholinergics) may have been used at this site more frequently than at other sites, and the relatively frequent prohibited use was detected at FDA inspection.

The use of long-acting anticholinergics (other than as specified in the study protocol) at this site may or may not have been related to the severity of the underlying disease, other potentially confounding study variables, or the study outcome at this site.

d. Assessment of data integrity:

FDA findings at this site included deficiencies potentially important to the reliability of the efficacy data. However, given that these deficiencies appear to have been limited to a small fraction of the study visits/assessments, the data from this clinical site appear to be reliable.

4. **William Bailey, MD (Site 3708)**

University of Alabama, Birmingham
1808 7th Ave South, Building 356
Birmingham, AL 35249

a. What was inspected:

- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring, IRB oversight, adverse event reporting, and adherence to protocol and applicable regulations
- Data verification: primary efficacy endpoint data, adverse event data and reporting, concomitant medication use, protocol deviations, and subject discontinuation
- Subjects: 114 subjects were screened, 70 enrolled, and 36 completed the study. The remaining 34 subjects were withdrawn from the study, mainly because subjects opted to not risk being in the placebo arm for the entire duration of the study. Subject records were reviewed for 32 subjects.

b. General observations and commentary:

No significant deficiencies were observed and a Form FDA 483 was not issued. All primary efficacy endpoint data were verified to be accurate and no unreported adverse events were noted. Study monitoring oversight appeared to be adequate.

c. How FDA inspectional findings compare with sponsor's site monitoring results:

- Sponsor's monitoring of this site consisted of 52 site visits over 5 years by a single monitor. Each visit typically required 2 days to complete a comprehensive review of informed consent, safety information, and selected subject case histories. CRFs for 72 subjects were completely reviewed by end of study. Given the high enrollment at this site and the initial inexperience of the site personnel, the scope of the sponsor's monitoring was increased to assure adequate GCP and to train the study coordinators about GCP.
- Findings: No significant persistent issues were identified. Adherence to the protocol was good to excellent, safety procedures were consistently followed, and CRF data were well-supported by source documentation. Minor deficiencies were readily addressed; for example, upon identification by the study monitor of a one-month delay in obtaining IRB re-approval, the site revised their study procedures to track and manage all IRB approvals by one study coordinator.
- Comparison: The sponsor's findings while the study was on-going at this site are consistent with FDA's inspectional findings.

d. Assessment of data integrity: The data from this study site appear to be reliable.

5. **Jiri Erban, MD (Site 0707)**

SPLIN s.r.o.
Čimická 37/446
182 00 Praha 8; Czech Republic

a. What was inspected:

- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring, IRB oversight, adverse event reporting, and adherence to protocol and applicable regulations

- Data verification: primary efficacy endpoint data, adverse event data and reporting, concomitant medication use, protocol deviations, and subject discontinuation
- Subjects: 30 subjects were screened, 27 enrolled, and 10 completed the study. Subject records were reviewed completely for 10 subjects who completed the study.

b. General observations and commentary:

No significant deficiencies were observed and a Form FDA 483 was not issued. All primary efficacy endpoint data were verified to be accurate and no unreported adverse events were noted. Study monitoring oversight appeared to be adequate.

c. How FDA inspectional findings compare with sponsor's site monitoring results:

- Sponsor's monitoring of this site consisted of 23 site visits over 5 years by 3 different monitors. Each visit typically required 1 day to complete a comprehensive review of informed consent, safety information, and case report forms (CRF) for 6 to 8 subjects.
- Findings: No significant issues were identified throughout monitoring. The study was conducted by the principal investigator, a single sub-investigator and a study nurse. Adherence to the protocol was excellent, safety procedures were consistently followed, and CRF data were well-supported by source documentation. Minor deficiencies were readily addressed.
- Comparison: The sponsor's findings while the study was on-going at this site are consistent with FDA's inspectional findings.

d. Assessment of data integrity: The data from this study site appear to be reliable.

6. **Rodolfo Posadas-Valay, MD (Site 2004)**

Ceprep Hospital Universitario
Av. Madero Y Gonzalitos S/N
Monterrey, Nuevo Leon, Mexico

a. What was inspected:

- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring, IRB oversight, adverse event reporting, and adherence to protocol and applicable regulations
- Data verification: primary efficacy endpoint data, adverse event data and reporting, concomitant medication use, protocol deviations, and subject discontinuation
- Subjects: 32 subjects were screened, 27 enrolled, and 24 completed the study. Subject records for 26 enrolled subjects (including 24 completing study) were reviewed for the verification of the primary efficacy endpoint data and other selected study data (including adverse event reporting), documentation of informed consent, and evidence of IRB approval and continuing IRB oversight.

b. General observations and commentary:

Study monitoring by Fractals, Inc. (contract research organization) for this clinical site appeared to be thorough and helpful to GCP compliance at this site (17 visits between April 2003 through September 2008). A Form FDA 483 was issued for the following GCP deficiencies:

- Study evaluations were not performed according to the timeframe specified in the study protocol. For example:

- Visit 20 assessment was consistently out of the protocol-specified time window for Subjects 10752, 10755, 10756, 10757, and 10759. The visits were delayed by approximately 2 to 4 weeks, from December 2007 (per protocol) to January 2008 (actual visits).
- Visit 19 assessment was not performed for Subject 10642.

- For Subjects 10739, 10734, 10748, and 10754, serious adverse events were not reported immediately to the sponsor, in deviation of the study protocol which specified immediate reporting to the sponsor by telephone.
- Study documentation appeared to be internally discrepant or incomplete. For example:
  - None of the 26 subject records reviewed contained source documentation of smoking history.
  - For Subject 10756, the use of Atrovent, a medication prohibited by the study protocol, was noted in the subject diary but was not shown on the CRF.
- At study completion, the return of the 219 study kits (each containing 240 doses of the study drug) back to the sponsor was not documented as part of study records.

c. How FDA inspectional findings compare with sponsor's site monitoring results:

- Sponsor's monitoring of this site consisted of 19 site visits by 4 different monitors. The study was conducted by the principal investigator and two study coordinators whose primary duty was to perform PFTs. Source documents and CRFs were completed by the principal investigator.
- Findings: No significant deficiencies were persistently noted. Adherence to the protocol was adequate, with no major protocol deviations. Monitoring observations included fewer reports of adverse events and concomitant therapies (relative to other sites in UPLIFT), for which the principal investigator was advised to provide more extensive progress notes to supplement the study worksheets. Minor observed GCP deficiencies included delays in reporting safety information to the IRB, which were addressed over multiple monitoring visits.
- Comparison: While less detailed, the sponsor's report of the monitoring results appears to be consistent with FDA's inspectional findings. FDA findings regarding the reporting of adverse events and concomitant medication use had been noted by the sponsor's monitors while the study was on-going at this site, and these deficiencies appear to have been corrected over the course of the study. FDA findings regarding out-of-window PFTs and study medication accountability appear not to have been identified at study monitoring. A comparison of the monitoring results with FDA findings suggests that the sponsor's audit is less rigorous but sufficient to identify and correct major GCP deficiencies with the potential to importantly affect data reliability.

d. Assessment of data integrity:

A review of the final establishment inspection report, Dr. Posadas-Valay's response to the Form FDA 483 citations, and a comparison of FDA findings with the sponsor's monitoring results indicate that the GCP deficiencies noted at inspection did not importantly affect subject rights, subject safety, or study outcome at this clinical site. The data from this study site appear to be reliable.

7. **Wanchai Dejsomritrutai, MD (Site 3404)**

Dept of Medicine, Faculty of Medicine
Siriraj Hospital, Mahidol University
Bangkoknoi, Bangkok 10700, Thailand

a. What was inspected:

- Scope of inspection: subject eligibility, informed consent, study monitoring, IRB oversight, adverse event reporting, and adherence to protocol and applicable regulations
- Data verification: primary efficacy endpoint data, adverse event data and reporting, concomitant medication use, protocol deviations, and subject discontinuation
- Subjects: 22 subjects were screened, 20 enrolled, and 10 completed the study. Subject records for all enrolled subjects were reviewed for the verification of the primary efficacy endpoint data and other selected study data (including adverse event reporting), documentation of informed consent, and evidence of institutional review board (IRB) approval and continuing IRB oversight.

b. General observations and commentary:

All audited study data were verified to be accurate, including the primary efficacy endpoint data. Study records were not adequate to assess the quality of study monitoring (by Quintiles, Inc.) for this clinical site. A Form FDA 483 was issued for the following GCP deficiencies:

- The principal investigator did not maintain complete and/or accurate source documentation. For example:
  - There was no documentation of providing subjects with copies of the original and amended signed informed consent forms.
  - Patient diaries for 13 (of 20) randomized subjects were either missing or incomplete.
- The principal investigator did not capture complete and/or accurate study data on CRF. For example:
  - CRF for Subject 26639 did not capture the use of concomitant medication Consinut (chlorpheniramine and pseudoephedrine) as reported by the subject at Visit 9.
  - CRF for Subject 26640 did not capture all concomitant medications used by the subject (Triamcinolone cream, reported at Visit 8; ciprofloxacin and Roxithromycin, reported at Visit 5).
- The principal investigator did not ensure that study-related activities were performed according to the study protocol. Specifically, study personnel performed more than the maximum number (five) of PFT trial runs, for Subject 26645 (Visit 3; May 7, 2000) and for Subject 26656 (Visit 11; December 20, 2000).

c. How FDA inspectional findings compare with sponsor's site monitoring results:

- Sponsor's monitoring of this site consisted of 31 site visits over 5 years by several monitors (from sponsor and 2 CROs).
- Findings: The relatively large number of monitoring visits and the involvement of 2 different CROs reflect the significant GCP deficiencies identified at this clinical site, as well as the performance of the first CRO. Adherence to the protocol was acceptable but documentation was often insufficient for: obtaining informed consent, timeliness of SAE reporting, source documentation of study results, and clinical investigator's oversight. In implementing corrective actions, the sponsor: (1) retrained the site staff on adverse event reporting, (2) reassigned a new study monitor, (3) increased monitoring frequency, (4) performed repeat verification of all CRFs, and (5) conducted audits by the sponsor's regional staff (safety manager and clinical monitor). The site was successfully brought into an acceptable level of GCP compliance.

- Comparison: In lieu of listing observed GCP deficiencies, the sponsor's monitoring report acknowledged significant deficiencies and focused on the corrective actions implemented. FDA findings are consistent with the sponsor's report, appear to represent the same findings that triggered the sponsor to increase monitoring oversight, and indicate that the sponsor's monitoring was effective in bringing this clinical site into GCP compliance.

d. Assessment of data integrity:

A review of the final establishment inspection report, Dr. Dejsomritrutai's response to the Form FDA 483 citations, and a comparison of FDA findings with the sponsor's monitoring results indicate that the GCP deficiencies noted at inspection did not importantly affect subject rights, subject safety, or study outcome at this clinical site. The data obtained at this clinical site appeared to be reliable.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The UPLIFT study (Protocol 205.235) involved nearly 6000 patients at 490 clinical sites worldwide. Statistical considerations indicated that a minimum of 7 well-selected clinical site inspections were necessary to adequately assess the quality of study conduct at the large number of clinical sites. Based on prior inspectional history and using the compliance-related information provided by the sponsor, 4 domestic and 3 foreign clinical sites were identified for inspection. The major site-specific risk attributes considered included enrollment, previous inspectional history, site-specific study outcome (efficacy contribution, mortality and SAE rates), protocol deviation reporting rate, and financial disclosure information.

The conduct of the UPLIFT study at the 7 identified clinical study sites were audited between 11 May and 24 July 2009. Adequate adherence to applicable GCP regulations and standards were confirmed at all 7 sites. GCP deficiencies were observed at 4 of the 7 sites, but the deficiencies were unlikely to have importantly affected site-specific study outcomes. The FDA inspections confirmed acceptable GCP at the clinical sites inspected, and more importantly, validated the sponsor's more extensive internal monitoring performed periodically for all study sites while the study was on-going. The data from the UPLIFT study appear to be reliable as reported under the NDA supplement.

{See appended electronic signature page}

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/s/

JONG-HOON LEE
09/14/2009

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09/14/2009

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	August 02, 2009
To:	Badrul A. Chowdhury Director, Division of Pulmonary and Allergy Products Office of New Drugs
Through:	Solomon Iyasu, M.D., M.P.H. Director, Division of Epidemiology Tarek Hammad, M.D., Ph.D., M.Sc., M.S. Associate Director of Epidemiology, Division of Epidemiology Office of Surveillance and Epidemiology
From:	Simone P. Pinheiro, M.Sc, Sc.D. Epidemiologist David Moeny, RPh Drug Use Analyst Division of Epidemiology Office of Surveillance and Epidemiology
Subject:	Review of published epidemiologic literature suggesting safety concerns with tiotropium and ipratropium.
Drug Name(s):	Spiriva (tiotropium bromide monohydrate) and Atrovent HFA (ipratropium bromide)
Submission Number:	S029
Application Type/Number:	NDA # 021-395 (Spiriva) , NDA # 21-527 (Atrovent HFA)
Applicant/sponsor:	Boehringer Ingelheim
OSE RCM #:	2009-312

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TABLE OF CONTENTS

EXECUTIVE SUMMARY 1
1 BACKGROUND/HISTORY 1
2 reviewer's comments 4
2.1 Literature Review 4
2.1.1 Anticholinergics and risk of stroke 4
2.1.2 Anticholinergics and risk of cardiovascular events 6
2.1.3 Anticholinergics and mortality risk 8
2.1.4 Summary of literature search and DEPI review plan 11
2.2 Singh S, Loke YK, Furberg CK. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with COPD – A systematic review and meta-analysis. JAMA 2008; 300: 1439-1450. [3] 11
2.2.1 Summary of Study 11
2.2.2 OSE Comments on Study Objectives 12
2.2.3 OSE Comments on Study Design 12
2.2.4 OSE Comments on Informed Consent (if any) 13
2.2.5 OSE Comments on Data Sources 13
2.2.6 OSE Comments on Study Time Period(s) 13
2.2.7 OSE Comments on Study Population 13
2.2.8 OSE Comments on Measurement of Exposure 14
2.2.9 OSE Comments on Disease Outcome of Interest 15
2.2.10 OSE Comments on Sample Size 15
2.2.11 OSE Comments the Analysis / Results 15
2.2.12 OSE Comments on strength of evidence 16
2.3 Lee TA, Pickard AS, Au DH, Bartle B, and Weiss KB. Risk for death associated with medications for recently diagnosed COPD. Ann of Int Med 2008; 149: 380-391 [4] 19
2.3.1 Summary of Study 19
2.3.2 OSE Comments on Study Objectives 20
2.3.3 OSE Comments on Study Design 20
2.3.4 OSE Comments on Informed Consent (if any) 20
2.3.5 OSE Comments on Data Sources 20
2.3.6 OSE Comments on Study Time Period(s) 21
2.3.7 OSE Comments on Study Population 21
2.3.8 OSE Comments on Measurement of Exposure 21
2.3.9 OSE Comments on Disease Outcome of Interest 21

2.3.10 OSE Comments on Sample Size 22
2.3.11 OSE Comments on Study Analysis / Results 22
2.3.12 OSE Comments on Strength of Evidence 22
2.4 Macie C, Wooldrage K, Manfreda J, Anthonisen N. Cardiovascular morbidity and the use of inhaled bronchodilators. Int J of COPD 2008; 1: 163-169 [5] 24
2.4.1 Summary of Study 24
2.4.2 OSE Comments on Study Objectives 25
2.4.3 OSE Comments on Study Design 25
2.4.4 OSE Comments on Informed Consent (if any) 25
2.4.5 OSE Comments on Data Sources 25
2.4.6 OSE Comments on Study Time Period(s) 25
2.4.7 OSE Comments on Study Population 25
2.4.8 OSE Comments on Measurement of Exposure 25
2.4.9 OSE Comments on Disease Outcome of Interest 26
2.4.10 OSE Comments on Sample Size 26
2.4.11 OSE Comments on Analyses and/or Study Results 26
2.4.12 OSE Comments on Strength of Evidence 26
2.5 Ogale SS, Lee TA, Au DH, Boudreau DM, Sullivan SD. Cardiovascular events associated with ipratropium bromide in COPD. Chest 2009 (*epub ahead of print*) [6] 28
2.5.1 Summary of Study 28
2.5.2 OSE Comments on Study Objectives 29
2.5.3 OSE Comments on Study Design 29
2.5.4 OSE Comments on Informed Consent (if any) 29
2.5.5 OSE Comments on Data Sources 29
2.5.6 OSE Comments on Study Time Period(s) 30
2.5.7 OSE Comments on Study Population 30
2.5.8 OSE Comments on Measurement of Exposure 30
2.5.9 OSE Comments on Disease Outcome of Interest 30
2.5.10 OSE Comments on Sample Size 31
2.5.11 OSE Comments on Analyses / Study Results 31
2.5.12 OSE Comments on Strength of Evidence 31
3 DRUG UTILIZATION 33
3.1 Determining Settings of Use 33
3.2 Data Sources and Methods 33
3.3 Results 34

3.4 Drug utilization Discussion 35
4 SUMMARY of review AND RECOMMENDATIONS 36
5 REFERENCEs 37
6 APPENDICES 40
Appendix 1 – Singh *et al*, main tables and figures 40
Appendix 2: Lee *et al*, main study tables 43
Appendix 3: Macie *et al*, main tables 45
Appendix 4: Ogale *et al*, main tables and figures 46
Appendix 5. Drug Utilization Data Tables 48

EXECUTIVE SUMMARY

Inhaled anticholinergics have been considered both effective and safe for the management of chronic obstructive pulmonary disease (COPD). Indeed, the American Thoracic Society and the Global Initiative for Chronic Obstructive Lung Disease recommend inhaled anticholinergics in the treatment of COPD [1,2].

However, a few recent publications and reports raised concerns about the safety of inhaled anticholinergics, including tiotropium bromide (TB) and ipratropium bromide (IB). These included a meta-analysis conducted by Singh and colleagues [3], which implicated anticholinergics in increasing rates of cardiovascular events; two large nested case-control studies, which suggested IB increased risk of death [4] and of certain cardiovascular events [5]; and a large cohort study by Ogale and colleagues [6], which suggested that IB and TB may increase the risk of cardiovascular events. The Office of Surveillance and Epidemiology was consulted to review these studies.

The limitations of the meta-analysis by Singh et al [3], including a biased selection of studies, lack of information on participants who discontinued trial and failure to use person-time data, and the limitations of the observational studies [4-6], of which the most important refers to their inability to adjust for important risk factors for the outcomes, may explain the reported positive associations between anticholinergics and adverse events. Additionally, these findings do not agree with the findings of previously published meta-analyses [7-10], nor do they agree with the recently published findings from a large 4-year large randomized, placebo-controlled clinical trial [11], none of which suggested an association between anticholinergics and cardiovascular events or mortality.

In conclusion, the currently available data implicating TB and IB in increasing risk of these outcomes is not compelling. While the Agency continues will continue to monitor the safety of these products, we do not recommend the pursuit of meta-analysis by the Agency at this time.

1 BACKGROUND/HISTORY

Tiotropium Bromide

Tiotropium bromide is a long acting anticholinergic with specificity for muscarinic receptors approved as Spiriva HandiHaler (Spiriva® Boehringer Ingelheim). This product is a dry powder capsule formulation approved on January 30, 2004 (NDA # 21-395) for the long-term, once daily management of bronchospasm associated with chronic obstructive pulmonary disease (COPD).

On November 16 of 2007, Boehringer Ingelheim (BI) submitted a 505(b)(1) application for a novel inhalation device, the Respimat Inhalation Spray, to deliver TB for oral

inhalation. The PDUFA date for this application is September 16, 2009. During the development program, several safety issues surfaced.

On November 2005, prior to submitting the NDA, BI informed the Division of Pulmonary and Allergy Products (DPAP) about an imbalance in fatal adverse events favoring the placebo group in one of the 48-week clinical trials (study 205.255). Because the Division was concerned about the impact of this signal on the approved product Spiriva HandiHaler, the Division presented the preliminary mortality data to the Drug Safety Oversight Board (DSOB) on June of 2006. The DSOB noted the mortality signal to be weak due to the fact that (*i*) it was only present in one of the studies, (*ii*) there were no deaths in the placebo group, suggesting that the increase in mortality may have been due to the unusually low background mortality rate in that particular study, (*iii*) there were no specific patterns in the causes of deaths, and (*iv*) the safety data on HandiHaler were reassuring. The DSOB recommended that BI obtain vital status follow up data on 100% of patients who dropped out of the trials as there was substantial differential discontinuation between the placebo and TB treatment groups.

In November of 2007, BI submitted preliminary results of a routine pooled safety analysis of 29 clinical trials with Spiriva HandiHaler (n=25 studies) and Respimat (n=4 studies) (unpublished report). In this analysis, BI noted an increase in risk of stroke in patients treated with TB *vs.* placebo, RR and 95% CI of 1.37 (0.73, 1.56). While this analysis did not adjust for multiplicity and the association with stroke was not statistically significant, consistently with the Agency's commitment to inform the public about ongoing safety reviews, the Agency released an Early Communication on March of 2008 describing preliminary information regarding Spiriva and potential risk of stroke [12].

Additionally, the results of a recently published meta-analysis of 15* randomized clinical trials raised questions about the safety of inhaled anticholinergic agents, particularly in regards to risk of cardiovascular outcomes and premature deaths [3,13]. In this analysis, TB was associated with a borderline significant 49% increase in risk of cardiovascular outcomes [RR and 95% CI: 1.49 (0.98 - 2.26)] compared to comparator groups, which included both placebo and active controls.

Ipratropium Bromide

Ipratropium bromide is an anticholinergic agent that appears to inhibit vagally-mediated reflexes by antagonizing the action of acetylcholine. Atrovent HFA (®Boehringer Ingelheim) is a pressurized metered-dose aerosol unit for oral inhalation that contains a solution of IB. Atrovent HFA was approved on November of 2004 (NDA # 21-527) for maintenance treatment of bronchospasm associated with COPD.

Recently, 4 published reports raised concerns about the safety of IB. A meta-analysis of 15 randomized trials suggested a 70% increase in risk of cardiovascular events (including

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* Erratum published on JAMA 301(12), 2009 which excludes data from 2 previously published trials, leaving 15 trials in the meta-analysis.

nonfatal MI, nonfatal stroke, and cardiovascular deaths) with use of IB (95% CI: 1.19 – 2.42) [3]. Additionally, a large nested case-control study including 352,631 COPD patients who utilized the Veterans Health Administration health care services, suggested that use of IB was associated with a higher risk of all-cause and cardiovascular-related deaths; OR and 95% CI were 1.11 (1.08, 1.15) and 1.34 (1.22, 1.47), respectively [4]. In another large nested case-control study of 222,272 Manitoba residents, use of IB was associated with increased risk of certain cardiovascular events (CVEs) - including supraventricular tachycardia (RR and 95% CI of 1.38 (1.10, 1.72)) and cardiac heart failure (RR and 95% CI of 1.38 (1.10, 1.72)) - although no increase in risk of myocardial infarction (MI) was observed (RR and 95% CI of 1.00 (0.85, 1.18)) [5]. Finally, a recent large cohort study suggested that anticholinergics (particularly IB) may increase risk of CVEs (RR and 95% CI of 1.29 (1.21, 1.38)) [6].

Division of Epidemiology (DEPI) Review Plan (DRP)

The Division of Epidemiology (CDER/OSE/DEPI) was consulted to review the studies/reports that recently raised concerns about the safety of inhaled anticholinergics in the management of COPD. DEPI undertook a comprehensive literature search to review the epidemiologic data concerning the association between TB/IB and various safety endpoints, including cardiac, vascular, and mortality outcomes.

The majority of previously published studies concerning the safety of inhaled anticholinergics in the management of COPD do *not* suggest that these agents may increase the risk of cardiovascular events or death (summarized in session 2.1 of this review). However, four recent publications have raised concerns regarding the cardiovascular safety of anticholinergics. This review focuses on the critical evaluation of these recently published studies, including a meta-analysis of 15 trials by Singh et al [3] (regarding the safety of both TB and IB), two large nested case-control studies by Lee et al [4] and Macie et al [5] (concerning the safety of IB regarding higher risk of death and of certain cardiovascular outcomes, respectively), and a large cohort study by Ogale et al [6], which suggested that anticholinergics may increase risk of cardiovascular events. The main objective of this review is to assess the strength and validity of these recent findings, and to discuss possible reasons for the discrepancies between these findings and the findings of previously published epidemiologic data.

Documents and databases evaluated in this review included:

- A comprehensive review of the published scientific evidence concerning the safety of inhaled anticholinergics (TB and IB)
- Report of a meta-analysis conducted by Singh et al [3],
- Report of a nested case-control study conducted by Lee et al [4],
- Report of a nested case-control study conducted by Macie et al [5],
- Report of a cohort study conducted by Ogale et al [6],
- Analyses of drug utilization patterns for TB and IB using the following databases:
    - SDI Physician Drug and Diagnosis Audit to measure indicators for use of TB and IB

- IMS Health, IMS National Sales Perspectives to determine retail and non-retail channels of distribution for TB and IB
- Wolters Kluwer Concurrent Product Analyzer to measure outpatient use of TB and IB by diagnosis code
- Wolters Kluwer SOURCE PHAST Prescription Monthly to estimate nationally projected numbers of prescriptions dispensed and unique patient counts for U.S. mail order and retail pharmacies (2005-2008)

The limitations of the meta-analysis by Singh et al [3], including a biased selection of studies, lack of information on participants who discontinued trial, and failure to use person-time data, along with the limitations of the observational studies [4-6], of which the most important refers to their inability to adjust for important risk factors for the outcomes, may explain the positive associations between anticholinergics and adverse cardiovascular events and deaths observed in these studies. Additionally, these findings do not agree with the findings of previously published meta-analyses [7-10], nor do they agree with the recent findings of a large, 4-year, randomized clinical trial [11], none of which suggest a positive association between inhaled anticholinergics and risk of serious CVEs or mortality. Therefore, the data do not provide convincing evidence to implicate use of inhaled anticholinergics in increasing risk of serious CVEs or mortality. We additionally assessed patterns of use for IB and TB between 2005 and 2008. The projected number patients (through US retail/mail order pharmacies) receiving IB prescriptions for COPD decreased steadily from 2005 to 2008 (p-trend=0.004), whereas for TB, the projected number of patients (through US retail/mail order pharmacies) receiving TB prescriptions for COPD has increased steadily from 2005 to 2008 (p-trend=0.05).

2 REVIEWER'S COMMENTS

2.1 LITERATURE REVIEW

A comprehensive literature search (in MEDLINE via PubMed, Embase, and Web of Science) was conducted to review the epidemiologic evidence concerning the association between TB / IB and various safety endpoints, including cardiac, vascular, and mortality outcomes. This review is summarized by to safety endpoint.

2.1.1 Anticholinergics and risk of stroke

In November of 2007, the sponsor submitted preliminary results of a routine pooled safety pooled analysis of 29 clinical trials with Spiriva HandiHaler (n=25 trials) and Respimat (n=4 trials). In this analysis, the sponsor noted an increase in risk of stroke in patients treated with tiotropium *vs.* placebo, RR and 95% CI of 1.37 (0.73, 1.56) (unpublished report). While this analysis did not adjust for multiplicity and the association with stroke was not statistically significant, consistently with the Agency's commitment to inform the public about ongoing safety reviews, the Agency released an Early Communication on March of 2008 describing preliminary information regarding Spiriva and potential risk of stroke [12].

Recently, a large, multi-center (470 sites), multinational (37 countries) 4-year randomized, placebo-controlled double-blind trial with Spiriva HandiHaler (Understanding Potential Long-term Impacts of Function with Tiotropium - *UPLIFT*) was completed [11]. UPLIFT was conducted to assess the long-term efficacy of TB, and included 5,993 patients, males and females aged at least 40 years, who had moderate to severe COPD and a smoking history of at least 10 pack-years. Patients were randomized 1:1 to receive either 18 μg of TB or placebo once daily. In both arms, patients were allowed to take other respiratory medications, with the exception of inhaled anticholinergics. Data on vital status were systematically requested for patients who prematurely discontinued study participation 4 years after initiation of study drug. Vital status information was known for 98 and 97% of patients in the TB and placebo arms, respectively. Reports of serious and fatal adverse events were collected while patients were receiving a study drug (including the last day plus 30 days). There was no difference in the rates of stroke between the TB and the placebo groups; the RR (95% CI) was 0.95 (0.70, 1.29).

In September of 2008, BI submitted to the Agency preliminary results of a pooled analysis of 30 placebo-controlled, double blind randomized clinical trials (RCT) that also included data from UPLIFT (unpublished report). This meta-analysis, which included 19,545 patients (10,846 on TB and 8,699 on the placebo arm) also indicated similar stroke incidence in the TB vs. placebo groups. These results were consistent with the results of the only currently published meta-analysis that examined the relation between anticholinergic and stroke risk [3], discussed in greater detail in session 2.2 of this report.

To our knowledge, there are no published observational studies that examined the relation between use of TB in the management of COPD and risk of stroke. One relatively large nested-case control in the Manitoba Population Health Research Repository reported that COPD patients who had a stroke were slightly more likely to have used IB in the year preceding the date of the event compared to COPD controls – a finding of borderline statistical significance [5]. The main limitation of this study (discussed in greater detail in session 2.4) was its inability to account for important risk factors of the outcomes, including COPD severity, smoking, BMI, and cardiac co-morbidities (beyond use of cardiac medications). Confounding by these factors may have introduced a spurious association between IB and cardiovascular events. These studies are summarized in table 1.

Table 1: Anticholinergics and risk of **stroke**

Ref	Design	Size	Exp	Main Results	Comments
Kesten et al 2008, *unpublished*	meta-analysis of RCTs	30 placebo-controlled RCTs; n=19,545 patients	TB	RR: 1.03 (0.79, 1.35)	Included short and long-term BI-sponsored trials. **UPLIFT alone 0.95 (0.70, 1.29)** [11]
Singh et al [3]	meta-analysis of RCTs	17 RCTs; n=13,645 patients	TB and IB	RR: 1.46 (0.81, 2.62)	10 TB RCTs, 5 IB RCTs. Placebo + active control

					trials.
Macie et al [5]	nested case-control	4961 stroke cases/49,487 controls	IB	RR: 1.13 (1.00, 1.27)	No adjustment for important confounders

* **TB**: tiotropium bromide **IB**: ipratropium bromide

2.1.2 Anticholinergics and risk of cardiovascular events

A recently published meta-analysis by Singh et al [3] suggested that use of TB and IB is associated with increased rates of cardiovascular events (measured as a composite of nonfatal MI, nonfatal stroke, and cardiovascular death) (reviewed in detail in session 2.2 of this report). These findings do not agree with the results of two previously published meta-analyses [7,8] and of one unpublished pooled analysis that included results from UPLIFT [11].

A meta-analysis including 9 trials (n=8002 COPD patients) of long duration (≥12 weeks after randomization) suggested that use of TB was not related to increased rates of several cardiac events compared to placebo (n=6 trials), IB (n=2 trials) or salmeterol (n=1 trial) [8]. This meta-analysis minimized selection bias by employing pre-specified inclusion and exclusion criteria and a systematic search of both published and unpublished trials not limited to any language. All included trials used almost identical designs regarding inclusion and exclusion criteria and included patients similar in disease severity and LABA use. Bias due to selective reporting of secondary outcomes and non-intention to treat analyses was minimized by obtaining supplemental data for most studies. Summary estimates were obtained by pooling studies of similar comparator agents (*e.g.* TB vs. placebo, TB *vs.* IB, and TB *vs.* salmeterol).

Another meta-analysis of 19 randomized, double-bind, placebo-controlled clinical trials of tiotoprium 18 μg daily (delivered via HandiHaler), including a total of 7,819 patients and 3,821 person-years, suggested similar rates of cardiovascular events between tiotropium and placebo groups [7]. All trials were sponsored by Boehringer Ingelheim (BI) and had similar protocols; most included patients with COPD although a limited number of trials included asthma patients. All reported safety information was collected in identical manner in the trials and the entire safety database with complete information was available for analysis, minimizing selection bias due to selective reporting of adverse events. Use of person-time analysis accounted for duration of exposure.

Finally, preliminary results of a report submitted by BI on Sept of 2008, which combined the results of 30 placebo-controlled randomized clinical trials, including results from UPLIFT, suggested similar rates of cardiac and vascular events between tiotropium bromide and placebo groups (unpublished report). All included trials had similar protocols. All reported safety information was collected in identical manner in the trials and the entire safety database with complete information was available for analysis, minimizing selection bias due to selective reporting of adverse events.

Observational data on inhaled anticholinergics and risk of cardiovascular events are scant. In a cohort study including 2862 COPD patients (470 person-years of exposure to TB and 746 person years of exposure to single-ingredient long-acting beta-agonists (LABA)) enrolled in U.K. THIN (The Health Information Network) primary care practices, no differences in cardiovascular outcomes were observed between patients taking TB against those taking LABA [14]. A recent nested case-control study [5], IB was associated with increased risk of supra-ventricular tachycardia (SVT) and heart failure (HF), but confounding may explain their findings (discussed in session 2.4 of this report). Finally, a recent cohort study [6] suggested that anticholinergics may increase risk of CVEs, but confounding may also explain these findings (discussed in greater detail in session 2.5 of this report). The main findings of these studies are summarized in table 2. Evidence for the association between cardiovascular-related mortality and anticholinergics is discussed in session 2.1.3.

Table 2: Anticholinergics and risk of **cardiovascular events**

Ref	Design	Size	Exp	Main Results	Comments
Singh et al [3]	meta-analysis of RCTs	17 RCTs; 13,645 patients	TB and IB	RR of MI: 1.52 (1.04, 2.22) and CV death: 1.92 (1.23, 3.00)	12 TB RCTs, 5 IB RCTs. Placebo + active control trials.
Kesten et al [7]	meta-analysis	19 placebo-controlled RCTs, 7,819 patients	TB	RR of various CV events compatible with 1.0; eg, RR and 95%CI of fatal CV events: 0.57 (0.26,1.26)	BI sponsored trials, complete follow-up info
Barr et al [8]	meta-analysis	9 placebo-controlled RCTs, 8002 patients	TB	RR of various CV events compatible with 1.0; eg, RR and 95%CI of MI: 1.0(0.2, 3.9) and of CHF: 0.8 (0.4, 1.6)	All trials ≥12 weeks, 6 placebo-controlled trials
Kesten et al, 2008 *unpublished*	meta-analysis	30 placebo-controlled RCTs; 19,545 patients	TB	RR of cardiac events: 0.91 (0.83, 1.01) and vascular events: 0.97 (0.87, 1.08)	Included short and long-term BI sponsored trials. **UPLIFT alone RR of CV: 0.84 (0.73, 0.98)**
Macie et al [5]	nested case-control	11,316 cases (SVT, MI, HF)/112,920 controls	IB	RR of MI: 1.00 (0.85, 1.18), SVT: 1.38 (1.10, 1.72) and CHF: 1.47 (1.31, 1.64)	No adjustment for potentially important confounders
Jara et al [14]	cohort	1061 TB, 1801 LABA	TB vs. LABA	RR of CV events compatible with 1.0; eg, RR and	Problems with definition study time

				95% CI of MI: 1.29 (0.45,3.66) and of CHF: 0.65(0.37,1.12)	
Ogale et al [6]	Cohort	82,717 newly diagnosed COPD patients	IB, TB	RR of CVEs: 1.29 (1.21, 1.38)	Lack of adjustment for important risk factors

* **TB**: tiotropium bromide **IB**: ipratropium bromide; LABA: long-acting beta-agonist

2.1.3 Anticholinergics and mortality risk

A meta-analysis conducted by Singh et al [3] suggested increased rates of all-cause and cardiovascular-related mortality in anticholinergic *vs.* comparators (which included active control/placebo). These findings do not agree with the findings of four previously published meta-analyses [7-10] and of one recently published pooled analysis by BI which included UPLIFT (unpublished report).

A meta-analysis including 9 trials (n=8002 COPD patients) of long duration (≥12 weeks) suggested that use of TB was not related to increased mortality compared to placebo (n=6 trials), IB (n=2 trials) or salmeterol (n=1 trial) [8]. This meta-analysis minimized selection bias by employing pre-specified inclusion and exclusion criteria and a systematic search of both published and unpublished trials not limited to any language. All included trials were of high quality, used almost identical designs regarding inclusion and exclusion criteria, and included patients similar in disease severity and LABA use. Bias due to selective reporting of secondary outcomes and non-intention to treat analyses was minimized by obtaining supplemental data for most studies.

Another meta-analysis of 19 randomized, double-bind, placebo-controlled clinical trials of TB 18 μg daily (delivered via HandiHaler), including a total of 7,819 patients and 3,821 person-years, also failed to suggest an association between TB and risk of premature death (including all-cause, cardiovascular, or respiratory mortality) or serious cardiovascular outcomes [7]. All trials were sponsored by BI and had similar protocols; most included patients with COPD although a limited number of trials included asthma patients. All reported safety information was collected in identical manner in the trials and the entire safety database with complete information was available for analysis, minimizing selection bias due to selective reporting of adverse events. Use of person-time analysis accounted for duration of exposure.

Salpeter and colleagues [9] published a meta-analysis of 7 placebo-controlled trials of inhaled anticholinergic agents in COPD (n=5,622 participants) which suggested a 70% decreased rates of respiratory deaths in the anticholinergics compared to placebo arms, and similar rates of all-cause deaths between anticholinergics and placebo arms. Pooled analysis of 3 randomized trials (n=1,659 participants) comparing anticholinergics vs. beta-agonists in COPD suggested a non-significant 90% decreased risk in respiratory death and 80% lower risk in all-cause mortality among those taking anticholinergics

compared to those taking beta-agonists. In this meta-analysis, systematic literature search was conducted only through published studies; therefore, publication bias cannot be ruled out. Additionally, it is unclear whether information on the outcomes of interest was obtained for those who dropped out of the study so that selection bias may have influenced their results.

A pooled analysis of 9 randomized clinical trials showed similar all-cause mortality rates in anticholinergic vs. placebo groups. This analysis included long-term trials (≥12 weeks) of COPD patients. Systematic literature search was conducted only through studies published in the English language; therefore, publication bias may have influenced their findings. Additionally, selection bias cannot be ruled out as information on withdrawal and follow-up was not available for some of the studies. Mortality was not the primary outcome in any of the included trials [10].

Finally, preliminary results of a report submitted by BI on Sept of 2008 (unpublished report), which combined the results of 30 placebo-controlled randomized clinical trials, including results from UPLIFT [11], suggested slightly lower mortality rates in the TB compared to placebo participants. All included trials had similar protocols. All reported safety information was collected in identical manner in the trials and the entire safety database with complete information was available for analysis, minimizing selection bias due to selective reporting of adverse events. Use of person-time analysis accounted for duration of exposure. The results of UPLIFT alone suggested a non-statistically significant decrease in mortality rates favoring the TB arm. The RR (95% CI) for all deaths was 0.89 (0.79, 1.02).

The observational data also did not provide evidence of an association between use of TB and increased risk of death. A population-based cohort study including 10,603 residents of Denmark who were of at least 40 years of age and who had been hospitalized for COPD suggested no differences in incidence of death between those who were and those who were not prescribed TB [15]. Two cohort studies compared mortality rates between TB and LABA users; one reported similar rates [14] while another suggested a modest decrease in mortality rates favoring TB users [16]. The observational data for IB and mortality are less consistent. A nested case-control study suggested that use of IB is associated with a higher risk of all-cause and cardiovascular-related deaths [4], but confounding by extraneous factors may explain the modest increase in risk (discussed in greater detail in session 2.3 of this report) . A small cohort study suggested a 60% statistically significant increased risk of all-cause mortality with use of IB [17]. However, this association was largely driven by COPD and lung cancer-related deaths, and confounding by disease severity may explain this increase in risk. No association between IB use and all-cause mortality was observed in a larger cohort study [18]. The main findings of these studies are summarized in table 3.

Table 3: Anticholinergics and risk of **death**

Ref	Design	Size	Exp	Main Results	Comments

Singh et al [3]	meta-analysis	17 RCTs; 13,645 patients	TB and IB	RR of all-cause: 1.29 (1.00, 1.65)	12 TB RCTs, 5 IB RCTs. Placebo + active control trials.
Kesten et al, 2008 *unpublished*	meta-analysis	30 placebo-controlled RCTs ; 19,545 patients	TB	RR of all-cause: 0.88 (0.77, 1.00)	Included short and long-term BI sponsored trials. **UPLIFT alone : 0.86 (0.75, 0.99)**
Kesten et al [7]	meta-analysis	19 placebo-controlled RCTs, 7,819 patients	TB	RR of all-cause: 0.76 (0.50, 1.16)	BI sponsored trials, complete follow-up info
Barr et al [8]	meta-analysis	9 RCTs, 8002 patients	TB	RR of all-cause: 0.91 (0.58, 1.42)	All trials ≥12 weeks, 6 placebo-controlled trials
Salpeter et al [9]	meta-analysis	7 placebo-controlled RCTs, 9580 patients	TB and IB	RR of all-cause death: 0.80 (0.5, 1.2)	RR of resp death: 0.3 (0.1, 0.8)
Wilt et al [10]	meta-analysis	9 RCTs	TB and IB	TB all cause 0.94 (0.60, 1.47), IB all-cause: 1.20 (0.81, 1.78)	5 placebo-controlled trials, IB trials fairly small
Lee et al [4]	nested case-control	32,130 cases and 320,501 participants	IB *vs.* short act beta-agonist	all cause: 1.11 (1.08, 1.15), CV deaths 1.34 (1.22, 1.47)	no adjustment for COPD severity or smoking
Sin and Tu [18]	retrosp cohort	25,804 discharged COPD patients	IB	all-cause: 1.03 (0.98, 1.08)	population-based study, adj for multiple factors including disease severity
Ringbaek and Viskum [17]	retrosp cohort	827 COPD patients	IB	all-cause: 1.6 (1.2, 2.1)	association driven by COPD- and lung cancer-related deaths – No assoc with CVD-related deaths
De Luise et al [15]	retrosp cohort	10,603 COPD participants	TB	all cause: 0.77 (0.65, 0.91), deaths r/t cardiac endpoints compatible with 1.	population-based study. Adj for markers of disease severity
Jara et al [14]	cohort	1061 TB, 1801 LABA	TB vs. LABA	all cause: 0.93 (0.59, 1.44)	Problems with definition study time
Gershon et al [16]	retrosp cohort	7,218 COPD participants	TB vs. LABA	all cause: 0.80 (0.70, 0.93)	population-based study, adj for markers of disease severity

* **TB**: tiotropium bromide **IB**: ipratropium bromide; LABA: long-acting beta-agonist

2.1.4 Summary of literature search and DEPI review plan

The preponderance of data concerning the safety of TB and IB in the management of COPD did not suggest that either agent may increase risk of cardiovascular events or death. However, four recent publications have raised concerns regarding the safety of anticholinergics [3-6]. This review focuses on the critical evaluation of these published studies, and to discuss possible reasons for the discrepancies between their findings and the findings of previously published studies.

2.2 SINGH S, LOKE YK, FURBERG CK. INHALED ANTICHOLINERGICS AND RISK OF MAJOR ADVERSE CARDIOVASCULAR EVENTS IN PATIENTS WITH COPD – A SYSTEMATIC REVIEW AND META-ANALYSIS. JAMA 2008; 300: 1439-1450. [3]

2.2.1 Summary of Study

To examine the association between inhaled anticholinergics (TB and IB) and risk of cardiovascular outcomes, a systematic review and meta-analysis of randomized clinical trials was conducted. Two investigators - independently and in duplicate - conducted systematic literature searches of relevant randomized clinical trials of inhaled anticholinergics in patients with COPD published in English language in MEDLINE (through PubMed), the Cochrane Database of systematic reviews, regulatory authority Web sites in the United States and the United Kingdom, and manufacturers' trial registries with no date restrictions. Disagreements between these two investigators regarding relevance of articles were resolved by a third reviewer through a consensus process. The inclusion criteria for trials were (i) randomized clinical trial (RCT) with more than 30 days of follow-up, (ii) including patients with COPD of any severity, (iii) having an inhaled anticholinergic as the intervention vs. control group (active or placebo), and (iv) *reporting data* on the incidence of serious cardiovascular adverse events, including MI, stroke, or cardiovascular death.

The primary outcome measure was specified *a priori* as a composite of nonfatal MI, nonfatal stroke (including transient ischemic attack), and cardiovascular death (including sudden death). The secondary outcome measure was specified as all-cause mortality. Two reviewers independently and separately extracted data on MI, stroke, cardiovascular death, and all-cause mortality among trial reporting of serious adverse events. A third reviewer adjudicated in the event of discrepancy between the two reviewers.

Pooled relative risks (RR) and 95% confidence intervals (CI) for the outcomes were estimated using fixed-effect models when substantial statistical heterogeneity across studies was not present. Statistical heterogeneity was assessed using the I^2 statistic [19]. The Rosenberg method [20] was used to assess the impact of unpublished studies in the pooled analysis. The number needed to harm (NNT) – or the number of patients with COPD who need to be treated with inhaled anticholinergics vs. comparators for one additional case of cardiovascular event – was estimated by applying the RR and estimates in a large population–based study.

A total of 703 potentially relevant citations were identified, of which 103 (n=66 tiotropium bromide, n=37 ipratropium bromide) were considered for inclusion. Of these, 86 were excluded because these were not randomized trials of anticholinergics with greater than 30 days of follow-up (n=15), did not report cardiovascular adverse events (n=69), or had no events in both study groups (n=2), leaving 17 studies (n=12 tiotropium bromide, n=5 ipratropium bromide) for the pooled analysis. Two of these studies were later excluded due to double counting of trials [21]. The trials included a total of 13,645 participants, 6,984 receiving anticholinergics and 6,661 receiving active control or placebo. Eight trials evaluated inhaled anticholinergics vs. placebo while the remaining trials evaluated anticholinergics vs. active comparators, including salmeterol, a combination of salmeterol and fluticasone, or albuterol. Of the included trials, 5 studies were of duration longer than 48 weeks (range 48 weeks to 5 years). Although trial quality was assessed, it is not clear whether and how this information was used in the pooled analysis.

Inhaled anticholinergics were found to significantly increase the risk of cardiovascular outcomes, the RR and 95% CI for anticholinergics vs. active control/placebo were 1.60 (1.22, 2.10). Among the individual components of the cardiovascular outcomes, anticholinergics increased risk of MI (RR and 95% CI for anticholinergics vs. active control/placebo in 13 trials were 1.52 (1.04, 2.22) and cardiovascular deaths; the RR and 95% CI for anticholinergics vs. vs. active control/placebo in 12 trials was 1.92 (1.23, 3.00). Anticholinergics were not significantly associated with risk of stroke; the RR and 95% CI for anticholinergics vs. vs. active control/placebo in 7 trials were 1.46 (0.81, 2.62). Tests for heterogeneity by study were not significant for primary endpoints. Anticholinergics were not associated with a significant increase in all-cause mortality (secondary outcome), the RR and 95% CI for anticholinergics vs. vs. active control/placebo in 15 trials were 1.29 (1.00, 1.65). Analyses based on random-effect models yielded results similar in magnitude and direction.

The NNH was also estimated assuming a baseline MI event rate of 10.9/1000 person-years and a baseline cardiovascular mortality event rate of 31.9/1000 person-years. The NNH for MI and cardiovascular death with inhaled anticholinergics was 174 per year (75 - 1835 per year) and 40 per year (18 – 185 per year).

Finally, the fail-safe number was estimated to assess the impact of unpublished studies in the pooled results. Sixteen non-significant long-term trials, each with a sample size of 1450, would be required to reverse the increase in risk of cardiovascular outcomes observed in the 5 long-term trials.

2.2.2 OSE Comments on Study Objectives

None

2.2.3 OSE Comments on Study Design

In the study by Singh et al, the differences/heterogeneity across the individual trials makes the summary estimates difficult to interpret, despite non-significant statistical tests

for heterogeneity. Because tests for heterogeneity are customarily limited in statistical power, it is essential that investigators additionally use expert judgment to determine when and whether summary estimates are appropriate. There are several potentially important differences in the trials included in the meta-analysis by Singh et al. First, the included trials utilize different comparator groups; it is unclear whether estimates of studies comparing anticholinergic vs. placebo are comparable to estimates of studies comparing anticholinergics vs. active drugs (e.g. salmeterol, ipratropium). Further, the length of follow-up varies substantially across studies (6 weeks to 5 years). Because risk of cardiovascular outcome/mortality may differ according to length of drug exposure, pooling of studies of varying duration of follow up is not advisable. Finally, while TB and IB belong to the same class and may share many of the same side effects, the short- versus long-acting nature of the drugs can have significant implications for systemic effects such as cardiovascular events. Therefore, pooled estimates for TB and IB are difficult to interpret.

2.2.4 OSE Comments on Informed Consent (if any)

None

2.2.5 OSE Comments on Data Sources

Literature search was conducted through both published and unpublished trials independently by two reviewers (disagreements resolved by a third reviewer), which is likely to minimize the impact of publication bias and also to some extent, of selection bias. However, studies were restricted to the English language, which could have introduced publication/selection bias to the extent that 'positive' findings are more likely to be both published in English and to be included in the meta-analysis. There are also some important concerns regarding the inclusion criteria used to select studies that may have resulted in selection bias. These are discussed in session 2.2.7.

2.2.6 OSE Comments on Study Time Period(s)

Because cardiovascular risk associated with anticholinergics may vary according to length of drug exposure, the pooling of estimates across studies of long and shorter follow up may not be appropriate.

2.2.7 OSE Comments on Study Population

Arguably, the major limitation of the meta-analysis by Singh et al lies on their method of study inclusion, which was based on the availability of reported data on adverse events. Because none of the trials was designed to prospectively examine safety endpoints, trials with an imbalance of events between study arms may be both more likely both to report on adverse events and to be included in the meta-analysis. Indeed, despite the seriousness of the adverse events considered by Singh et al, 69 studies were not included due to failure to report on cardiovascular adverse events (study figure 1, appendix 1). According to the fail-safe number method by Rosenberg, inclusion of 16 negative trials with an average sample size of 1450 participants would render the results of Singh et al non-significant.

Selection bias from differential loss to follow up is also likely to have influenced the findings of Singh et al. Withdrawal/discontinuation proportions varied across the included trials (6.1 to 41.9% for those on anticholinergic arm, 6.6 to 28% among those on placebo arm and 11.0 – 35.2% among those in the active comparator arm); in most studies, the discontinuation proportions were 4.9 to 16% higher in placebo vs. anticholinergic groups (study table 2, appendix 1). Most of the included COPD randomized trials stopped patient follow-up at the time they discontinued the study drug therapy so that adverse effect information was unavailable after patients were withdrawn. This is particularly problematic in trials comparing anticholinergics against an inferior compound (e.g. placebo), as patients receiving no relief from their symptoms may be more likely to drop out of the study. Differential discontinuation rates are likely to result in a biased study population because those who decide to continue on the placebo arm may be, on average, healthier than those receiving the superior treatment. This bias is likely to introduce a spurious association between anticholinergics and the outcomes of interest.

Another important issue refers to the notable differences in the characteristics of participants included in the selected studies. Study table 1 (appendix 1) points to substantial differences in the mean age, gender distribution, mean predicted FEV_1 and smoking history across studies. These characteristics, among others such as cardiac co-morbidities and BMI, are potentially important confounders and are likely to have biased the findings by Singh et al.

Finally, one of the trials included in the meta-analysis [22] was effectively a single-blind trial, as different inhalation devices were used in the delivery of the study drug and the comparator drug (patients were randomized to comparator drug via Diskus/Accuhaler or to tiotropium bromide via Handihaler). Therefore, it may not be appropriate to include this trial in the meta-analysis. This study is the second largest included TB trial; inclusion of this trial could have biased the estimates away from the null value.

2.2.8 OSE Comments on Measurement of Exposure

Duration of study drug exposure varied across included studies (short term trials ranged from 6 to 26 weeks; long term trials ranged from 46 weeks to 5 years). Because it is likely that risk differs with length of exposure, pooled estimates of studies of long and short duration are difficult to interpret.

Also, while treatment dose is uniform across most trials (e.g. daily 18 μg of TB via Handihaler), one small study randomized participants to substantially lower doses of TB [23]. Because risk of adverse events is likely to differ with drug dosage, sensitivity analysis excluding this particular trial would be informative.

Additionally, while TB and IB belong to the same class and may share many of the same side effects, the short- versus long-acting nature of the drugs can have significant implications for systemic effects such as cardiovascular events. Therefore, pooled estimates for TB and IB are difficult to interpret.

2.2.9 OSE Comments on Disease Outcome of Interest

Most of the trials included in the meta-analysis were conducted to examine the effectiveness of anticholinergics in the management of COPD; none of the trials was prospectively designed to uniformly assess cardiovascular outcomes associated with anticholinergic use. Instead, cardiovascular outcomes were ascertained through routine serious adverse event reporting within each trial. These outcomes were not adjudicated and may not have been defined in a uniform fashion across the trials. Therefore, misclassification of outcome is a concern both for the meta-analysis as a whole, which may include different definitions of outcome, and for the individual studies included in the meta-analysis. Within each individual study, misclassification of the disease (measurement error) in the randomized, double-blind setting is likely to be non-differential, which may attenuate the associations. However, due to the seriousness of the outcomes under study, misclassification may not have played a major role in the study findings.

2.2.10 OSE Comments on Sample Size

Despite the relatively large number of participants included in this meta-analysis, the number of events in each individual trial was small, with 40% of the trials with 0 events in the placebo arm. Of note, the results of the largest study included in this meta-analysis [24] has been questioned as the increase in risk of cardiovascular events was restricted to participants who did not use IB [25].

2.2.11 OSE Comments the Analysis / Results

There are several important issues regarding the analysis of Singh et al. First, there appears to be a discrepancy in the number of serious cardiovascular events reported in the study by Wedzicha et al [22] (34 and 23 in the tiotropium and placebo groups, respectively) those included in the analysis by Singh et al (23 and 13 in the tiotropium and placebo groups). This discrepancy may have biased the association away from the null value. Additionally, there were double-counting of participants, as some studies report on the same study populations (i.e. Brusasco et al [26] reported findings already reported by Donohue et al [27]; Casaburi et al [28] reported findings already reported by Casaburi et al [29]). This issue has been recently addressed by investigators of the meta-analysis; corrected findings did not differ substantially from the previously reported results.

Moreover, the largest trial driving the association between IB and cardiovascular events is the Lung Health Study [24]. *Post-hoc* analysis of this trial questioned their results as the increase in risk was restricted to patients who failed to comply with the study drug [25].

Another issue includes the difficulty in interpreting estimates pooled across TB and IB studies. While these two compounds belong to the same class and may share many of the same side effects, the short- versus long-acting nature of the drugs can have significant implications for systemic effects such as cardiovascular events. Similarly, studies

comparing TB vs. placebo and those comparing TB vs. an active comparator are pooled together in the analysis by Singh et al. The nature and design of these two types of trials are fundamentally different, and the active controls may have side effects of their own. Therefore, these pooled estimates are difficult to interpret. Pooling estimates across trials of different duration of follow-up are also difficult to interpret.

Further, the analysis by Singh et al failed to account for person-time data. Therefore, participants who discontinued treatment early in the trial – who were both less exposed to the treatment and had less time to develop the outcomes of interest –and those who completed the study follow-up contributed equal weight to the analysis. As most included trials had higher discontinuation rates among placebo, failure to use person-time data is likely to bias the results in favor of the placebo.

Finally, the analysis by Singh et al failed to account for potentially important confounders. Populations of selected studies differed in several characteristics (including differences in age, gender distribution, predicted FEV_1, smoking history, as well as others such as BMI and cardiac co-morbidity), which is likely to have resulted in biased estimates. The fact that randomized studies were included in the meta-analysis does not mean that comparisons between trials are randomized comparisons [30]. Therefore, trial differences in the distribution of important risk factors for the outcomes of interests are likely to bias the study findings, although the direction of this bias is difficult to predict as no information regarding these potential confounders according to outcome is provided. A more appropriate approach would include analyses stratified on these risk factors (at the trial level or by considering specific strata within each trial).

2.2.12 OSE Comments on strength of evidence

The strengths of this meta-analysis include the fact that the literature search included both published and unpublished trials and that it was conducted independently by two reviewers.

Limitations of this study are also noted. These are discussed according to their ability to bias the results (i) towards the null value (i.e. attenuate the findings), (ii) away from the null value (i.e. strengthen or introduce a spurious association), or (iii) in a direction which is difficult to predict.

i. Limitations that may bias results towards the null value

Misclassification of outcome: None of the included trials was prospectively designed to examine risk of death, cardiovascular outcomes or stroke; thus, these outcomes were not adjudicated in most trials, which may have resulted in misclassification of the outcome (likely to be non-differential between the study groups). However, due to the seriousness of the outcomes under study, it is possible that misclassification did not play a major role in the study findings.

ii. Limitations that may bias results away from the null value

Potential data entry errors: There appears to be some discrepancy in the number of cases included in the meta-analysis by Singh et al. The number of serious cardiovascular events reported in the study by Wedzicha et al [22] was 34 and 23 in the tiotropium and placebo groups, respectively – and not 23 and 13 as reported by Singh et al. This discrepancy may have biased the RR away from the null value.

Inclusion criteria resulting in biased selection of studies: This is particularly important as none of the included trials was designed to evaluate risk of cardiovascular adverse events. Therefore, studies with an imbalance in the number of adverse events are both more likely to provide information on adverse events as well as to be included in the meta-analysis. It would be important to obtain information on adverse events for the studies not included in the analysis, particularly as a substantial number of studies were excluded due to failure to report on the adverse events of interest (n=69).

Lack of information for participants who discontinued the study: Most of the included COPD randomized trials stopped patient follow-up at the time they discontinued the study drug therapy so that adverse effect information was unavailable after patients were withdrawn. Because of this, an authentic intent-to-treat analysis of safety endpoints is not possible for these trials. The discontinuation rates vary in each of the COPD trials, and these drop outs tend to occur early in the trial. Analyses based on data censored at discontinuation are likely to introduce biases that are difficult to disentangle. This is particularly problematic in trials comparing anticholinergics against an inferior compound (e.g. placebo), as patients receiving no relief from their symptoms may be more likely to drop out of the study. Differential discontinuation rates are likely to result in bias in these instances because those who decide to continue on the placebo arm may be, on average, healthier than those receiving the superior treatment. Indeed, Kesten et al [31] reported that the incidence of adverse events – including deaths – tends to be higher during the discontinued period compared to the period during which participants were on the assigned study treatment. In the meta-analysis by Singh et al, withdrawal/discontinuation proportions varied across studies (6.1 to 41.9% for those on anticholinergic arm, 6.6 to 28% among those on placebo arm and 11.0 – 35.2% among those in the active comparator arm); in most studies, the discontinuation proportions were 4.9 to 16% higher in placebo vs. anticholinergic groups. It would be informative to compare the baseline distribution of risk factors for cardiovascular outcomes (e.g. smoking, diabetes, hypertention, use of cardioprotective agents) for those who withdrew vs. those who remained in each of the study arms; however, most trials lacked this information.

Failure to account for person-time data: Therefore, participants who discontinued treatment early in the trial – who were both less exposed to the treatment and had less time to develop the outcomes of interest –and those who completed the study follow-up contributed equal weight to the analysis. As most included trials had higher discontinuation rates among placebo, failure to use person-time data is likely to bias the results in favor of the placebo.

Inclusion of single-blind trial: One of the trials included in the meta-analysis [22] was effectively a single-blind trial due to differences in the inhalation device for the delivery of the study drug vs. comparator drug (patients were randomized to comparator drug via Diskus/Accuhaler or to tiotropium bromide via Handihaler). Therefore, inclusion of this trial in the meta-analysis may not be appropriate. As this is the second largest study on tiotropium (n=1323, RR=1.75); inclusion of this trial could have biased the estimates away from the null value.

Inclusion of trial with different exposure dose: Also, while treatment dose is uniform across most trials (e.g. daily 18 ug of tiotropium via Handihaler), one study randomized participants to substantially smaller doses of tiotropium [23]. This was a small trial that suggested a non- significant increase in risk of cardiovascular events with tiotropium.

Inclusion of trial with anomaly in results: The largest trial driving the association between ipratropium and cardiovascular events is the Lung Health Study [24]. Post hoc analysis of this trial questioned their results as the increase in risk was restricted to patients who failed to comply with the study drug [25].

iii. Limitations that may bias results either away or towards the null value

Combining data for TB and IB trials: While these two compounds belong to the same class and may share many of the same side effects, the short- vs. long-acting nature of the drugs can have significant implications for systemic effects such as cardiovascular events. Therefore, pooled estimates for TB and IB are difficult to interpret.

Combining data from placebo and active controlled trials: The nature and design of these two types of trials are fundamentally different, and the active controls may have side effects of their own. Estimates pooled across studies that compared study drugs vs. placebo and those comparing study drug vs. active comparator are difficult to interpret.

Failure to account for potential confounders: Populations of selected studies differed in several characteristics (including differences in age, gender distribution, predicted FEV_1, smoking history, as well as others such as BMI and cardiac co-morbidity), which is likely to have resulted in biased estimates. Therefore, trial differences in the distribution of important risk factors for the outcomes of interests are likely to bias the study findings, although the direction of this bias is difficult to predict as no information regarding these potential confounders according to outcome is provided. A more appropriate approach would include analyses stratified on these risk factors (at the trial level or by considering specific strata within each trial).

Considering the limitations of this meta-analysis, the study of Singh et al is not particularly helpful in determining the potential cardiovascular risks associated with inhaled anticholinergics used in the management of COPD. All previously published meta-analyses of randomized trials failed to show an increase in cardiovascular events with the use of anticholinergics [7,8]. Moreover, the results of UPLIFT [11], a large 4-year randomized clinical trial, do not replicate the findings of Singh et al. Unlike in most

trials included in Singh et al, vital status were systematically requested for patients who prematurely discontinued participation in UPLIFT 4 years after initiation of study drug. Also, the use person time data may more appropriately have accounted for patients who discontinued the trial prematurely. Finally, the size of UPLIFT (n=5993) is comparable with that of Singh et al (n=7084 across TB trials).

2.3 LEE TA, PICKARD AS, AU DH, BARTLE B, AND WEISS KB. RISK FOR DEATH ASSOCIATED WITH MEDICATIONS FOR RECENTLY DIAGNOSED COPD. ANN OF INT MED 2008; 149: 380-391 [4]

2.3.1 Summary of Study

This is a report of a case-control study nested within the U.S. Veterans Health Administration health care system to examine the relation between respiratory medications and risk of death (all-cause, respiratory, cardiovascular). The full cohort comprised of patients newly diagnosed with COPD, who were at least 45 years of age, used the Veterans Health Administration health care services for at least 1 year prior to their COPD diagnosis, and had received respiratory medications. Cases were identified from all deaths occurring during follow-up (10/1999 – Sept 2003) using the Veterans Affair Vital Status database. Cause of death was ascertained through the National Health Index Plus (National Center for Health Statistics) for a random sample of 40% of the death cases. Four groups of case patients were defined, including respiratory, cardiovascular, respiratory or cardiovascular and all-cause deaths. Control participants were randomly selected at an approximately 10:1 ratio among eligible participants who were alive at the time of the case diagnosis. Controls were matched to case patients individually on sex, age (45-54, 55-64, 65-75, 75-84, and ≥84 years categories), and year of diagnosis. This study was approved by the Hines Veterans Affairs Hospital, Hines, Illinois Institutional Review Board.

Exposure was defined according to medication prescribed 180 days preceding each participant's index date (National Veterans Affairs pharmacy database). Any exposure to corticosteroid, IB, long-acting beta-agonists, theophylline, and short acting beta-agonists 180 days prior to index date was identified as primary exposure to study drug. Mutually exclusive medication regimens were also created by investigators based on medication exposure (note: it is *not* clear how this was operationalized).

Covariates identified during the year preceding diagnosis until the index date were considered for the analysis. These variables included medication use (e.g. systemic steroids, anti-hypertensives, lipid lowering medications, anti-arrhythmics, and diabetes medications), co-morbid conditions, number of hospitalizations, number of COPD exacerbations, and number of outpatient physician visits. Information on COPD severity and smoking were not available for the analysis.

Conditional logistic regression models were used to estimate odds ratios and 95% confidence intervals separately for respiratory-specific, cardiovascular-specific, and all-cause mortality. Adjusted OR represent the risk of events for patients receiving medication compared to those who had not received inhaled corticosteroids, IB, long-

acting beta-agonists, or theophylline in the previous 6 months. Several sensitivity analyses were conducted, included restricting the comparison group to patients who were actively treated with a short-acting beta-agonist, (ii) restricting analyses to patients 65 or older (who are less likely to use health services outside of the VA system), (iii) excluding patients who received a combination of IB and short-acting beta-agonists in a single inhaler, and (iv) matching on history of chronic heart failure. Additionally, (v) dose-response was examined by classifying exposure in quartiles of average daily dose usage. Moreover, investigators used an array approach to estimate the effect of unmeasured confounding.

A total of 145,020 patients were identified, of whom 32,130 died. Cause of death was determined for 11,897 of these patients; of whom 2405 died from respiratory-related deaths and 3,159 died from cardiovascular-related deaths. Compared to matched controls, participants who died of cardiovascular-related deaths had higher rates of cardiovascular conditions, including hypertension, ischemic heart disease, diabetes and chronic heart failure.

In multivariable analysis, inhaled corticosteroids and long-acting beta-agonists were with moderate decreases in risk of all-cause mortality, corticosteroids were also associated with lower risk of respiratory and cardiovascular-related deaths. Ipratropium was associated with a moderate increase in risk of death (all-cause mortality, respiratory and cardiovascular-related deaths). Theophilline was associated with increased rates of respiratory-related deaths.

There was evidence of a dose-response relationship with increased dose of medications, but specific results are not available in the manuscript. Sensitivity analysis using external information on disease severity and smoking attenuated with ORs for IB and mortality from 1.15 to 1.02 and from 1.15 to 1.08, respectively (no information on confidence interval was given).

2.3.2 OSE Comments on Study Objectives

None

2.3.3 OSE Comments on Study Design

None

2.3.4 OSE Comments on Informed Consent (if any)

None

2.3.5 OSE Comments on Data Sources

A limitation of the National Veterans Affairs databases is that they do not capture outpatient care provided to veterans outside of the Veterans Affairs health system – which may include the private sector. However, this may have been in part remedied by supplementing the study with information from the Centers for Medicare and Medicaid Services and by sensitivity analysis restricted to participants who were 65 years or older.

Another important limitation of this data source is the fact that they lack important clinical details that cannot be determined from ICD coding. Some important information not available includes smoking history, BMI, and severity of COPD (e.g. GOLD). All these are important risk factors for mortality and potentially important confounders of the association between respiratory medications and mortality.

2.3.6 OSE Comments on Study Time Period(s)

None

2.3.7 OSE Comments on Study Population

There are notable differences between cases and controls which may indicate differences in disease severity among study groups. Respiratory death cases were less likely than controls to have co-morbid conditions including hypertension, ischemic heart disease, and cancer, although they were more likely to have chronic heart failure. Cardiovascular death cases were more likely than controls to have co-morbid conditions and to use medications including cardiac medications, diuretics, hypoglycemic agents, and non-steroidal anti-inflammatory drugs. All cases (respiratory, cardiovascular, and all cause deaths) had substantially higher number of overall and recent (in the previous 6 months) COPD exacerbations and were more likely to be hospitalized compared to their controls (study table 1, appendix 2). Cases were generally more likely to use respiratory medications compared to controls (study table 2, appendix 2).

Taken together, the differences may indicate more severe respiratory disease among cases compared to their matched controls. As patients on respiratory medications are more likely to have more severe disease than those who were not receiving inhaled corticosteroids, IB, long acting beta-agonists, or theophylline (comparison group), confounding by disease severity may explain, at least in part, the association between IB and mortality (although it would not explain the protective effects of ICS). Information on COPD severity (e.g. GOLD stages) was not available in this study. Adjustment for markers of disease severity is likely to result in residual confounding by disease severity.

Finally, the study population is largely composed of males. Therefore, results of this study may not be generalizable to female patients with COPD.

2.3.8 OSE Comments on Measurement of Exposure

Misclassification of exposure is likely in this study. Drug prescription was used as surrogate for drug exposure, which requires the assumption that participants used the drugs as prescribed. Additionally, exposure is defined as any exposure to the respiratory medication 180 days prior to index date. Therefore, changes in medication regimen within 6 months of index date are not captured in this study. This type of misclassification, however, is unlikely to differ between cases and controls (exposure information obtained from the National Veterans Affairs pharmacy database). Non differential misclassification may have attenuated their findings.

2.3.9 OSE Comments on Disease Outcome of Interest

Underlying cause of death was determined through the National Health Index Plus for a randomly selected sample of cases. It is not clear how adjudicated deaths correlate with cause of deaths defined in National Death Index Plus data. Determining cause of death for persons with COPD is particularly problematic as these individuals tend to have several co-morbidities. Deaths of patients with more severe COPD may be more like likely to be classified as COPD deaths. If cases were more likely to have more severe disease than controls and therefore be more likely to have their deaths classified as COPD-related deaths, this bias would have attenuated the association between IB and non-COPD mortality.

2.3.10 OSE Comments on Sample Size

Sample size was sufficient to detect moderate effects (reported by authors).

2.3.11 OSE Comments on Study Analysis / Results

This study failed to control for important risk factors of the outcomes of interest, including – but not limited to - smoking history, BMI, and COPD severity. COPD patients have an increased risk of death from cardiovascular diseases due to their smoking history and reduced lung function [32]. Patients with more severe COPD are more likely to be prescribed respiratory medications. Therefore, when unaccounted for, these factors are likely to bias the association between respiratory medications and mortality away from the null value (i.e. introducing a spurious association or artificially strengthen the association). In smoking-adjusted analysis using external data, all-cause mortality estimates were indeed attenuated from 1.15 to 1.08; COPD-severity adjusted analysis (using external data) attenuated estimates from 1.15 to 1.02 (confidence intervals were not provided; thus it is unknown whether adjusted estimates remained significant). It would be informative to present results of analyses adjusted for *both* smoking and COPD severity; these multivariate analyses would tend to further attenuate the estimates towards the null value.

2.3.12 OSE Comments on Strength of Evidence

This study has a few strengths. Its large sample size allowed for the detection of small to moderate estimates of effects. Also, its prospective nature minimized possibility of recall bias.

Limitations of this study are also noted. These are discussed according to their ability to bias the results (i) towards the null value (i.e. attenuate the findings) or (ii) away from the null value (i.e. strengthen or introduce a spurious association).

i. Limitations that may bias results towards the null value

Misclassification of exposure due to hospitalization: It is unclear whether prescriptions during hospitalizations were captured in this study. If those who died were also more likely to be hospitalized within 6 months of death, the resulting bias may attenuate the association between respiratory drug use and risk of death.

Misclassification of exposure due to switching of drug: Exposure is defined as any exposure to the respiratory medication 180 days prior to index date. Therefore, changes in medication regimen within 6 months of index date are not captured in this study. This type of misclassification may bias the estimates, but the direction of the resulting bias is difficult to predict as several different exposures are being considered in this study.

Misclassification of outcome: Cause of death, which was not adjudicated in this study, tends to be problematic particularly for COPD patients, who generally have co-morbidities. Deaths of patients with more severe COPD may be more likely to be classified as COPD deaths. Cases prescribed IB may both tend to have more severe COPD than controls as well as to be more likely to have their deaths classified as COPD deaths, therefore attenuating the association between IB use and non-COPD related deaths. This misclassification may also explain why theophylline, known to have cardiac side effects, was associated with increased respiratory mortality but not with cardiovascular mortality, as theophylline users may tend to have more severe COPD.

ii. Limitations that may bias results away from the null value

Failure to account for important potential confounders: The most important limitation of this study includes failure to control for important risk factors of the outcomes of interest, including – but not limited to - smoking history, BMI, and COPD severity. COPD patients have an increased risk of death from cardiovascular diseases due to their smoking history and reduced lung function (Sin and Mann 2003; Sin eta al 2005). Indeed, baseline differences point to greater disease severity among cases compared to controls. Additionally, patients with more severe COPD are more likely to be prescribed respiratory medications. Therefore, when unaccounted for, these factors are likely to bias the association between respiratory medications and mortality away from the null value (*i.e.* introducing a spurious association or artificially strengthen the association). In smoking-adjusted sensitivity analysis (using external data), all-cause mortality estimates were indeed attenuated from 1.15 to 1.08. Sensitivity analyses adjusting for COPD severity based on information from NHANES (National Health and Nutrition Examination Surveys) also attenuated ipratropium estimates from 1.15 to 1.02. It would be informative to present results of analyses adjusted for *both* smoking and COPD severity (using information on these from external populations), likely to further attenuate the estimates towards the null value.

Therefore, despite its large size, the study by Lee et al may not be particularly helpful in determining risk of mortality associated with use of IB bromide due to its limitations. The most important limitation included the inability to properly account for important risk factors of the outcome including COPD severity and smoking. Sensitivity analyses adjusting for these factors using external data suggest substantial attenuation of the association between IB and mortality risk. Therefore, confounding by these factors is likely to explain the small increase in mortality risk associated with IB use.

2.4 MACIE C, WOOLDRAGE K, MANFREDA J, ANTHONISEN N. CARDIOVASCULAR MORBIDITY AND THE USE OF INHALED BRONCHODILATORS. INT J OF COPD 2008; 1: 163-169 [5]

2.4.1 Summary of Study

This is a case-control study nested within a cohort comprised of all permanent residents of the Province of Manitoba, 35 years or older, who had a physician visit between January of 1996 and December of 2000 for bronchitis, COPD, or asthma. The Manitoba Population Health Research Repository integrates anonymous records of all inpatient and outpatient physician contacts, vital statistics, and prescription records. Physicians are remunerated on basis of claims for payment describing services provided and diagnosis. The Drug Programs Information Network (DPIN) database is created by provincial retail pharmacies entering prescriptions in real time.
This study was approved by the Ethics Board of University of Manitoba and the health Information Privacy Committee of Manitoba Health.

Cases were those with a hospitalization for selected cardiovascular events (CVEs). CVEs included supra-ventricular tachycardia (ICD-9 427.0, 427.31, 427.32, 427.61), myocardial infarction (ICD-9 410), heart failure (CID-9 428), and stroke (ICD-9 430-438). Controls were selected among those who did not have a hospitalization for a CVE before or at the index date of the case. Controls were matched to cases on sex, age, and duration of insurance coverage.

Exposure to respiratory drug was defined according to receipt of a beta-agonist, ipratropium bromide, or inhaled steroids 60 or 365 days prior to index date (those exposed within 365 days included those exposed within 60 days). Three groups of respiratory medications were examined, including inhaled beta agonists (BA), inhaled ipratropium bromide (IB), and inhaled corticosteroids (ICS).

Conditional logistic regression was used to obtain odds ratios and 95% confidence intervals. Multivariate models considered use of other respiratory drugs, respiratory diagnostic group, number of physician visits for respiratory diagnoses, non-cardiac co-morbidities and cardiac drugs. Non-cardiac co-morbidities included diabetes, renal failure, liver disease, peptic ulcer, malignancy, collagen vascular disease, and dementia. Cardiac drugs included anti-arrhythmics, nitrates, furosemide, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, other anti-hypertensives and cholesterol lowering agents.

A total of 222,272 Manitoba residents with a respiratory diagnosis were identified within the 5 years ending on December 2000. A total of 2,054 cases of SVT were indentified and matched to 20,501 controls on sex, age, and duration of insurance coverage. Similarly, 3,855 cases of MI, 5,407 cases of CHF, and 4,961 cases of stroke were identified and matched to 38,490; 53,929; and 49487 controls on sex, age, and duration of insurance coverage, respectively.

Compared to controls, cases were substantially more likely to take cardiac medications, suggesting that cases were more likely to have cardiovascular co-morbidities at index date. Use of IB 60 days prior to index date was associated with a 38% increase in risk of SVT and with a 47% increase in risk of CHF. Use of IB one year prior to index date was associated with a 27% increase in risk of SVT, a 55% increase in risk of cardiac heart failure, and with a borderline significant increase in risk of stroke of 13%. IB was unassociated with risk of MI. Other respiratory medications were also analyzed in this study, including beta agonists and corticosteroids. Beta agonists were also associated with increased risk of SVT, CHF, and stroke. Inhaled corticosteroids were associated with a small decrease in risk of CHF and stroke.

2.4.2 OSE Comments on Study Objectives

None

2.4.3 OSE Comments on Study Design

None

2.4.4 OSE Comments on Informed Consent (if any)

None

2.4.5 OSE Comments on Data Sources

The databases utilized provided a rich source of record-linked information on exposure, outcome, and medical services utilized (including inpatient and patient physician contacts).

2.4.6 OSE Comments on Study Time Period(s)

Controls were matched to cases on several factors including length of insurance coverage, which may help ensure that controls had duration of follow-up at least as long as the time to the event for the corresponding case.

2.4.7 OSE Comments on Study Population

This study included patients with a diagnosis of asthma, COPD and bronchitis. Because COPD is a risk factor for cardiac outcomes, it would be appropriate to restrict the study to COPD patients. Indeed, cases are generally more likely to have COPD than their matched controls (study table 1, appendix 3). Confounding by COPD could explain, at least in part, the association between respiratory medications and cardiovascular outcomes.

2.4.8 OSE Comments on Measurement of Exposure

Prescription dispensed served as surrogate for exposure, a metric that is generally used in pharmacoepidemiology studies. Non-prescription medications, such as use of aspirin in cardioprophylaxis, would not be captured in this study. However, prevalence of misclassification is likely to be non-differential between medication and non medication groups, which bias the results towards the null value (attenuate the results). Additionally,

dietary and lifestyle factors, which could confound the relation between respiratory medication use and cardiac events, are not available in this study.

Further, although this study considered first hospitalization due to cardiac outcomes, it did not seem to have taken into account hospitalization due to respiratory co-morbidities. If cases were more likely to be hospitalized than controls, this type of bias would tend to attenuate the association between respiratory medication and cardiac outcome as medications dispensed during hospitalization may not be captured in the database [33].

2.4.9 OSE Comments on Disease Outcome of Interest

Outcome definition was based in ICD coding only. Therefore, misclassification of outcome is possible although it is unlikely to vary differentially between cases and controls.

2.4.10 OSE Comments on Sample Size

None

2.4.11 OSE Comments on Analyses and/or Study Results

This study suggested that IB (as well as beta agonists) may increase risk of certain cardiovascular events including SVT and HF (but not of MI). However, because this study was not restricted to COPD patients, it is likely that greater prevalence of COPD among cases may explain the positive association between ipratropium and cardiac events (as COPD is generally associated with both increased likelihood of use of respiratory medications as well as with cardiac co-morbidities). Indeed, the difference in COPD prevalence between heart failure cases and their matched controls is substantial (41.7 vs. 29.9%, respectively); while comparatively small between MI cases and their matched controls (29.5 vs. 25.6%, respectively). Therefore, differences in COPD prevalence could explain the positive association between ipratropium and risk of HF and the lack of association between these agents and MI.

Additionally, COPD severity, which is also associated with both use of respiratory medications and with cardiac comorbidities, was not accounted for in this study and may also have confounded their results. Further, multivariate analysis did not adjust for cardiac co-morbidities beyond cardiac medications. Laboratory data was also not available in this dataset. Therefore, residual confounding by cardiac co-morbidity is likely to have influenced their results. Other important risk factors of cardiac outcomes, including smoking and BMI were also not accounted for in the analyses and are likely to have confounded their results. Due to the small to moderate size of their reported effect estimates, it is possible that confounding by COPD, severity of COPD cardiac co-morbidities, smoking, and BMI would explain the increase in risk associated with use of ipratropium bromide.

2.4.12 OSE Comments on Strength of Evidence

This study has a few strengths. Its large sample size allowed for the detection of small to moderate differences in risk of cardiovascular events between users and non users of respiratory medications. The databases utilized provided a rich source of record-linked information on exposure, outcome, and medical services utilized (including inpatient and patient physician contacts).

Limitations of this study are also noted. These are discussed according to their ability to bias the results (i) towards the null value (i.e. attenuate the findings) or (ii) away from the null value (i.e. strengthen or introduce a spurious association).

i. Limitations that may bias results towards the null value

Exposure misclassification due to hospitalizations: Although this study considered first hospitalization due to cardiac outcomes, it did not consider other hospitalizations (e.g. due to respiratory co-morbidities). Because medications dispensed during hospitalization may not be captured in the study, this type of bias would tend to attenuate the association between respiratory medication and cardiac outcome.

Misclassification of exposure: Prescription dispensed served as surrogate for exposure, although this metric is generally used in pharmacoepidemiology studies. Non prescription medications, such as use of aspirin for cardioprophylaxis, would not be captured in this study. This type of misclassification is likely to be non-differential with respect with case-control status, which may attenuate the study findings.

ii. Limitations that may bias results away from the null value

Confounding by presence of COPD: As shown in study table 1 (appendix 3), cases were generally more likely to have COPD compared to their matched controls. Long term use of anticholinergics may be more likely among COPD patients than among asthma or bronchitis patients. Therefore, confounding by COPD may have confounded the association between ipratropium bromide and cardiovascular events.

Confounding by important risk factors of the outcomes: This study failed to account for important risk factors for the outcomes. These factors include severity of COPD, history of smoking, and BMI, all likely to be associated with both use of respiratory medications and with cardiac comorbidities and to confound the association between respiratory medications and cardiac outcomes. Additionally, dietary and lifestyle factors, which could confound the relation between respiratory medication use and cardiac events, are not available in this study.

Therefore, despite its relatively large size, the study by Macie et al may not be particularly helpful in determining risk of cardiovascular events associated with use of IB bromide due to its limitations. The most important limitations included their failure to restrict the study to COPD patients and their inability to properly account for important risk factors of the outcome including COPD severity and smoking. Therefore, confounding by COPD and by important risk factors of the outcomes are likely to explain

the moderate increase in the risk of cardiovascular events associated with IB use reported in this study.

2.5 OGALE SS, LEE TA, AU DH, BOUDREAU DM, SULLIVAN SD. CARDIOVASCULAR EVENTS ASSOCIATED WITH IPRATROPIUM BROMIDE IN COPD. CHEST 2009 (*EPUB AHEAD OF PRINT*) [6]

2.5.1 Summary of Study

This was a cohort study conducted within the Veteran's Health Administration healthcare databases (inpatient and outpatient data, pharmacy data and vital status information). This study consisted of newly diagnosed COPD patients who had at least one inpatient primary diagnosis or two outpatient primary or secondary diagnosis of COPD (ICD-9 CM 490-492.8, 496) within a twelve month period between October 1998 and September 2002. Patients with a diagnosis of asthma as well as those who had been dispensed asthma medications not approved for COPD were excluded. Cohort entry was marked by the date of the second outpatient encounter or the date of discharge for the first hospitalization. Participants were followed until their first hospitalization for CVE, death, or end of study follow-up period. This study was approved by the Hines VA Hospital and University of Washington Institutional Review Boards.

The primary endpoint was a composite measure of cardiovascular events (CVEs), including a first hospitalization of a primary diagnosis of acute coronary syndrome (ICD-9-CM 410-411.89), heart failure (ICD-9-CM 425-425.4, 425.7-425.9, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.9) or cardiac dysrrhythmia (ICD-9-CM 427-428.93, 785.0).

The main exposure was *any* exposure to inhaled anticholinergics, which included 60 μg of ipratropium bromide by MDI or 0.5 mg by nebulizer four times a day, OR 18 μg of tiotropium daily for 30 days. Exposure was defined as any exposure to anticholinergics over the past year, number of months since last exposure to anticholinergics (recency of exposure), and number of 30-day equivalents of inhaled anticholinergics over the past year (cumulative exposure). These were time-dependent covariates in that at each event, exposure within the past year was recalculated for patients experiencing the event/s and for those who had been in the cohort for the same amount of time but had not experienced the event/s.

Baseline covariates included age, sex, race, year at cohort entry, distance to nearest VA hospital, cardiovascular risk factors based on both diagnosis and mediations, including prior cardiovascular disease, hypertension, hyperlipidemia, and diabetes during the year preceding cohort entry. Site of initial diagnosis of COPD (inpatient vs. outpatient) was used as a proxy for COPD severity at diagnosis.

Time dependent-covariates included number of inpatient and outpatient COPD exacerbations, number of canisters of SABA dispensed within the past year, and other respiratory medications including long acting beta-agonists, inhaled corticosteroids,

theophylline, supplemental oxygen, oral or nebulized beta agonists, *nebulized anticholinergics*, and other anticholinergics within the past year.

Multivariate Cox proportional hazards were used to determine the association between exposure to anticholinergics and risk of cardiovascular events, after adjusting for all non time dependent and time dependent covariates. All exposure characteristics (any use, recently, and cumulative) were included in the modes. Likelihood ratio tests were used to assess whether effect estimates varied by use of ICS within the past year and prior CVD.

A total of 82,717 patients (and 274,025 patient-years) newly diagnosed with COPD were included in this study. During follow-up, 6,234 CVEs were identified. The majority (44%) of these events referred to heart failure.

Exposure to anticholinergics compared to no exposure within the past year was associated with 29% increased risk of CVEs in multivariate models. Remote exposure (>6 months) was not associated with risk of CVEs. There was no evidence of dose response; among those last exposed in the previous 6 months or less, patients dispensed 4 or less 30-day equivalent of anticholinergics had a 40% increase in risk of CVEs, while those who were dispensed more than 4 30-day equivalents had a 23% increase in risk. Additionally, estimates varied significantly according to presence of CVD at baseline; use of anticholinergics was associated with higher risk of cardiovascular events among those without history of cardiovascular disease.

2.5.2 OSE Comments on Study Objectives

None

2.5.3 OSE Comments on Study Design

Investigators did not exclude participants with cardiovascular disease at baseline. Therefore, *prevalent* cardiovascular disease cases may be also included in this study. This is not ideal as the risk profile for prevalent is likely to differ from that of incident cases. However, analyses stratified by baseline history of CVD may have partially addressed this issue (it would be helpful to know the number of patients/person-moments included in these analyses; this information is not provided).

2.5.4 OSE Comments on Informed Consent (if any)

None

2.5.5 OSE Comments on Data Sources

A limitation of the National Veterans databases is that they do not capture outpatient care provided to veterans outside of the Veterans Affairs health system. Another important limitation of this data source is the fact that they lack important clinical details that cannot be determined from ICD coding. Some important information not available includes smoking history, BMI, and severity of COPD (e.g. GOLD). All these are important risk factors for mortality and potentially important confounders of the association between respiratory medications and mortality. Finally, information on cause

of death is not available from this data source. Therefore, cardiovascular-related deaths, including sudden deaths, are not included as cases.

2.5.6 OSE Comments on Study Time Period(s)

None

2.5.7 OSE Comments on Study Population

Information on baseline characteristics of participants *according exposure status* is not provided in this study report. Therefore, it is difficult to assess whether the exposed and non-exposed groups are comparable and whether there are important covariates that need to be taken into consideration. It is likely that patients prescribed respiratory medications have more severe COPD and perhaps more co-morbidities, which could explain, at least in part, the association between anticholinergics and CVEs.

2.5.8 OSE Comments on Measurement of Exposure

The main exposure is any exposure to inhaled anticholinergics, which includes 60 μg of ipratropium bromide by MDI or 0.5 mg by nebulizer four times a day, OR 18 μg of tiotropium daily for 30 days. The manuscript does not specify which device used for the delivery of tiotropium. Misclassification of exposure is likely in this study, as drug prescription was used as surrogate for drug exposure, which requires the assumption that participants used the drugs as prescribed. However, this misclassification is unlikely to differ between those who subsequently developed CVEs and those who did not.

Also, the prevalence of tiotropium use is extremely low (n=78 of 329,255 prescriptions dispensed). It would be helpful to analyze the data restricted to ipratropium users.

2.5.9 OSE Comments on Disease Outcome of Interest

Incomplete ascertainment of outcome is an important issue in this study, as hospitalizations for cardiovascular events that occurred outside of the VA system were not captured in this study. Also, information on cause of death was not available for over 50% of the cohort; thus, cases of cardiovascular-related death or sudden cardiac death were not captured as "cardiovascular event" cases in this study.

Additionally, misclassification of outcome is likely to play a role in the findings of this study. The primary endpoint was a composite measure of several cardiac endpoints, including acute coronary syndrome, heart failure, and cardiac dysrrhythmia. The reliability of identifying heart failure and cardiac arrhythmia based on ICD codes is questionable. Additionally, because payment for services is linked to diagnosis-related groups, over-reporting of cardiovascular diagnosis is possible. However, it is unlikely that misclassification of outcome differed between those who were prescribed anticholinergics and those who were not prescribed anticholinergics; therefore, this misclassification may have attenuated the findings.

Finally, investigators did not analyze the association between anticholinergics and risk of cardiovascular events individually (e.g. myocardial infarction). Therefore, it is not possible to know whether/which particular event drove the reported association.

2.5.10 OSE Comments on Sample Size

None.

2.5.11 OSE Comments on Analyses / Study Results

A few unexpected findings are noted. As shown in study figure 1 (appendix 4), theophylline was associated with a borderline significant 19% *decrease* in risk of CVEs. As the cardiac side effects for theophylline are well known, this unusual finding may point to the effect of channeling bias, as patients with greater susceptibility to cardiac events may be prescribed other medications, including IB. This type of bias could explain, at least in part, the positive association between IB and risk of CVEs (as well as the inverse association between theophylline and CVEs).

Also, it is unexpected that nebulizer anticholinergics were unassociated with risk of CVEs (RR=1.03) (study figure 1, appendix 4), while the exposure of interest, which included anticholinergics delivered either via nebulizer or MDI was significantly associated with increased risk of CVEs. Additionally, the decrease in risk for CVEs with increase cumulative exposure to anticholinergics (40% and 23% increase in risk with lower and higher cumulative exposure, respectively) is difficult to explain (study table 2, appendix 4). It would be helpful to have information on numbers/percentages of patients in each exposure category to assess the robustness of these findings (not provided in the manuscript).

Data on important risk factors of cardiovascular disease including smoking, BMI, laboratory measures of hyperlipidemia, is another fundamental limitation of this study. Presence of these factors may have influenced prescription of IB as physicians may be more likely to prescribe IB for patients with cardiovascular disease history. Confounding by these factors is likely to bias estimates away from the null. Similarly, failure to adjust for COPD severity, which is likely to be closely associated with cardiac comorbidities, is also likely to bias the estimates away from the null value. Attempt to adjust for COPD severity by considering inpatient *vs.* outpatient COPD diagnosis, which is unlikely to represent COPD severity, is not reassuring. Given the magnitude of the increase in risk reported in this study (RR=1.29), it is possible and likely the RR for CVEs would approximate 1.0 after proper adjustment for relevant confounders.

2.5.12 OSE Comments on Strength of Evidence

The main strengths of this study include its relatively large size and its prospective nature.

Several important limitations are also noted. These are discussed according to their ability to (i) bias the results towards the null, (ii) away from the null value, or (iii) in a direction that is difficult to predict.

i. Limitations that may bias the findings towards the null value

Misclassification of exposure: Drug prescription was used as surrogate for drug exposure, which requires the assumption that participants used the drugs as prescribed. However, this misclassification is unlikely to differ between those who developed CVEs and those who did not and may have attenuated the study findings.

Misclassification of outcome: The primary endpoint was a composite measure of several cardiac endpoints based on ICD coding, including acute coronary syndrome, heart failure, and cardiac dysrrhythmia. The reliability of identifying heart failure and cardiac arrhythmia based on ICD codes is questionable. Additionally, because payment for services is linked to diagnosis-related groups, over-reporting of cardiovascular diagnosis is possible. However, it is unlikely that misclassification of outcome differed between those who were prescribed anticholinergics and those who were not prescribed anticholinergics; therefore, this misclassification may have attenuated the findings.

Incomplete case ascertainment: Ascertainment of outcome was probably incomplete. Hospitalizations for cardiovascular events that occurred outside of the VA system were not captured in this study. Also, information on cause of death was not available for over 50% of the cohort; thus, cases of cardiovascular-related death or sudden cardiac death were not captured as "cardiovascular event" cases in this study.

ii. Limitations that may bias the findings away from the null value

Confounding: Lack of data on important risk factors of cardiovascular disease including smoking, BMI, laboratory measures of hyperlipidemia, is a fundamental limitation of this study. Presence of these factors may have influenced prescription of ipratropium as physicians may be more likely to prescribe anticholinergics for patients with no cardiovascular risk factors. Confounding by these factors is likely to bias estimates away from the null. Similarly, failure to adjust for COPD severity, which is likely to be closely associated with cardiac co-morbidities, is also likely to bias the estimates away from the null value. Attempts made by the investigators to adjust for COPD severity by considering inpatient *vs.* outpatient COPD diagnosis, which is unlikely to represent COPD severity, is not reassuring. Given the magnitude of the increase in risk reported in this study (RR=1.29), it is possible - and likely – that the RR for CVEs would approximate 1.0 after proper adjustment for relevant confounders.

iii. Limitations that may introduce bias in a direction that is difficult to predict

Failure to exclude TB users: While IB and TB belong to the same drug class and may share many of the same side effects, the short- versus long-acting nature of the drugs can have significant implications for systemic effects such as cardiovascular events. Therefore, pooling of these two exposures is not recommended. Because the number of

TB prescriptions is very small, it would have been appropriate to restrict the study to IB users vs. non users.

Due to its several limitations, of which lack of ability to properly account for important confounders is the most concerning – this study may not be helpful in determining risk of cardiovascular events with use of ipratropium/anticholinergics.

3 DRUG UTILIZATION

3.1 DETERMINING SETTINGS OF USE

The IMS Health, IMS National Sales Perspectives™ was used to determine the retail and non-retail channels of distribution for ipratropium and tiotropium oral inhalation products in terms packages of product sold (boxes, canisters, etc). During the years 2004 through 2008, U.S. retail and mail order pharmacies accounted for the majority of the wholesale sales for ipratropium and tiotropium. Retail and mail order pharmacies combined accounted for 53-66% of the annual wholesale distribution of ipratropium products and 77-82% of the distribution for tiotropium products. Since the majority of distribution was into the outpatient pharmacy setting pharmacies, we examined outpatient dispensing patterns to evaluate the use of ipratropium, ipratropium with albuterol combination, and tiotropium products.

3.2 DATA SOURCES AND METHODS

Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

Outpatient use of ipratropium and tiotropium products by diagnosis code was measured using data obtained from Wolters Kluwer Health's Concurrent Product Analyzer (CPA). From this data source, we obtained nationally projected counts of the number of patients who had received a prescription for ipratropium and/or tiotropium through U.S. mail order and retail pharmacies, stratified by the most recent respiratory diagnosis occurring within a one year look back period, as well as patient age and sex information. Diagnoses associated with the use of ipratropium and tiotropium were imputed from a subset of the patients by looking back 6 months from each prescription claim for the most recently billed medical claim for a respiratory diagnosis, Respiratory diagnoses were group into 4 categories: asthma, chronic obstructive pulmonary disease, chronic bronchitis, and emphysema. CPA data is provided for the calendar years 2005 through 2008.

Indications for use were also obtained using the SDI, Physician Drug and Diagnosis Audit (PDDA). PDDA is a survey of 3,100 U.S. office based physicians. Data are provided from years 2005 through 2008.

Nationally projected number of prescriptions dispensed and unique patient counts for U.S. mail order and retail pharmacies were obtained from the Wolters Kluwer SOURCE PHAST database . These data are provided for the years 2005 through 2008.

Complete descriptions of the databases are provided in Appendix 2.

3.3 RESULTS

Wolters Kluwer estimates that the nationally projected number of patients who received ipratropium containing products (including ipratropium/albuterol products) through U.S. mail order and retail pharmacies decreased by 16% between the years 2005 through 2008, falling from 3.6 million patients in year 2005 to 3.0 million during year 2008 (Appendix 1, Table 1). Wolters Kluwer estimates that during year 2008 asthma patients accounted for approximately 15% of the use (~458,617 patients), chronic obstructive pulmonary disease patients for nearly 16% of the use (~473,052 patients) and chronic bronchitis for nearly 3% of the use (~78,409 patients). There were nearly 2 million patients with other diagnoses (both respiratory and non-respiratory) which accounted for about 66% of the year 2008 projected patient count. The relative proportions for the previous years were similar.

The retail and mail order projected patient count for tiotropium increased from ~1.01 million patients during year 2005 to ~1.95 million patients during 2008, a 93% relative increase. Using the most currently billed respiratory diagnosis, Wolters Kluwer estimates COPD patients accounted for approximately 22% (~438,559 patients) of the total number of tiotropium patients during year 2008, and asthma patients accounted for nearly 14% (~269,967 patients). Approximately 60% of patients (~1.2 million patients) did not have a billed respiratory diagnosis during the 6 months prior to their tiotropium prescription.

Female patients accounted for approximately 57% of the total number of patients who received a retail or mail order ipratroprium prescription during each year from years 2005 through 2008, and roughly 55% of patients who received a tiotropium prescription (Appendix 1, Table 2). Patients under 65 years of age accounted for approximately 49% of ipratropium prescription patients and between 40% and 42% of tiotropium patients during each year of this analysis (Appendix 1, Table 3).

To provide a count of the total number of retail and mail order prescriptions dispensed for orally inhaled ipratropium and tiotropium, we obtained nationally projected estimates of prescription dispensing from Wolter Kluwer's PHAST (Appendix 1, Table 4). For all ipratropium products combined, the number of prescriptions dispensed decreased from 10.2 million prescriptions in year 2005 to 8.4 million prescriptions during year 2008, an 18% decrease. The declines seen with the single agent products were much greater than the decline seen with the albuterol combination product (25% and 15%, respectively). Prescriptions for tiotropium increased during each year from year 2005 through year 2008 from 3.3 million prescriptions to 7.5 million prescriptions.

Finally, we examined the intended indications for the use of ipratropium and tiotropium products from the SDI, PDDA, a survey of approximately 3,100 office based physicians (Appendix 1, Table 5). For all orally inhaled ipratropium products combined, the most frequently mentioned diagnosis associated with a mention of these products was chronic airway obstruction, which accounted for between 40% and 46% of the mentions during the years between 2005 through 2008. Asthma was the second most frequently mentioned diagnosis, accounting for between 17% and 22% of diagnosis mentions. For tiotropium, chronic airway obstruction was also the most frequently mentioned diagnosis,

accounting for 66% of mentions during year 2007 and 73% of mentions during year 2008. The number of tiotropium mentions prior to year 2007 we too low too evaluate.

Figure A (below) displays the nationally projected estimates of the number of patients using TB and IB for chronic obstructive disease via US retail and mail order pharmacies (based on Wolters Kluwer estimates presented in table 1, appendix 5). Prescriptions for IB decreased steadily from 2005 to 2008, while for TB, prescriptions increased steadily from 2005 to 2008. The estimated p-trend for IB and TB was 0.04 and 0.05, respectively.

3.4 DRUG UTILIZATION DISCUSSION

Findings from this consult should be interpreted in the context of the known limitations of the databases used. We estimated that ipratropium and tiotropium products are distributed primarily to retail and mail order pharmacy settings based on the IMS Health, IMS National Sales Perspectives™. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these retail and non-retail channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use.

The Wolters Kluwer data which provides projected patient counts in relation to the billed medical claims diagnosis is subject to a number of limitations. First, respiratory diagnoses were not captured for a substantial number of patients during the study period. This is likely due to possibility that chronic patients were not billed for a respiratory specific claim during the 6 month look back period rather than the use of the product for non-respiratory conditions. Secondly, since the medical claims represents a subset of all patients in the database, the projected estimates may not be as reliable.

Indications for use were obtained using SDI's PDDA, a monthly survey of 3,100 office based physicians. Although PDDA data are helpful to understand how drug products are prescribed by physicians, the small sample size and the relatively low usage of these products limits the ability to identify trends in the data. Low estimates may be seen in the first two years of tiotropium data and the data should not be trended during this period. In general, PDDA data are best used to identify the typical uses for the products in clinical practice.

4 SUMMARY OF REVIEW AND RECOMMENDATIONS

The limitations of the meta-analysis by Singh et al [3], including a biased selection of studies, lack of information on participants who discontinued trial and failure to use person-time data, and the limitations of the observational studies [4-6], of which the most important refers to their inability to properly account for important risk factors of the outcomes (*e.g.* smoking, BMI, COPD severity, cardiac co-morbidities), may explain the reported positive associations between anticholinergics and serious CVEs and mortality. Additionally, these findings do not agree with the findings of previously published meta-analyses [7-10], nor do they agree with the findings of a large 4-year randomized clinical trial on TB *vs.* placebo [11], none of which suggest an association between anticholinergics and increasing risk of cardiovascular events or mortality. Taken together, these data are not convincing in implicating use of inhaled anticholinergics in increasing risk of cardiovascular events or mortality. Assessment of drug utilization patterns suggest a decrease in use/prescriptions of ipratropium products coupled with an increase in use/prescriptions of tiotropium products from 2005 to 2008. In summary, the current available evidence implicating TB and IB in increasing risk of these outcomes is not compelling. Therefore, we do not recommend the pursuit of a meta-analysis by the Agency at this time.

5 REFERENCES

[1] Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. American Thoracic Society. Am J Respir Crit Care Med 1995; 152(5 Pt 2): S77-121.

[2] Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. Am J Respir Crit Care Med 2001; 163(5): 1256-76.

[3] Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. JAMA 2008; 300(12): 1439-50.

[4] Lee TA, Pickard AS, Au DH, Bartle B, Weiss KB. Risk for death associated with medications for recently diagnosed chronic obstructive pulmonary disease. Ann Intern Med 2008; 149(6): 380-90.

[5] Macie C, Wooldrage K, Manfreda J, Anthonisen N. Cardiovascular morbidity and the use of inhaled bronchodilators. Int J Chron Obstruct Pulmon Dis 2008; 3(1): 163-9.

[6] Ogale SS, Lee TA, Au DH, Boudreau DM, Sullivan SD. Cardiovascular Events Associated With Ipratropium Bromide in COPD. Chest 2009.

[7] Kesten S, Jara M, Wentworth C, Lanes S. Pooled clinical trial analysis of tiotropium safety. Chest 2006; 130(6): 1695-703.

[8] Barr RG, Bourbeau J, Camargo CA, Ram FS. Tiotropium for stable chronic obstructive pulmonary disease: A meta-analysis. Thorax 2006; 61(10): 854-62.

[9] Salpeter SR, Buckley NS. Systematic review of clinical outcomes in chronic obstructive pulmonary disease: beta-agonist use compared with anticholinergics and inhaled corticosteroids. Clin Rev Allergy Immunol 2006; 31(2-3): 219-30.

[10] Wilt TJ, Niewoehner D, MacDonald R, Kane RL. Management of stable chronic obstructive pulmonary disease: a systematic review for a clinical practice guideline. Ann Intern Med 2007; 147(9): 639-53.

[11] Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, Decramer M. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med 2008; 359(15): 1543-54.

[12] Early Communication about an Ongoing Safety Review of Tiotropium. 2008. Ref Type: Report

[13] Kesten S, Leimer I, Jara M. Risk of major adverse cardiovascular events with inhaled anticholinergics in patients with chronic obstructive pulmonary disease. JAMA 2009; 301(12): 1224-6.

[14] Jara M, Lanes SF, Wentworth C 3rd, May C, Kesten S. Comparative safety of long-acting inhaled bronchodilators: a cohort study using the UK THIN primary care database. Drug Saf 2007; 30(12): 1151-60.

[15] de Luise C, Lanes SF, Jacobsen J, Pedersen L, Sorensen HT. Cardiovascular and respiratory hospitalizations and mortality among users of tiotropium in Denmark. Eur J Epidemiol 2007; 22(4): 267-72.

[16] Gershon AS, Wang L, To T, Luo J, Upshur RE. Survival with tiotropium compared to long-acting Beta-2-agonists in Chronic Obstructive Pulmonary Disease. COPD 2008; 5(4): 229-34.

[17] Ringbaek T, Viskum K. Is there any association between inhaled ipratropium and mortality in patients with COPD and asthma? Respir Med 2003; 97(3): 264-72.

[18] Sin DD, Tu JV. Lack of association between ipratropium bromide and mortality in elderly patients with chronic obstructive airway disease. Thorax 2000; 55(3): 194-7.

[19] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327(7414): 557-60.

[20] Rosenberg MS. The file-drawer problem revisited: a general weighted method for calculating fail-safe numbers in meta-analysis. Evolution 2005; 59(2): 464-8.

[21] Kesten S, Leimer I, Jara M. Risk of major adverse cardiovascular events with inhaled anticholinergics in patients with chronic obstructive pulmonary disease. JAMA 2009; 301(12): 1224-6.

[22] Wedzicha JA, Calverley PM, Seemungal TA, Hagan G, Ansari Z, Stockley RA. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. Am J Respir Crit Care Med 2008; 177(1): 19-26.

[23] Voshaar T, Lapidus R, Maleki-Yazdi R, Timmer W, Rubin E, Lowe L, Bateman E. A randomized study of tiotropium Respimat Soft Mist inhaler vs. ipratropium pMDI in COPD. Respir Med 2008; 102(1): 32-41.

[24] Anthonisen NR, Connett JE, Enright PL, Manfreda J. Hospitalizations and mortality in the Lung Health Study. Am J Respir Crit Care Med 2002; 166(3): 333-9.

[25] Lanes S, Golisch W, Mikl J. Ipratropium and lung health study. Am J Respir Crit Care Med 2003; 167(5): 801-2.

[26] Brusasco V, Hodder R, Miravitlles M, Korducki L, Towse L, Kesten S. Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. Thorax 2003; 58(5): 399-404.

[27] Donohue JF, van Noord JA, Bateman ED, Langley SJ, Lee A, Witek TJ, Jr. et al. A 6-month, placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol. Chest 2002; 122(1): 47-55.

[28] Casaburi R, Mahler DA, Jones PW, Wanner A, San PG, ZuWallack RL et al. A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. Eur Respir J 2002; 19(2): 217-24.

[29] Casaburi R, Briggs DD, Jr., Donohue JF, Serby CW, Menjoge SS, Witek TJ, Jr. The spirometric efficacy of once-daily dosing with tiotropium in stable COPD: a 13-week multicenter trial. The US Tiotropium Study Group. Chest 2000; 118(5): 1294-302.

[30] Egger M, Simth GD, Altman DG. Systematic Reviews in Health Care - Meta-analysis in context. second ed. London: BMJ Books. 2001.

[31] Kesten S, Plautz M, Piquette CA, Habib MP, Niewoehner DE. Premature discontinuation of patients: a potential bias in COPD clinical trials. Eur Respir J 2007; 30(5): 898-906.

[32] Sin DD, Anthonisen NR, Soriano JB, Agusti AG. Mortality in COPD: Role of comorbidities. Eur Respir J 2006; 28(6): 1245-57.

[33] Suissa S. Immeasurable time bias in observational studies of drug effects on mortality. Am J Epidemiol 2008; 168(3): 329-35.

6 APPENDICES

APPENDIX 1 – SINGH *ET AL*, MAIN TABLES AND FIGURES

Figure 1

Figure 1. Study Selection

Table 2

Table 2. Quality Assessment of Included Trials

Source	Allocation Concealment	Adverse Event Monitoring	Withdrawal Rates, %	Loss to Follow-up, %
Anthonisen et al,[4] 2002	Adequate	Cardiovascular deaths reviewed and participants followed up every 3 mo		
Ipratropium			23.1	0.03
Placebo			21.5	0.02
Casaburi et al,[19] 2002	Unclear	Adverse events detected at regular intervals (first d, first wk, Q3 wk up to 13 wks; Q6 wks until study end)		
Tiotropium			18.7	NA
Placebo			27.8	NA
Wedzicha et al,[20] 2008	Adequate	Serious adverse events recorded up to 30 d poststudy		
Tiotropium			41.9	1.9
Salmeterol and fluticasone			35.2	2.2
Powrie et al,[21] 2007	Unclear	Adverse event, vital signs, laboratory results, and examination recorded during the study at 4, 16, 32 and 52 wk and 30 d poststudy		
Tiotropium			30.4	NA
Placebo			28.8	NA
Chan et al,[22] 2007	Unclear	Adverse events monitored throughout treatment period		
Tiotropium			22.2	NA
Placebo			27.5	NA
Casaburi et al,[23] 2000	Adequate	Adverse events recorded every 3 wk		
Tiotropium			6.1	NA
Placebo			11	NA
Brusasco et al,[24] 2003	Unclear	Adverse events tracked through baseline and 24 wk		
Tiotropium			15.4	NA
Salmeterol			18.8	NA
Placebo			25.7	NA
Donohue et al,[25] 2002	Unclear	Adverse events tracked through 24 wk		
Tiotropium			12	NA
Salmeterol			17	NA
Placebo			28	NA
Covelli et al,[26] 2005	Unclear	Electrocardiography and Holter performed at entry and 12 wk		
Tiotropium			10	NA
Placebo			17.7	NA
Niewoehner et al,[27] 2005	Adequate	Serious adverse events included if occurred within 30 d of study medication		
Tiotropium			16	0.07
Placebo			27	0.04
Bateman et al,[28] 2008	Unclear	Adverse events and vital signs, physical examination at each visit		
Tiotropium			NA	NA
Salmeterol and fluticasone			NA	NA
Moita et al,[29] 2008	Unclear	Adverse events and vital signs, physical examination at each visit		
Tiotropium			7.5	3.4
Placebo			6.7	2.4
Voshaar et al,[29,30] 2008	Unclear	Adverse event, vital signs, 12-lead electrocardiographic routine laboratories, and physical examination		
Tiotropium, 5 μg			8.8	NA
Tiotropium, 10 μg			10	NA
Ipratropium			17.4	NA
Placebo			12.1	NA
Combivent Inhalation Aerosol Study Group,[31] 1994	Unclear	Adverse events monitored every 2 wk		
Ipratropium and albuterol			13.2	2.7
Albuterol			12.7	2.3
Ipratropium			14.5	3.4

Source	Allocation Concealment	Adverse Event Monitoring	Withdrawal Rates, %	Loss to Follow-up, %
GlaxoSmithKline study SMS40315,[32] 2005 Salmeterol and ipratropium	Unclear	NA	12	NA
Salmeterol			16	NA
Ipratropium			17	NA
Placebo			16	NA
GlaxoSmithKline study SMS40314,[33] 2005 Salmeterol and ipratropium	Unclear	NA	15	NA
Salmeterol			11	NA
Ipratropium			11	NA
Placebo			19	NA
Mahler et al,[34] 1999 Ipratropium	Unclear	Adverse events and vital signs at 2 wk, laboratory examinations, and physical examination at beginning and end of treatment; electrocardiography at regular intervals	13.5	1.5
Salmeterol			6.6	0
Placebo			16	1.3

Abbreviation: NA, data not available.

APPENDIX 2: LEE *ET AL*, MAIN STUDY TABLES

Table 1

Table 1. Participant Characteristics

Characteristic	Respiratory Death		Cardiovascular Death		All-Cause Mortality	
	Case Patients (n = 2405)	Control Participants (n = 23 907)	Case Patients (n = 3159)	Control Participants (n = 31 534)	Case Patients (n = 32 130)	Control Participants (n = 320 501)
Men, %	98.2	98.5	99.2	99.3	98.7	98.8
Age, %						
45–54 y	4.7	4.7	6.8	6.9	7.1	7.1
55–64 y	12.9	12.9	13.9	13.9	15.4	15.4
65–74 y	35.3	35.5	35.6	35.6	35.9	35.9
75–84 y	40.8	41.0	38.7	38.8	37.3	37.4
≥85 y	6.4	6.0	5.0	4.9	4.3	4.2
Race, %						
White	85.4	84.0	84.2	83.8	83.0	83.7
Black	8.7	10.1	10.7	10.6	11.2	10.1
Hispanic	2.3	2.4	1.9	2.1	2.3	2.3
Other	0.6	0.9	0.5	0.8	0.6	0.9
Unknown	3.0	2.5	2.7	2.7	3.0	3.1
Comorbid conditions, %						
Hypertension	53.1	62.0	67.9	61.8	61.6	62.3
Ischemic heart disease	33.6	36.0	56.7	36.2	40.7	36.3
Diabetes	19.1	20.5	32.2	20.8	26.7	22.0
Osteoarthritis	18.9	24.3	20.3	23.6	19.5	23.0
Depression	11.2	10.5	12.2	11.5	12.3	11.7
Cancer	18.4	20.1	18.0	20.0	25.6	20.2
Chronic heart failure	22.9	13.4	38.1	13.0	24.3	13.8
Medications, %						
Hydrochlorothiazide	13.9	16.8	19.8	16.3	17.4	18.3
Loop diuretic	46.5	29.2	63.3	28.0	49.0	30.9
Potassium-sparing diuretic	10.6	9.5	19.3	9.5	15.1	10.4
β-Blocker	25.2	31.4	44.5	30.9	38.2	34.5
Calcium-channel blocker	32.2	33.9	36.1	34.0	35.3	34.8
ACE inhibitor	40.6	42.3	59.0	41.1	47.7	44.4
Angiotensin-receptor blocker	3.7	4.8	6.2	4.7	5.7	5.7
Antiarrhythmic	4.6	3.3	9.0	3.3	6.3	3.6
Digoxin	22.3	13.2	38.5	12.8	24.5	13.6
Lipid-lowering medication	24.7	40.9	42.7	40.6	36.6	44.4
Insulin	7.8	6.1	14.2	6.1	11.7	7.3
Oral hypoglycemic agent	13.4	15.8	22.7	15.9	19.4	17.6
Nonsteroidal anti-inflammatory drugs	24.7	33.4	26.3	33.5	28.8	34.4
Annual health care utilization						
Mean primary care visits (SD), n	3.6 (3.7)	4.1 (3.4)	4.5 (4.1)	4.0 (3.3)	4.2 (3.8)	4.0 (3.4)
Mean hospitalizations (SD), n	0.4 (0.7)	0.2 (0.6)	0.6 (1.1)	0.2 (0.6)	0.5 (1.0)	0.3 (0.7)
Cumulative COPD exacerbations, %						
0	9.4	43.1	15.3	44.6	14.7	40.5
1	18.8	28.5	23.4	28.4	22.3	27.7
2	19.7	13.4	19.8	13.0	20.2	14.1
≥3	52.2	15.0	41.6	14.0	42.8	17.8
Exacerbation in previous 6 mo, %	70.2	13.6	64.4	22.2	62.1	22.3

ACE = angiotensin-converting enzyme; COPD = chronic obstructive pulmonary disease.

Table 2

Table 2. **Medication Use Related to Chronic Obstructive Pulmonary Disease**

Regimen	Respiratory Death, %		Cardiovascular Death, %		Respiratory or Cardiovascular Death, %		All-Cause Mortality, %	
	Case Patients (n = 2405)	Control Participants (n = 23 907)	Case Patients (n = 3159)	Control Participants (n = 31 534)	Case Patients (n = 5564)	Control Participants (n = 55 441)	Case Patients (n = 32 130)	Control Participants (n = 320 501)
Medication use within 6 mo of index date								
Short-acting β-agonists	71.2	61.9	70.0	62.3	70.5	61.8	65.9	61.2
Inhaled corticosteroids	31.0	24.8	24.7	24.9	27.4	24.8	24.2	24.7
Ipratropium	65.8	52.4	65.3	52.4	65.5	52.1	60.8	52.5
Long-acting β-agonists	16.0	10.7	11.0	10.2	13.1	10.5	12.9	12.2
Theophylline	12.8	6.4	7.3	6.3	9.7	6.3	7.0	6.0
Medication regimen use within 6 mo of index date								
None or short-acting β-agonists only	24.5	37.2	26.4	37.0	25.6	37.3	31.1	37.2
Inhaled corticosteroids	3.7	4.9	3.6	5.0	3.6	5.0	3.3	4.5
Ipratropium	31.6	30.1	40.0	30.4	36.4	30.1	35.6	30.0
Long-acting β-agonists	1.3	1.4	1.1	1.4	1.2	1.4	1.3	1.6
Theophylline	2.4	1.8	1.9	1.9	2.1	1.9	1.6	1.6
Inhaled corticosteroids plus ipratropium	14.3	12.0	13.2	12.1	13.7	11.8	11.7	11.4
Inhaled corticosteroids plus long-acting β-agonists plus ipratropium	6.0	3.8	4.2	3.6	5.0	3.9	5.1	4.6
Long-acting β-agonists plus ipratropium	4.3	2.6	3.2	2.5	3.7	2.6	3.6	2.9
Inhaled corticosteroids plus long-acting β-agonists	1.4	1.7	1.1	1.6	1.2	1.6	1.4	1.9
Ipratropium plus theophylline	4.0	1.7	2.3	1.6	3.0	1.6	2.2	1.5
Inhaled corticosteroids plus ipratropium plus theophylline	3.2	1.4	1.4	1.4	2.2	1.4	1.5	1.2
Other	3.3	1.6	1.7	1.5	2.4	1.5	1.8	1.6

APPENDIX 3: MACIE *ET AL*, MAIN TABLES

Table 1

Table 1 Characteristics of cases (at first hospitalization) and controls

		SVT cases	Controls	MI cases	Controls	HF cases	Controls	Stroke cases	Controls
Number of subjects		2054	20501	3855	38490	5407	53929	4961	49487
Gender	Males	48.2		61.7		49.8		49.8	
Age	mean	71.2		69.1		76.0		73.4	
	25th , 75th percentile	64, 80		61, 79		70, 84		67, 82	
Respiratory Co-morbidity									
	Asthma	10.1	10.9	9.6	11.0	7.1	9.1	8.0	10.0
	COPD	27.1	26.3	29.5	25.6	41.7	28.9	31.5	27.9
	Asthma and COPD	10.5	9.1	10.8	9.5	13.3	10.1	9.4	10.0
	Bronchitis	52.3	53.7	50.1	53.9	37.9	52.1	51.1	52.2
Any Non-cardiac Co-morbidity		39.5	34.0	44.4	32.9	51.7	35.8	46.2	34.9
Drug dispensed within									
	IB 60 Days	7.8	4.8	6.6	4.7	14.9	5.4	5.6	5.0
	1 Year	11.2	7.6	10.3	7.5	20.4	8.4	10.1	7.9
	BA 60 Days	13.2	9.3	13.1	9.4	24.4	10.1	10.5	9.8
	1 Year	22.4	17.2	21.1	16.8	34.3	17.6	19.3	17.4
	ICS 60 Days	7.2	6.4	7.9	6.2	12.0	6.9	6.1	6.7
	1 Year	13.5	11.3	14.0	11.6	18.7	12.0	11.6	11.7
Cardiac Drugs									
	Antiarrhythmics	36.8	9.2	11.8	7.9	34.6	9.8	16.8	9.6
	Nitrates	31.0	16.1	30.1	13.7	40.7	16.6	25.0	16.4
	Antihypertensives	37.5	27.6	32.4	25.7	42.0	28.8	37.8	28.1
	Furosemide	33.9	17.3	23.8	14.5	65.0	18.8	27.8	18.2
	Betablockers	29.4	14.1	20.1	12.8	20.7	13.8	20.4	13.8
	Calcium Channel Blockers	16.5	7.6	12.4	6.6	15.2	7.7	11.3	7.4
	ACEI	37.1	21.9	30.2	20.5	52.4	21.6	34.9	21.9
	Anticholesterol	13.0	10.5	15.1	10.2	12.1	9.2	13.8	9.4
	Any	81.2	55.3	67.4	51.6	88.9	58.6	73.2	56.7

APPENDIX 4: OGALE *ET AL*, MAIN TABLES AND FIGURES

Figure 1

Table 2

Table 2. Crude and Adjusted RRs for CVEs				
	Crude	**Baseline Adj.**[a]	**Final Adj. Model**[b]	
	HR	**HR**	**HR (95% CI)**	**p-value**
Unexposed to Anticholinergics	1.00	1.00	1.00	-
Exposed to Anticholinergics	1.48 (1.40-1.56)	1.47 (1.39-1.55)	1.29 (1.21-1.38)	0.00
Recency of exposure: Past 6 months				
Anticholinergic equivalents (≤4)	1.55 (1.44-1.66)	1.51 (1.41-1.62)	1.40 (1.30-1.51)	0.00
Anticholinergic equivalents (>4)	1.49 (1.39-1.60)	1.52 (1.42-1.63)	1.23 (1.12-1.35)	0.00
Recency of exposure: > 6 months				
Anticholinergic equivalents (≤4)	1.17 (1.02-1.35)	1.13 (0.98-1.29)	1.08 (0.94-1.24)	0.27
Anticholinergic equivalents (>4)	1.13 (0.96-1.33)	1.14 (0.97-1.34)	0.95 (0.80-1.12)	0.57

[a] Adjusted for all baseline variables from table 1 and fiscal year of cohort entry

[b] Adjusted for all baseline variables from table 1, fiscal year of cohort entry, and all time-dependent variables from figure 1.

APPENDIX 5. DRUG UTILIZATION DATA TABLES

Table 1. Nationally projected estimates of the number of patients receiving ipratropium or tiotropium oral inhalation through U.S. retail and mail order pharmacies, stratified by recent diagnosis code, for years 2005 - 2008

	2005		2006		2007		2008	
	Projected Patients	***Share %***	**Projected Patients**	***Share %***	**Projected Patients**	**Share %**	**Projected Patients**	**Share %**
Ipratropium	3,579,872	*100.0%*	3,277,848	*100.0%*	3,112,357	100.0%	2,998,596	*100.0%*
Asthma	531,490	*14.8%*	503,765	*15.4%*	487,650	15.7%	458,617	*15.3%*
Ipratropium	178,745	*33.6%*	166,492	*33.0%*	162,987	33.4%	151,717	*33.1%*
Ipratropium/albuterol	352,745	*66.4%*	337,273	*67.0%*	324,663	66.6%	306,900	*66.9%*
Chronic Bronchitis	93,020	*2.6%*	84,444	*2.6%*	80,485	2.6%	78,409	*2.6%*
Ipratropium	27,556	*5.2%*	24,224	*4.8%*	23,897	4.9%	22,828	*5.0%*
Ipratropium/albuterol	65,465	*12.3%*	60,220	*12.0%*	56,589	11.6%	55,580	*12.1%*
COPD	602,451	*16.8%*	558,570	*17.0%*	526,286	16.9%	473,052	*15.8%*
Ipratropium	178,297	*33.5%*	160,983	*32.0%*	152,822	31.3%	132,706	*28.9%*
Ipratropium/albuterol	424,155	*79.8%*	397,587	*78.9%*	373,464	76.6%	340,346	*74.2%*
Emphysema	23,937	*0.7%*	22,399	*0.7%*	21,285	0.7%	20,140	*0.7%*
Ipratropium	6,747	*1.3%*	6,374	*1.3%*	5,982	1.2%	5,746	*1.3%*
Ipratropium/albuterol	17,190	*3.2%*	16,026	*3.2%*	15,303	3.1%	14,394	*3.1%*
Other	2,328,974	*65.1%*	2,108,670	*64.3%*	1,996,650	64.2%	1,968,379	*65.6%*
Ipratropium	668,145	*125.7%*	591,502	*117.4%*	564,779	115.8%	547,146	*119.3%*
Ipratropium/albuterol	1,660,829	*312.5%*	1,517,168	*301.2%*	1,431,870	293.6%	1,421,233	*309.9%*
Tiotropium	1,010,359	*100.0%*	1,464,634	*100.0%*	1,833,577	100.0%	1,954,702	*100.0%*
Asthma	146,804	*14.5%*	210,570	*14.4%*	262,236	14.3%	269,967	*13.8%*
Chronic Bronchitis	32,869	*3.3%*	46,711	*3.2%*	57,434	3.1%	60,824	*3.1%*
COPD	246,381	*24.4%*	348,452	*23.8%*	433,157	23.6%	438,559	*22.4%*
Emphysema	10,098	*1.0%*	14,576	*1.0%*	19,280	1.1%	21,073	*1.1%*
Other	574,206	*56.8%*	844,324	*57.6%*	1,061,469	57.9%	1,164,279	*59.6%*

Source: Wolters Kluwer Source Lx: Concurrent Product Analyzer, Data extracted 6/2009,
File: WK CPA 2009-312 Ipratropium market by diagnosis.xls

Table 2. Nationally projected estimates of the number of patients receiving ipratropium or tiotropium oral inhalation through U.S. retail and mail order pharmacies, stratified by recent diagnosis code, for years 2005 - 2008

	2005		2006		2007		2008	
	Projected Patients	***Share %***	**Projected Patients**	***Share %***	**Projected Patients**	***Share %***	**Projected Patients**	***Share %***
Ipratropium	3,579,872	*100.0%*	3,277,848	*100.0%*	3,112,357	*100.0%*	2,998,596	*100.0%*
Female	2,042,657	*57.1%*	1,875,011	*57.2%*	1,774,090	*57.0%*	1,714,163	*57.2%*
Ipratropium	622,258	*30.5%*	557,860	*29.8%*	534,108	*30.1%*	507,589	*29.6%*
Ipratropium / albuterol	1,420,399	*69.5%*	1,317,151	*70.2%*	1,239,982	*69.9%*	1,206,573	*70.4%*
Male	1,447,471	*40.4%*	1,332,939	*40.7%*	1,281,005	*41.2%*	1,230,290	*41.0%*
Ipratropium	409,571	*20.1%*	369,273	*19.7%*	357,831	*20.2%*	335,479	*19.6%*
Ipratropium / albuterol	1,037,900	*50.8%*	963,666	*51.4%*	923,175	*52.0%*	894,811	*52.2%*
Unspecified	89,744	*2.5%*	69,899	*2.1%*	57,262	*1.8%*	54,143	*1.8%*
Ipratropium	27,661	*1.4%*	22,442	*1.2%*	18,529	*1.0%*	17,074	*1.0%*
Ipratropium / albuterol	62,083	*3.0%*	47,457	*2.5%*	38,732	*2.2%*	37,069	*2.2%*
Tiotropium	1,010,359	*100.0%*	1,464,634	*100.0%*	1,833,577	*100.0%*	1,954,702	*100.0%*
Female	547,726	*54.2%*	808,609	*55.2%*	1,010,719	*55.1%*	1,078,520	*55.2%*
Male	439,054	*43.5%*	629,509	*43.0%*	794,839	*43.3%*	846,087	*43.3%*
Unspecified	23,579	*2.3%*	26,516	*1.8%*	28,019	*1.5%*	30,094	*1.5%*

Source: Wolters Kluwer Source Lx: Concurrent Product Analyzer, Data extracted 6/2009,
File: WK CPA 2009-312 Ipratropium market by gender.xls

Table 3. Nationally projected estimates of the number of patients receiving ipratropium or tiotropium oral inhalation through U.S. retail and mail order pharmacies, stratified by patient sex, for years 2005 - 2008

	2005		2006		2007		2008	
	Projected Patients	***Share %***	**Projected Patients**	***Share %***	**Projected Patients**	***Share %***	**Projected Patients**	***Share %***
Ipratropium	3,579,872	*100%*	3,277,848	*100%*	3,112,357	*100%*	2,998,596	*100%*
0-64	1,791,361	*50%*	1,613,035	*49%*	1,528,121	*49%*	1,481,243	*49%*
Ipratropium	524,157	*29%*	464,163	*29%*	449,617	*29%*	432,462	*29%*
Ipratropium / albuterol	1,267,204	*71%*	1,148,872	*71%*	1,078,504	*71%*	1,048,781	*71%*
65+	1,729,793	*48%*	1,610,939	*49%*	1,536,211	*49%*	1,468,497	*49%*
Ipratropium	517,528	*30%*	468,345	*29%*	445,259	*29%*	412,325	*28%*
Ipratropium / albuterol	1,212,265	*70%*	1,142,594	*71%*	1,090,953	*71%*	1,056,172	*72%*
Unknown	58,718	*2%*	53,874	*2%*	48,025	*2%*	48,856	*2%*
Tiotropium	1,010,359	*100%*	1,464,634	*100%*	1,833,577	*100%*	1,954,702	*100%*
0-64	423,952	*42%*	595,036	*41%*	734,689	*40%*	798,705	*41%*
65+	569,858	*56%*	848,026	*58%*	1,074,215	*59%*	1,128,679	*58%*
Unknown	16,549	*2%*	21,572	*1%*	24,673	*1%*	27,318	*1%*

Source: Wolters Kluwer Source Lx: Concurrent Product Analyzer, Data extracted 6/2009,
File: WK CPA 2009-312 Ipratropium market by age.xls

Table 4. Nationally projected number of prescriptions dispensed for ipratropium and tiotropium by U.S. retail and mail-order pharmacies, Years 2005 through 2008

	2005		2006		2007		2008	
	TRx (000)	%	TRx (000)	%	TRx (000)	%	TRx (000)	%
Total	13,593	*100.0%*	14,262	*100.0%*	15,460	*100.0%*	15,906	*100.0%*
Ipratropium Combined	10,250	*75.4%*	9,147	*64.1%*	8,724	*56.4%*	8,440	*53.1%*
Ipratropium	2,904	*28.3%*	2,437	*26.6%*	2,328	*26.7%*	2,174	*25.8%*
Atrovent	1,446	*0.0%*	99	*0.0%*	7	*0.0%*	1	*0.0%*
Atrovent HFA	63	*0.0%*	1,053	*0.0%*	1,035	*0.0%*	944	*0.0%*
Ipratropium Bromide	1,395	*0.0%*	1,284	*0.1%*	1,285	*0.1%*	1,229	*0.1%*
Ipratropium-albuterol	7,346	*0.1%*	6,710	*0.1%*	6,397	*0.1%*	6,266	*0.1%*
Combivent	6,192	*0.1%*	5,550	*0.1%*	5,203	*0.1%*	4,864	*0.1%*
Duoneb	1,154	*0.0%*	1,160	*0.0%*	787	*0.0%*	95	*0.0%*
Ipratropium-Albuterol	0	*0.0%*	0	*0.0%*	407	*0.0%*	1,307	*0.0%*
Tiotropium	3,343	*0.0%*	5,115	*0.0%*	6,736	*0.0%*	7,466	*0.0%*

Source: *Wolters Kluwer SOURCE PHAST Prescription Monthly*™, Extracted 6-18-2009, File: WK PHAST 2009-312 Ipratropium.xls

Table 5. Nationally projected indications for use of ipratropium and tiotropium by U.S. office based physicians, by top 4 diagnosis groups, for years 2005 through 2008.

	2005		2006		2007		2008	
	Uses (000)	*Share* %	Uses (000)	*Share* %	Uses (000)	*Share* %	Uses (000)	*Share* %
Ipratropium Combined	6,967	*100.0%*	6,031	*100.0%*	5,265	*100.0%*	4,868	*100.0%*
496 Chr Airway Obstruct Nec	3,027	*43.4%*	2,789	*46.2%*	2,080	*39.5%*	1,965	*40.4%*
493 Asthma	1,503	*21.6%*	1,106	*18.3%*	913	*17.3%*	876	*18.0%*
491 Chronic Bronchitis	746	*10.7%*	649	*10.8%*	897	*17.0%*	734	*15.1%*
486 Pneumonia, Organism Nos	255	*3.7%*	181	*3.0%*	309	*5.9%*	270	*5.5%*
All Others	1,436	*20.6%*	1,306	*21.7%*	1,065	*20.2%*	1,024	*21.0%*
Tiotropium Bromide	19	*100.0%*	6	*100.0%*	2,500	*100.0%*	2,720	*100.0%*
496 Chr Airway Obstruct Nec	1	*4.1%*	--	--	1,652	*66.1%*	1,974	*72.6%*
491 Chronic Bronchitis	--	--	--	--	168	*6.7%*	201	*7.4%*
493 Asthma	13	*67.5%*	1	*13.9%*	228	*9.1%*	199	*7.3%*
492 Emphysema	--	--	5	*86.1%*	56	*2.3%*	115	*4.2%*
All Others	5	*28.4%*	--	--	396	*15.9%*	230	*8.5%*

Source: SDI Physician Drug and Diagnosis Audit, Extracted 6=2--5, File:PDDA 2009-312 ipratropium 6-09

SDI Physician Drug & Diagnosis Audit (PDDA)

SDI's Physician Drug & Diagnosis Audit (PDDA) is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based

physician practices in the U.S. The survey consists of data collected from approximately 3,100 office-based physicians representing 29 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

SDI uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

Wolters Kluwer Concurrent Product Analyzer (CPA)

Data used in CPA are derived from Wolters Kluwer prescription and medical claims databases. CPA integrates activity from a variety of sources, including national retail chains, mail order pharmacies, mass merchandisers, pharmacy benefits managers and their data systems, and provider groups, physician offices, and outpatient treatment centers. Wolters Kluwer receives over 1.4 billion prescription claims annually, 292 Million medical claims, representing over 128.9 million unique patients. Approximately 18.9 million patients have both medical and prescription activity in the database.

CPA allows users to measure and evaluate concurrent drug therapy usage in unique patients during a selected time period. The data are projected to a national level.

Wolters Kluwer SOURCE PHAST Prescription Monthly™

The Wolters Kluwer Source PHAST Prescription Monthly is a syndicated view of U.S. retail and mail order pharmacy prescription activity, updated on a monthly basis. Source PHAST Prescription Monthly covers over 40,000 retail pharmacies in the sample including mail order and specialty pharmacies. The dispensed prescriptions in the sample represent approximately 80% of all U.S. retail prescriptions (cash, Medicaid, 3rd party) as well as 60% of all U.S. mail order prescriptions. The retail and mail order prescriptions are projected to the national level.

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/s/

SIMONE P PINHEIRO
08/04/2009

SOLOMON IYASU
08/04/2009

DSI CONSULT: Request for Clinical Inspections

Date: January 30, 2009

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Joseph Salewski, Branch Chief (Acting), GCP2
Tejashri Purohith-Sheth, MD
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Theresa M. Michele, MD, Medical Officer, through
Sally Seymour, MD, Deputy Director for Safety, through
Badrul Chowdhury, MD, PhD, Division Director
Division of Pulmonary and Allergy Products

From: Miranda Raggio, MSN, Division of Pulmonary and Allergy Products

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA-21-395 S-029
Sponsor/Sponsor contact information (to include phone/email):
Ms. Tacy Pack
Director, Drug Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.
(tel) 203-798-5545
(fax) 203-791-6262
(e-mail) tacy.pack@boehringer-ingelheim.com
Drug: Trade Name (generic): tiotropium bromide (Spiriva HandiHaler)
NME (Yes/No): No
Review Priority (Standard or Priority): Standard

Study Population includes < 18 years of age (Yes/No): No
Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication for Supplement: 1) reduction in COPD exacerbations, 2) reduction in mortality, and 3) reduction in respiratory failure
[note: the applicant is requesting these as claims in the clinical studies section of the label, not specific new indications]

PDUFA: September 17, 2009
Action Goal Date: September 3, 2009
Inspection Summary Goal Date: July 27, 2009

II. Protocol/Site Identification

Boehringer Ingelheim submitted an efficacy supplement for Spiriva HandiHaler requesting the following claims: 1) reduction in COPD exacerbations, 2) reduction in mortality, and 3) reduction in respiratory failure. To support these claims, BI submitted the UPLIFT study (Protocol 205.235: Understanding Potential Long-term Impacts on Function with Tiotropium). UPLIFT is a key study due to its length, scope, and safety implications of a 6000 patient, 4 year study. The study was conducted multinationally and included a total of 5 world regions (US, Western Europe, Eastern Europe, Latin America, and Asia), 37 countries, and 487 sites.

We are requesting audits of 3 to 4 domestic and 3 to 4 international sites for this application (total 6 to 8 sites), all from study #205-235 (UPLIFT). A larger number of sites are identified so that DSI can choose based on resourcing and any potential audit triggers identified by DSI. Given the size and importance of the study, preliminary discussions were held with Dr. Tejashri Purohit-Sheth in DSI regarding site selection for audit. She suggested that for this study, a larger number of sites should be audited than for most applications.

Rationale for Choice of Sites

The medical officer reviewed sites for audit selection based on the following criteria: 1) enrollment, 2) region, 3) previous audit (BI or FDA), 4) death, 5) protocol violations, and 6) financial disclosure. Enrollment was a primary criterion; only sites with 20 or more treated patients were included for consideration and sites were rank ordered by country, region, domestic/international, and for the study as a whole. An effort was made to include at least one site from each region, particularly as the majority of the mortality benefit was observed in Latin America and Asia. Next, sites audited in 2008 by FDA for the Spiriva program were excluded. Sites audited by Boehringer Ingelheim (BI) for this study were excluded unless there were significant deaths or protocol violations. No site had a particular imbalance in deaths; however sites with a mortality rate of >20% were considered for audit (overall vital status mortality for the study was 16.4%). Sites with >10% protocol violations were also considered for audit.

In addition to the criteria used by the medical officer for site selection, Dr. Joan Buenconsejo, FDA statistician for this application, reviewed sites for outliers based on mortality and FEV1. No particular outlier sites were identified.

The specific rationale for each site identified is given in Table 1 for domestic sites and Table 2 for international sites.

Table 1: Domestic Sites for Inspection (choose 3-4)

Site (Name, Address, Phone number, email, fax#)	Site #	Subjects Enrolled/Treated	Rationale for Selection
Donald P. Tashkin, MD David Geffen School of Medicine at UCLA 10833 Le Conte Ave. Los Angeles, CA 90095 phone: 310-825-3163 fax: 310-206-5088 e-mail: dtashkin@mednet.ucla.edu	3800	145/98	-high enroller (#1 US/#1 study) -protocol violations 14.3% (b) (4) -PI for entire study
William Bailey, MD University of Alabama of Birmingham 1808 7th Ave. South Boshell Diabetes Building #356 Birmingham, AL 35249 phone: 205-934-5560 e-mail: wcbailey@uab.edu	3708	125/84	-high enroller (#2 US/#2 study) -protocol violations 18.6%
Michael Eichenhorn, MD Henry Ford Hospital, K-17 2799 West Grand Blvd. Detroit, MI 48202 phone: 313-916-2436 e-mail: MEichen1@hfhs.org	3732	127/74	-high enroller (#3 US/#3 study) -not audited by BI or FDA
Murray Altose, MD Metro Health Medical Center 10701 East Boulevard Cleveland, OH 44106 phone: 216-421-3030 e-mail: Murray.Altose@med.va.gov	3701	78/51	-high enroller (#6 US/#6 study) -protocol violations 13.7% -not audited by BI or FDA
Gary Greenwald, MD Advances in Medicine 42362 Bob Hope Drive Rancho Mirage, CA 92270 phone: 760-341-9777 aim_garygreenwald@hotmail.com	3741	58/46	-high enroller (#7 US/#7 study) -deaths 34.8% -not audited by BI or FDA
Kees Mahutte, MD Long Beach VAMC Pulmonary Section (11-111P) 5901 East 7th St., Mail Code 03-119 Long Beach, CA 90822 phone: 662-826-8000 e-mail: Kees.mahutte@med.va.gov	3812	35/26	-high enroller (#9 US/#21 study) -protocol violations 30.8% -deaths 23.1% -not audited by BI or FDA

* The protocol for all sites is #205-235 (UPLIFT). The indications based on this protocol are reduction in COPD exacerbations, mortality, and respiratory failure.

Table 2: International Sites for Inspection (choose 3-4)

Site (Name, Address, Phone number, email, fax#)	Site #	Subjects Enrolled/Treated	Rationale for Selection
Pál Magyar, MD Professor, Head of Department of Pulmonology Semmelweis University 1025 Budapest, Diósárok u. l/c. Hungary	1310	51/41	-high enroller (#2 E Eur/#2 Int/ #9 study) -protocol violations 22% -deaths 22%
Wanchai Dejsomritrutai, MD, MSc Division of Respiratory Disease and Tuberculosis Department of Medicine Faculty of Medicine Siriraj Hospital Mahidol University Bangkok 10700, Thailand	3404	22/20	-high enroller (#2 Asia) -protocol violations 35% -deaths 45%
Alfredas Bagdonas, MD, PhD Associate Professor Chief, Department of Internal Medicine Kaunas Red Cross Clinical Hospital Laisves Avenue 17 3000 Kaunas, Lithuania	1802	36/30	-high enroller (#4 E Eur/#4 Int/ #12 study) -not audited by BI or FDA
Rodolfo Posadas-Valay, MD Medical Director, Center for the Prevention and Rehabilitation of Chronic Pulmonary Diseases Ceprep Hospital Universitario Av. Madero y Gonzalitos Monterrey, Mexico, NL	2004	32/27	-high enroller (#1 Latin Am/ #8 Int/#16 study) -not audited by BI or FDA -protocol violations unknown
Norbert Vetter, MD Head, Department of Internal Disease Sozialmedizinisches Zentrum Baumgartner Höhe Vienna, Austria	0301	31/27	-high enroller (#1 W Eur/#9 Int/ #17 study) -not audited by BI or FDA
Jiří Erban, MD SPLIN s.r.o. Čimická 37/446 182 00 Praha 8; Czech Republic phone: +420 603750009 e-mail: splin@cbox.cz	0707	30/27	-high enroller (#7 E Eur/#10 Int/ #18 study) -22% deaths -not audited by BI or FDA

* The protocol for all sites is #205-235 (UPLIFT). The indications based on this protocol are reduction in COPD exacerbations, mortality, and respiratory failure.

III. Site Selection/Rationale

Protocol Summary and Tiotropium Safety Signals

Study 205.235 (UPLIFT) was a randomized, double-blind, placebo-controlled parallel group trial assessing the rate of decline of lung function over 4 years with tio HH in patients with COPD. A total of 5993 patients with moderate to severe COPD ($FEV_1 \leq 70\%$ predicted) were randomized, 2986 to tio HH and 3006 to placebo. The co-primary endpoints were the yearly rate of decline in trough (pre-bronchodilator) FEV_1 and yearly rate of decline in post-bronchodilator FEV_1. Key secondary endpoints were time to first COPD exacerbation and time to first COPD exacerbation leading to hospitalization. There was no difference in rate of decline of either pre- or post-bronchodilator FEV_1, although benefits in lung function and SGRQ were maintained throughout the study. Tio HH significantly increased the time to first COPD exacerbation and time to first COPD exacerbation leading to hospitalization. In addition, patients in the tio HH group had significantly fewer COPD exacerbations (0.85 vs. 0.73, $p<0.0001$) and exacerbation days (13.6 vs. 12.1, $p=0.001$) per patient year. The safety endpoints included all adverse events, all-cause mortality, and lower respiratory mortality. All deaths were adjudicated by a central committee, and patients who discontinued trial medication were followed for outcome. Vital status was known for 97.6% of randomized patients. No increased incidence of stroke, cardiovascular events, or pneumonia was observed in the tio HH group compared to placebo. There was a lower rate of death during treatment with tio HH than with placebo (Hazard Ratio 0.84; 95% CI, 0.73-0.97).

Three potential safety signals are under FDA evaluation for tiotropium: 1) mortality, 2) stroke, and 3) cardiovascular events. It is anticipated that the UPLIFT study will play a key role in resolution of issues regarding these potential signals. First, an increased number of deaths in the tiotropium groups compared to placebo were observed in the Phase 3 pivotal trials for Spiriva Respimat (205.254 and 205.255), reviewed under NDA 21-936 (Complete Response, September 16, 2008). No increase in mortality has been observed in the HandiHaler program, but the issue is relevant because both products contain the same active ingredient, tiotropium bromide. The current submission will likely form the primary basis of the complete response to NDA 21-936. Second, in November 2007, BI submitted an information amendment to the IND providing data regarding an increased incidence of stroke with tiotropium in a pooled analysis of 29 studies involving both the HandiHaler and Respimat devices. The third potential safety signal, increased cardiovascular events, is based on two recent publications which reported increased risk for cardiovascular events and cardiovascular mortality in patients who received tiotropium or ipratropium (a short-acting anticholinergic).[1,2]

Domestic Inspections:

Reasons for inspections (please check all that apply):

- __x__ Enrollment of large numbers of study subjects
- ____ High treatment responders (specify):
- ____ Significant primary efficacy results pertinent to decision-making
- ____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- __x__ Other (specify): protocol violations, financial disclosure, deaths

International Inspections:

Reasons for inspections (please check all that apply):

____ There are insufficient domestic data
____ Only foreign data are submitted to support an application
__x__ Domestic and foreign data show conflicting results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
__x__ Other (specify): significant safety issues to resolve with this compound, international sites form 74.4% of the data from this study

Five or More Inspection Sites:

We have requested these sites for inspection (international and/or domestic) because of the following reasons:

- key study for evaluation of serious safety issues (mortality, cardiovascular risk, stroke) with a highly prescribed product for a common disease
- extremely large study with 487 sites in 37 countries
- applicant is requesting important efficacy claims (reduction in mortality, COPD exacerbations, and respiratory failure)
- international sites provided 74% of data in the study

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.

IV. Tables of Specific Data to be Verified (if applicable)

In addition to standard audit procedures, please verify the following data points:

- deaths
  - during study
  - vital status (includes deaths for patients discontinuing prematurely)
  - investigator determined cause of death
  - adjudicated cause of death
- adverse events, with particular attention to cardiovascular events and stroke
- respiratory failure
- COPD exacerbations

Should you require any additional information, please contact Miranda Raggio at Ph: 301-796-2109 or Theresa M. Michele, MD at Ph: 301-796-1593.

V. References

1. Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease. JAMA 2008; 300 (12): 1439-1450.

2. Lee TA, Pickard S, et al. Risk of Death Associated with Medications for Recently Diagnosed Chronic Obstructive Pulmonary Disease. Annals of Internal Medicine 2008; 149: 380-390.

Concurrence: (as needed)

Theresa Michele, MD, Medical Officer
Sally Seymour, MD, Medical Team Leader, and Deputy Director for Safety
Badrul Chowdhury, MD, PhD Director, Division Director (for foreign inspection requests only)

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/s/

Badrul Chowdhury
2/6/2009 02:32:16 PM

REGULATORY PROJECT MANAGER LABELING REVIEW
(PHYSICIAN LABELING RULE)

Division of Pulmonary and Allergy Products

Application Number: NDA 21-395 S-029, SE8 (labeling with new clinical information)

Name of Drug: SPIRIVA HandiHaler® (tiotropium bromide inhalation powder)
Applicant: Boehringer Ingelheim

Material Reviewed:

Submission Date: November 17, 2008

Receipt Date(s): November 17, 2008
Submission Date of Structure Product Labeling (SPL): November 17, 2008

Type of Labeling Reviewed: Word/SPL

Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The following issues/deficiencies have been identified in your proposed labeling.

Highlights

1. Do not use the "TM" or "R" symbols after the drug names in Highlights or the Table of Contents. You can use these symbols once upon first use in the FPI. We recommend this because the symbol will not appear in the SPL version of the labeling, and we want the Word version to match the SPL version as much as possible.

Full Prescribing Information (FPI)

1. No deficiencies noted.

Recommendations

Boehringer Ingelheim should address the identified deficiencies/issues and re-submit labeling. This updated version of labeling will be used for further labeling discussions.

_____
Miranda Raggio
Regulatory Project Manager
Finalized 1-21-09

Supervisory Comment/Concurrence:

_____
Sandy Barnes
Chief, Project Management Staff
Intialed 1-16-09

Drafted: Miranda Raggio/January 14, 2009
Revised/Initialed:Sandy Barnes/

Finalized:Miranda Raggio/

CSO LABELING REVIEW OF PLR FORMAT

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/s/

Miranda Raggio
1/21/2009 10:18:59 AM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-395/S029

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 21395 SUPPL # 029 HFD # 570

Trade Name Spiriva HandiHaler

Generic Name tiotropium bromide

Applicant Name Boehringer Ingeleheim

Approval Date, If Known Original Approval 1-30-04

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b) (1), SE8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Three

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21395 Tiotropium Bromide

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study 205.235, Phase IIIb, four year, randomized double-blind, placebo-controlled, parellel group trial in COPD patients

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study 205.235 as noted above

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 ! !
IND # 46,687 YES ☒ ! NO ☐
! Explain:

Investigation #2 ! !
IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Miranda Raggio
Title: Regulatory Project Manager
Date: 12-2-09

Name of Office/Division Director signing form: Badrul A. Chowdhury, M.D, Ph.D.
Title: Director, Division of Pulmonary and Allergy Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21395	SUPPL-29	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	SPIRIVA HANDIHALER

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/s/

MIRANDA B RAGGIO
12/17/2009

BADRUL A CHOWDHURY
12/17/2009

EXCLUSIVITY REQUEST

This information regarding claimed exclusivity is submitted pursuant to 21 CFR 314.50(j).

1) The applicant, Boehringer Ingelheim Pharmaceuticals, inc., believes that the upon approval of this supplement to NDA 21-395, SPIRIVA® HandiHaler® (tiotropium bromide inhalation powder) will be entitled to a three year period of marketing exclusivity under provisions of 21 CFR 314.108, and is, therefore claiming exclusivity.

2) Reference is made to 21 CFR 314.108(b)(5) to support the applicant's claim to exclusivity.

3) As the applicant claims exclusivity under 21 CFR 314.108(b)(5), the following information is provided to show that the application contains a new clinical investigation that is essential to approval of this application and were conducted or sponsored by the applicant:

   (i) New Clinical Investigation

   The applicant, through the undersigned representative, hereby certifies that to the best of the applicant's knowledge the clinical investigation included in this application meets the definition of "new clinical investigation" set forth in 21 CFR 314.108(a).

   (ii) Essential for Approval

   The applicant, through its undersigned representative, asserts that no published studies or publicly available reports of clinical investigations are known to the applicant that are relevant to the conditions (4 year SPIRIVA HandiHaler placebo-controlled clinical trial in which COPD patients in both treatment groups were permitted the use of all inhaled respiratory medications with the exception of inhaled anticholinergics) for which the applicant is seeking approval, other than information describing the new clinical investigation which was conducted or sponsored by the applicant and is included in this application. Accordingly, the applicant provides no list of published studies or publicly available reports of clinical investigations known to the applicant through a literature search that are relevant to the conditions for which the applicant is seeking approval. The applicant, through its undersigned representative, hereby certifies that the applicant has searched the scientific literature and, to the best of the applicant's knowledge and in the applicant's opinion no published studies or publicly available reports provide a sufficient basis for the approval of the conditions for which the applicant is seeking approval without reference to the new clinical investigation in the application.

EXCLUSIVITY REQUEST

The present application is requesting three years exclusivity from the date of approval of this supplement to NDA 21-395, for claims proposed for inclusion in the Clinical Trial section of the package insert for SPIRIVA HandiHaler (tiotropium bromide inhalation powder).

(iii) Conducted or Sponsored By

The following table provides the new clinical investigation that is included in this application and which is, in the opinion of the applicant, essential to the approval of this application. The applicant is the sponsor named in the Form FDA 1571 for an investigational new drug application (IND) under which the clinical investigation was conducted; an identification of the IND number is provided in the table. The following information is provided in support of this certification.

Trial Number	**Trial Description**	**Is the Applicant the named sponsor in Form FDA 1571 for the IND which under which the trial was conducted?**	**Country**	**IND Number**
205.235	Phase IIIb, four-year, randomized double-blind, placebo-controlled, parallel group trial in COPD patients	Yes	Multi-national	46,687

By: Tacy Park

Title: Director, Drug Regulatory Affairs

Date: October 15, 2008

PeRC

REQUEST FOR WAIVER OF PEDIATRIC STUDIES

SPIRIVA® HandiHaler® (tiotropium bromide inhalation powder) NDA 21-395 was approved January 30, 2004 for the maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. FDA noted in the NDA approval letter for the original application that pediatric study requirements were waived.

This NDA Supplement (sNDA) provides additional 4-year clinical data supporting the use of SPIRIVA HandiHaler for the same indication and also presents new clinical information on the reduction of exacerbations, as well as additional safety information.

For this sNDA, Boehringer Ingelheim Pharmaceuticals, Inc. is requesting a full waiver of the pediatric requirement stated in 21 CFR Section 314.55 (c) (2), that each application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration shall contain data that are adequate to assess the safety and effectiveness of the drug product for the claimed indication in all relevant pediatric sub-populations.

COPD is a progressive degenerative respiratory disorder that results primarily from smoking tobacco. Unlike the onset of asthma which typically first occurs during childhood or adolescence, COPD most often develops in current and former smokers who are in their mid-40s. COPD is not a disease affecting the pediatric population. Although COPD and asthma have some similar characteristics such as coughing and wheezing, they are two distinct conditions most notably in terms of disease onset, frequency of symptoms, and reversibility of airway obstruction in response to treatment.

Section 8 of the SPIRIVA HandiHaler Prescribing Information, i.e., Use in Specific Populations, sub-section 8.4 Pediatric Use, states that this disease does not normally occur in children and that the safety and effectiveness of SPIRIVA in pediatric patients have not been established.

Debarment Certification

DEBARMENT CERTIFICATION

Certification Requirement Section 306(k)(l) of the Act 21 U.S.C. 355a(k)

Boehringer Ingelheim Pharmaceuticals, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Signature: Christopher D Corsico

Name of Applicant: Christopher Corsico, M.D.
Vice President, Drug Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.

Date: 14 October 2008

Mailing Address: Boehringer Ingelheim Pharmaceuticals Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Drug Evaluation II

FACSIMILE CORRESPONDENCE

Date: December 16, 2009

To: Jeffrey R. Snyder/Tacy Pack

Company: Boehringer Ingelheim

Phone: 203-778-7727

Fax: 203-837-4928

From: Miranda Raggio, RN, BSN, MA
Regulatory Health Project Manager
Division of Pulmonary and Allergy Products

Phone: 301-796-2109

Subject: NDA 21-395 S-029 Labeling Comments #4

# of Pages: 22

Comments: Please call with any questions. Thanks, miranda

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NDA 21-395 S029 Labeling Comments #4

We are currently reviewing your November 17, 2008, supplemental NDA for SPIRIVA HandiHaler, and are providing labeling comments based on your revised label submitted on December 16, 2009. Submit revised labeling incorporating the changes in the comments listed below.

Patient Information Leaflet

1. Under "Who should not take SPIRIVA HandiHaler?", remove the word (b) (4) from the sentence (b) (4) allergic reactions may include itching, rash, or swelling of the lips, tongue, or throat (trouble swallowing)."
2. Under "What should I tell my doctor before using SPIRIVA HandiHaler?" , move the first bullet "have a severe allergy to milk proteins. Ask your doctor if you are not sure." to the end of that section
3. Under the first bullet of "What are the possible side effects of SPIRIVA HandiHaler?", remove the term (b) (4).

Submit your response to me via telephone facsimile to 301-796-9728 or email at Miranda.Raggio@fda.hhs.gov by COB on December 16, 2009. Your response will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact Miranda Raggio, Regulatory Project Manager, at 301-796-2109.

NDA 21-395 S029 Labeling Comments #4

Drafted by Miranda Raggio/12-16-09
Initialed by T. Michele/12-16-09
Sally Seymour/12-16-09
Finalized by Miranda Raggio/12-16-09

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21395	SUPPL-29	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	SPIRIVA HANDIHALER

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/s/

MIRANDA B RAGGIO
12/16/2009

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Drug Evaluation II

FACSIMILE CORRESPONDENCE

Date: December 15, 2009

To: Jeffrey R. Snyder/Tacy Pack

Company: Boehringer Ingelheim

Phone: 203-778-7727

Fax: 203-837-4928

From: Miranda Raggio, RN, BSN, MA
Regulatory Health Project Manager
Division of Pulmonary and Allergy Products

Phone: 301-796-2109

Subject: NDA 21-395 S-029 Labeling Comments

# of Pages: 22

Comments: Please call with any questions. Thanks, miranda

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NDA 21-395 S029 Labeling Comments #3

We are currently reviewing your November 17, 2008, supplemental NDA for SPIRIVA HandiHaler. Submit revised labeling incorporating changes shown in the attached marked up labeling. We may have additional comments as we continue our review.

Submit your response to me via telephone facsimile to 301-796-9728 or email at Miranda.Raggio@fda.hhs.gov by 10am on December 16, 2009. Your response will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact Miranda Raggio, Regulatory Project Manager, at 301-796-2109.

21 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21395	SUPPL-29	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	SPIRIVA HANDIHALER

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/s/

MIRANDA B RAGGIO
12/15/2009

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: December 11, 2009

To: Jeffrey R. Snyder/Tacy Pack	**From: Miranda Raggio**
Company: Boehringer Ingelheim	Division of Pulmonary and Allergy Drug Products
Fax number: 203-778-7727	**Fax number:** 301-796-9728
Phone number: 203-837-4928	**Phone number:** 301-796-2109

Subject: NDA 21-395 S-029 Labeling Comments

Total no. of pages including cover: 20

Comments:

Document to be mailed: YES xNO

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We are currently reviewing your November 17, 2008, supplemental NDA and your revised label submitted on November 12, 2009, for SPIRIVA Handihaler, and are providing additional preliminary labeling comments . Submit revised labeling incorporating the changes shown in the attached marked up labeling. We may have additional comments as we continue our review.

Submit your response to me via telephone facsimile to 301-796-9728 or email at Miranda.Raggio@FDA.HHS.Gov by COB December 15, 2009. Your response will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact Miranda Raggio, Regulatory Project Manager at 301-796-2109.

19 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21395	SUPPL-29	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	SPIRIVA HANDIHALER

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/s/

EUNICE H CHUNG
12/11/2009
on behalf of M Raggio

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Drug Evaluation II

FACSIMILE CORRESPONDENCE

Date: December 3, 2009

To: Jeffrey R. Snyder/Tacy Pack

Company: Boehringer Ingelheim

Phone: 203-778-7727

Fax: 203-837-4928

From: Miranda Raggio, RN, BSN, MA
Regulatory Health Project Manager
Division of Pulmonary and Allergy Products

Phone: 301-796-2109

Subject: NDA 21-395 S-029 Labeling Comments

# of Pages: 22

Comments: Please call with any questions. Thanks, miranda

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If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2109. Thank you.

NDA 21-395 S029 Labeling Comments #2

We are currently reviewing your November 17, 2008, supplemental NDA and your revised label submitted on November 12, 2009, for SPIRIVA HandiHaler, and are providing preliminary labeling comments. Submit revised labeling incorporating changes shown in the attached marked up labeling and the comments listed below. We may have additional comments as we continue our review.

HIGHLIGHTS of PRESCRIBING INFORMATION

1. The Adverse Reactions Section should contain a list of adverse reactions that are included in Table 1. Inclusion of adverse reactions from the Spiriva HandiHaler placebo controlled trials is acceptable. See comment below regarding Table 1.

FULL PRESCRIBING INFORMATION

2. We want to have consistency across labels for dry powder inhalers with lactose. If the lactose in Spiriva HandiHaler may contain milk proteins, include this information in Section 11, DESCRIPTION, e.g. (may contain milk proteins) and add a contraindication in patients with severe hypersensitivity to milk proteins to Section 4, CONTRAINDICATIONS.
3. We note that you have (b) (4) in Section 6, ADVERSE REACTIONS. Replace these data in Table 1 and the sentence immediately after Table 1 as per the currently approved label.
4. In Section 14, CLINICAL STUDIES, (b) (4) from Figure 3.
5. In Section 14, CLINICAL STUDIES, subsection *Exacerbations,* first paragraph on the VA study, include 95% Confidence Intervals for the Odds Ratios of the proportion of COPD patients who experienced exacerbations and proportion of patients who were hospitalized due to exacerbation. In the second paragraph, include the 95% confidence interval for the ratio of time to first exacerbation.

Submit your response to me via telephone facsimile to 301-796-9728 or email at Miranda.Raggio@fda.hhs.gov by COB on December 9, 2009. Your response will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact Miranda Raggio, Regulatory Project Manager, at 301-796-2109.

22 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21395	SUPPL-29	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	SPIRIVA HANDIHALER

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/s/

MIRANDA B RAGGIO
12/03/2009

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Drug Evaluation II

FACSIMILE CORRESPONDENCE

Date: November 5, 2009

To: Jeffrey R. Snyder/Tacy Pack

Company: Boehringer Ingelheim

Phone: 203-778-7727

Fax: 203-837-4928

From: Miranda Raggio, RN, BSN, MA
Regulatory Health Project Manager
Division of Pulmonary and Allergy Products

Phone: 301-796-2109

Subject: NDA 21-395 S-029 Initial Labeling Comments

# of Pages: 22

Comments: Please call with any questions. Thanks, miranda

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NDA 21-395 S029 Labeling Comments #1

We are currently reviewing your November 17, 2008, supplemental NDA for SPIRIVA HandiHaler, and are providing preliminary labeling comments. Submit revised labeling incorporating changes shown in the attached marked up labeling and the comments listed below. We may have additional comments as we continue our review.

General Labeling Comments

1. We have not included comments regarding your proposed language for the UPLIFT trial (Protocol 205.235), including information regarding exacerbations and respiratory failure. We will provide comments regarding these issues after the Pulmonary Allergy Drugs Advisory Committee meeting to be held on November 19, 2009.

HIGHLIGHTS of PRESCRIBING INFORMATION

2. The Adverse Reactions section of HIGHLIGHTS should contain a list of adverse reactions that are included in Table 1. Inclusion of adverse reactions from the Spiriva HandiHaler placebo controlled trials is acceptable.

FULL PRECRIBING INFORMATION

3. In Section 4, CONTRAINDICATIONS, include hypersensitivity to tiotropium or any ingredients in Spiriva HandiHaler. Include descriptions of hypersensitivity reactions that have occurred in patients receiving Spiriva HandiHaler from clinical trials and post-marketing. For example, "In clinical trials and post-marketing experience with Spiriva HandiHaler, cases of X, X, X have been reported."
4. In Section 5.2, WARNINGS AND PRECAUTIONS, Immediate Hypersensitivity Reactions, include a brief list of hypersensitivity reactions that have occurred in clinical trials or post-marketing with Spiriva HandiHaler or refer back to Section 4 for the list.
5. Delete Section 5.4, WARNING AND PRECAUTIONS, (b) (4) and create two separate sections (5.4 and 5.5) to highlight the potential eye and urinary issues with Spiriva HandiHaler. For example:

   5.4 Worsening of Narrow-Angle Glaucoma

   5.5 Urinary Retention.
6. In the two distinct sections noted in Comment #5 above, include relevant information from clinical trials or post-marketing regarding these potential effects. Include information for prescribers and patients, e.g. "Prescribers and patients should be alert for be signs of acute narrow-angle glaucoma, e.g. eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema. Instruct patients to consult a physician immediately should any of these signs and symptoms develop".

7. In Section 6, ADVERSE REACTIONS, revise the 3rd bullet regarding anticholinergic effects to be consistent with the revised sections 5.4 and 5.5.
8. We note that you have (b) (4) Replace these data in Table 1 and the sentence immediately after Table 1 as per the currently approved label. The purpose of inclusion of these data is to provide a more complete picture of the Spiriva HandiHaler adverse reaction profile. While we generally do not include active controlled clinical trial information in product labels, inclusion of active controlled clinical trial information can be useful in certain situations, e.g. transitioning from a short acting to long acting product, such as Spiriva HandiHaler.
9. Include a brief description of demographic data from your trials in Section 6.1., ADVERSE REACTIONS, Clinical Trials Experience.Include a description of the overall clinical trial database from which adverse reaction data have been drawn, including a discussion of overall exposure (number of patients, dose schedule, duration) and demographics of the exposed population.
10. The multiple different presentations of adverse reaction data in Section 6, ADVERSE REACTIONS, seem disjointed, i.e. Table 1, ≥3% but <1% greater than placebo, 1-3%, <1% and Additional Adverse Reactions. Consider combining some of the information to improve the readability of the section.
11. We have revised Section 12.2, CLINICAL PHARMACOLOGY, Pharmacodynamics, to include QT study language that was approved for Supplement S-027 on November 13, 2008.

Patient's Instuctions for Use

12. Revise the Patient Instructions for Use (PIU) to include language that was approved for Supplement S-014 on March 3, 2009. Also include figures in the PIU you submitted as an amendment to S-029 on July 28, 2009.

Submit your response to me via telephone facsimile to 301-796-9728 or email at Miranda.Raggio@fda.hhs.gov by noon on 11-16-09. Your response will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact Miranda Raggio, Regulatory Project Manager, at 301-796-2109. Note..I am out of the office the week of November 9th. If you have questions regarding this fax during that time please contact Sadaf Nabavian at Sadaf.Nabavian@fda.hhs.gov.

19 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21395	SUPPL-29	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	SPIRIVA HANDIHALER

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/s/

MIRANDA B RAGGIO
11/05/2009

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Drug Evaluation II

FACSIMILE CORRESPONDENCE

Date: October 6, 2009

To: Jeff Snyder

Company: Boehringer Ingelheim

Phone: 203-778-7727

Fax: 203-837-4928

From: Miranda Raggio, RN, BSN, MA
Senior Regulatory Health Project Manager
Division of Pulmonary and Allergy Products

Phone: 301-796-2109

Subject: NDA 21-395 S029 Telecon Meeting Minutes

# of Pages: 4

Comments: Please call with any questions. Thanks, miranda

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NDA 21-395 S029

Attached is a courtesy copy of the meeting minutes from our teleconference on September 16, 2009, per your request.

MEMORANDUM OF TELECON

DATE: September 16, 2009

APPLICATION NUMBER: NDA 21-395 S-029

BETWEEN:

Name: Jeff Snyder, Executive Director, Drug Regulatory Affairs (DRA)
Chris Corsico, M.D., VP, DRA
Tacy Pack, Director, DRA
Dr. Steven Kesten, Medical
Deb Burkhart, Medical
Shirani Tonge, Biometrics and Data Management
Dr. Harry Ulrich, Drug Surveillance and Information
Dr. Amy VanAndel, DRA
Dawn Collette, Medical
Dr. Mike Tsianco, Biometrics and Data Management
Dr. Shailendra Menjoge, Biometrics and Data Management
Bihong Lu, DRA
Damon Daulerio, DRA
Phyllis Christesen, Pfizer, DRA
Franklin Cerasoli, Pfizer, Medical
Dr. Thor Voigt, Sr. VP Medical, DRA
Dr. Inge Leimer, Corp Statistics

Phone: 1-866-606-4717, Passcode (b) (4)
Representing: Boehringer Ingelheim (BI)

AND

Name: Badrul A. Chowdhury, M.D., Ph.D., Division Director, DPAP, HFD-570
Theresa Michele, M.D., Medical Reviewer, DPAP, HFD-570
Miranda Raggio, BA, BSN, MA, Regulatory Project Manager, DPAP, HFD-570

SUBJECT: UPLIFT Supplement to NDA 21-395, S-029: Advisory Committee (AC) Meeting

A teleconference was arranged for September 16, 2009, to inform BI of the Division's focus at the upcoming November 19, 2009, Advisory Committee meeting. The Division made the following points:

1. The submission of the ERASMUS study to NDA 21395/S-029 extended the PDUFA clock. The new PDUFA goal date is 12-17-09. An official review extension letter will be sent to BI.

2. The scope of the AC meeting will focus on two trials- the UPLIFT trial (205.235) and the VA

trial (205.266). Two specific items will be discussed in this public forum: 1) the COPD exacerbations claim, which is new for this class of drug and 2) the stroke, cardiovascular event, and mortality safety signals which were the subject of the Early Communication (EC) of March 18, 2008, and the EC update of October 7, 2008.

In order to have full disclosure of the safety issues, two data elements which are not included in the original supplemental NDA or the public domain will be brought into the discussion. These elements are the ERASMUS study and the three one year Respimat clinical trials, 205.254, 205.255, and 205.372. The focus of the discussion around these clinical trials will be in relation to mortality data pertinent to the HandiHaler product.

3. Members of the Drug Safety and Risk Management Committee will be present at the AC meeting.

4. The Division will not be discussing the questions to be posed to the Advisory Committee prior to the release of the Federal Register Notice, and no further meetings between BI and the Division are planned at this time.

A brief period of questions and answers followed, as highlighted below:

1. BI asked if the information from studies 205.254, 205.255, and 205.372, submitted to IND (b) (4) will be redacted. The Division responded that no redaction will occur, as the discussion of this safety data will be an expansion of the information already released to the public in the EC's mentioned above.

2. BI noted that efficacy data may be pertinent to the AC discussion, and expressed the opinion that this efficacy data is important to provide the proper foundation for this public discussion. The Division acknowledged this point.

3. BI asked what level of granularity with regard to mortality the Division planned to present at the AC meeting. The Division stated that the goal of the meeting is to provide a balanced and fair presentation of data so that the AC advisors can make objective decisions. The Respimat details presented will be limited to those necessary for the AC to make appropriate determinations. The Division notified BI that they are free to supply additional details of the mortality data or efficacy data related to Respimat in their briefing package.

4. BI asked if it would be possible to have additional meetings with the Division prior to October 28, 2009, when the briefing documents will be submitted to the AC planning group. The Division stated that this is not the traditional approach to AC preparation, but that BI's request is noted and will be reconsidered closer to the October 28, 2009, date.

5. BI asked if they could send specific questions to the Division prior to the AC meeting. The Division responded that BI may send requests for feedback but noted that a response will be dependent on the Division's priorities and workload at the time of the submission.

6. The Division stated that it is looking forward to an interesting AC meeting, as safety data for the HandiHaler and Respimat reveals a unique and not completely understood difference between the two products. The Division stated that data will be presented in as clear a fashion as possible to the AC members.

7. BI asked if the AC comes to a positive conclusion about the risks of Respimat if the Division will be open to further post-AC meeting discussion related to this issue. The Division responded in the affirmative.

BI acknowledged understanding of all of the points discussed. The meeting was concluded with the Division and BI agreeing to continue to communicate in a timely and transparent fashion.

Miranda Raggio, RN, BSN, MA
TITLE: Regulatory Project Manager

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21395	SUPPL-29	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	SPIRIVA HANDIHALER

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/s/

MIRANDA B RAGGIO
09/17/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PDUFA GOAL DATE EXTENSION
PRIOR APPROVAL SUPPLEMENT

NDA 21-395/S-029

Boehringer Ingelheim
900 Ridgebury Road
PO Box 368
Ridgefield, CT 06877-0368

Attention: Tacy Pack, Director
Drug Regulatory Affairs

Dear Ms. Pack:

Please refer to your November 17, 2008, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Spiriva HandiHaler.

On September 15, 2009, we received your September 10, 2009, major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is December 17, 2009.

If you have any questions, call Miranda Raggio, Senior Regulatory Project Manager, at (301)-796-2109.

Sincerely yours,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Division of Pulmonary and Allergy Products
Office of New Drugs
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21395	SUPPL-29	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	SPIRIVA HANDIHALER

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/s/

BADRUL A CHOWDHURY
09/18/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: OSE/DEPI: Attention: Solomon Iyasu, Division Director	FROM (*Name, Office/Division, and Phone Number of Requestor)*: Miranda Raggio, RPM, DPAP/ODEII/OND 301-796-2109

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
9-2-09	46,687	21-395 S029	SE8	8-3-09 submitted to IND 46,687

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Sprivia(titropium bromide)	Standard	Respiratory	October 7, 2009

NAME OF FIRM: Boehringer Ingelheim

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☒ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:

The ERASMUS study is a nested case control epidemiology study of Spiriva in patients with COPD from Erasmus University (Netherlands). The study included a population of 6788 COPD patients over 6 years (2000-2007) and compared the safety of tiotropium to no anticholinergic use and to LABA use. Endpoints included MI, ventricular arrhythmia, heart failure, renal failures, stroke and TIA, death, diabetes and a combined cardiovascular/cerebrovascular endpoint. The executive summary notes that no differences were found in these endpoints between Spiriva and no use of anticholinergic drugs or Spiriva and LABAs.

Please provide a review of the trial report, with an emphasis on stroke, death, and cardiovascular endpoints, to be presented at the Spiriva HandiHaler AC meeting on November 19. The written review should be completed no later than October 9, so that it can be included in the background package for the AC meeting.

I have the word version of this study report. Please let me know who this consult will be assigned to and I will get the study report to them. Dr. Teresa Michele has the original hard copy. Thanks,m

SIGNATURE OF REQUESTOR Miranda Raggio, RN, BSN, MA	METHOD OF DELIVERY (Check one) ☐ DFS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
IND 46687	ORIG 1	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	BA 679 BR(TIOTROPIUM BROMIDE)POWDER INH
NDA 21395	SUPPL 29	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	SPIRIVA HANDIHALER

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/s/

MIRANDA B RAGGIO
09/02/2009

NDA/BLA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

Application Information		
NDA # 21395 BLA#	NDA Supplement #:S- 029 BLA STN #	Efficacy Supplement Type SE- 8
Proprietary Name: Spiriva HandiHaler Established/Proper Name: tiotropium bromide Dosage Form: inhalation powder Strengths: 18 mcg		
Applicant: Boehringer Ingelheim Agent for Applicant (if applicable):		
Date of Application: 11-17-08 Date of Receipt: 11-17-08 Date clock started after UN:		
PDUFA Goal Date: 9-17-09	Action Goal Date (if different): 9-3-09	
Filing Date: 1-17-09 Date of Filing Meeting: 1-6-09		
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3S		
Proposed Indication(s): supplement provides for the addition of UPLIFT data to the Clinical Trials and Adverse Reactions sections of the PI.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***Refer to Appendix A for further information.***	☒ 505(b)(1) ☐ 505(b)(2) ☒ 505(b)(1) ☐ 505(b)(2)	
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.***	☒ Standard ☐ Priority ☐ Tropical disease Priority review voucher submitted	
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐		
Part 3 Combination Product? ☐	☐ Drug/Biologic ☒ Drug/Device ☐ Biologic/Device	
☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR	

	601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 46687	
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒ YES ☐ NO
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.***	☒ YES ☐ NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	☒ YES ☐ NO
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ora/compliance_ref/aiplist.html*** **If yes**, explain: **If yes**, has OC/DMPQ been notified of the submission? **Comments**:	☐ YES ☒ NO ☐ YES ☐ NO
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	☒ YES ☐ NO
User Fee Status **Comments:**	☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).*	
Exclusivity	

Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm*** **If yes**, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)*** **Comments**:	☐ YES ☒ NO ☐ YES ☐ NO
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.* **Comments**:	☒ YES # years requested: 3 ☐ NO
If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***): Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***	☒ Not applicable ☐ YES ☐ NO
505(b)(2) (NDAs/NDA Efficacy Supplements only)	
	☒ **Not applicable**
1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES ☐ NO
2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).	☐ YES ☐ NO
3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?	☐ YES ☐ NO

Note: *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*	

4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:	☐ YES ☐ NO

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Format and Content

Do not check mixed submission if the only electronic component is the content of labeling (COL). **Comments**:	☐ All paper (except for COL) ☐ All electronic ☒ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	UPLIFT Data sent in paper form
If electronic submission: paper forms and certifications signed (non-CTD) or electronic forms and certifications signed (scanned or digital signature)(CTD)? ***Forms*** *include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.* **Comments**:	☒ YES ☐ NO
If electronic submission, does it follow the eCTD guidance? (*http://www.fda.gov/cder/guidance/7087rev.pdf*) **If not,** explain (e.g., waiver granted):	☐ YES ☐ NO

Form 356h: Is a signed form 356h included? ***If foreign applicant, both the applicant and the U.S. agent must sign the form.*** Are all establishments and their registration numbers listed on the form? **Comments**:	☒ YES ☐ NO ☒ YES ☐ NO
Index: Does the submission contain an accurate comprehensive index? **Comments**:	☒ YES ☐ NO
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain:	☒ YES ☐ NO
Controlled substance/Product with abuse potential: Abuse Liability Assessment, including a proposal for scheduling, submitted? Consult sent to the Controlled Substance Staff? **Comments**:	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
BLAs/BLA efficacy supplements only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	 ☐ YES ☐ NO
Patent Information (NDAs/NDA efficacy supplements only)	
Patent information submitted on form FDA 3542a? **Comments**: 7 non-expired patents listed in Orange Book. Statement that patent information previously submitted is included in this NDA	☐ YES ☒ NO
Debarment Certification	
Correctly worded Debarment Certification with authorized signature?	☒ YES ☐ NO

If foreign applicant, both the applicant and the U.S. Agent must sign the certification. ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"* **Comments**:	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
Field Copy Certification: that it is a true copy of the CMC technical section (***applies to paper submissions only***) ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☒ Not Applicable (*electronic submission or no CMC technical section*) ☐ YES ☐ NO
Financial Disclosure	
Financial Disclosure forms included with authorized signature? ***Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.* **Comments**:	☒ YES ☐ NO
Pediatrics	
PREA ***Note***: *NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.* Are the required pediatric assessment studies or a full waiver of pediatric studies included? **If no,** is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included? • ***If no, request in 74-day letter.*** • **If yes**, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO

Comments:	
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).*** **Comments**:	☐ YES ☒ NO
Prescription Labeling	
Check all types of labeling submitted. **Comments**:	☐ **Not applicable** ☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use ☐ MedGuide ☐ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)
Is electronic Content of Labeling submitted in SPL format? ***If no, request in 74-day letter.*** **Comments**:	☒ YES ☐ NO
Package insert (PI) submitted in PLR format? **If no**, was a waiver or deferral requested before the application was received or in the submission? **If before**, what is the status of the request? ***If no, request in 74-day letter.*** **Comments**:	☒ YES ☐ NO ☐ YES ☐ NO
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? **Comments**:	☒ YES ☐ NO
MedGuide or PPI (plus PI) consulted to OSE/DRISK? (*send WORD version if available*) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
REMS consulted to OSE/DRISK? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP?	☒ Not Applicable ☐ YES ☐ NO

Comments:	

OTC Labeling	
Check all types of labeling submitted. **Comments**:	☒ **Not Applicable** ☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)
Is electronic content of labeling submitted? ***If no, request in 74-day letter.*** **Comments**:	☒ YES ☐ NO
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.*** **Comments**:	☐ YES ☐ NO
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.*** **Comments**:	☐ YES ☐ NO
Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP? **Comments**:	☒ YES ☐ NO
Meeting Minutes/SPA Agreements	
End-of Phase 2 meeting(s)? ***If yes, distribute minutes before filing meeting.*** **Comments**: Unable to locate minutes	☐ YES Date(s): ☒ NO
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? ***If yes, distribute minutes before filing meeting.*** **Comments**: Unable to locate minutes	☐ YES Date(s): ☒ NO
Any Special Protocol Assessment (SPA) agreements? ***If yes, distribute letter and/or relevant minutes before filing meeting.*** **Comments**:	☐ YES Date(s): ☒ NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: 1-6-09

NDA/BLA #: 21-395, S-029

PROPRIETARY/ESTABLISHED NAMES: Spiriva HandiHaler/tiotropium bromide inhalation powder

APPLICANT: Boehringer Ingelheim

BACKGROUND: Spiriva HandiHaler was approved 1-30-04. This supplement provides for the addition of UPLIFT Trial data to the Clinical Trials and Adverse Reaction sections of the product label

(Provide a brief background of the drug, (e.g., molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Miranda Raggio	Y
	CPMS/TL:	Sandy Barnes	N
Cross-Discipline Team Leader (CDTL)	Sally Seymour		Y
Clinical	Reviewer:	Theresa Michele	Y
	TL:	Sally Seymour	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
OSE	Reviewer:		
	TL:	Sean Bradley	Y
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		

	TL:		

Clinical Pharmacology	Reviewer:	Sandra Suarez	Y
	TL:	Wei Qiu	Y
Biostatistics	Reviewer:	Joan Beunconsejo	Y
	TL:	Qian Li	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Luqi Pei	Y
	TL:	Tim Robison	Y
Statistics, carcinogenicity	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Ramesh Ragavachari	Y
	TL:		
Facility (*for BLAs/BLA supplements*)	Reviewer:		
	TL:		
Microbiology, sterility (*for NDAs/NDA efficacy supplements*)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Other reviewers			

OTHER ATTENDEES:

505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO

Electronic Submission comments **List comments**:	☒ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☒ YES Date if known: ☐ NO ☒ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO ☐ YES ☐ NO
• Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ Not Applicable ☒ YES ☐ NO
• Sterile product? **If yes**, was Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**)	☐ YES ☒ NO ☐ YES ☐ NO

FACILITY (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT
Signatory Authority: Miranda Raggio **GRMP Timeline Milestones**: Primary Reviews due 7-24-09; Secondary Reviews due 8-5-09 Mid-cycle meeting 4-15-09; Labeling meeting 7-17-09; Wrap-Up meeting: 7-15-09 **Comments**:

	REGULATORY CONCLUSIONS/DEFICIENCIES
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): ☐ Standard Review ☐ Priority Review

	ACTIONS ITEMS
☐	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
☐	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If BLA or priority review NDA, send 60-day letter.
☐	Send review issues/no review issues by day 74
☒	Other Filing Review initialed by SB on 4-23-09

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/s/

Miranda Raggio
4/23/2009 01:04:09 PM
CSO

NDA 21-395 S029

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Drug Evaluation II

FACSIMILE CORRESPONDENCE

Date: March 10, 2009

To: Tacy Pack, Director/DRA

Company: Boehringer Ingelheim

Phone: 203-798-5545

Fax: 203-791-6262

From: Miranda Raggio, RN, BSN, MA
Regulatory Health Project Manager
Division of Pulmonary and Allergy Products

Phone: 301-796-2109

Subject: N21-395, S-029 Information Request

# of Pages: 3

Comments: Please call with any questions. Thanks, miranda

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NDA 21-395 S029

We are currently reviewing your NDA submission dated November 17, 2008, received November 17, 2008, for SPIRIVA HandiHaler. We have the following request for information:

> *In Appendix 16.1.9.2, you provided documentation (Statdoc) on the results from the analyses of efficacy endpoints. This document included the SAS output for all the analyses conducted.*
>
> *Provide the SAS code used to generate the results for the analyses of the primary and secondary endpoints presented in the Study Report and in Appendix 16.1.9.2. The 'variables names' noted in the codes should match the 'variable names' included in the datasets provided on November 17, 2008. There appear to be some variables in the SAS output that are not in the datasets (e.g. dayclass, analyr). Provide documentation on how these variables are derived from the datasets.*

Please fax your response to my attention at 301-796-9728 by close of business on March 13, 2009. An official copy of your response must subsequently be submitted to the NDA.

If you have any questions, please contact Miranda Raggio, Regulatory Project Manager, at 301-796-2109.

NDA 21-395 S029

Drafted by Miranda Raggio/3-9-09
Initialed by Sandy Barnes/ 3-9-09
Joan Buenconsejo/3-10-09
Qian Li/3-10-09

Finalized by Miranda Raggio/3-10-09

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/s/

Miranda Raggio
3/10/2009 11:55:24 AM
CSO

NDA 21-395 S029

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Drug Evaluation II

FACSIMILE CORRESPONDENCE

Date: March 6, 2009

To: Tacy Pack, Director/DRA

Company: Boehringer Ingelheim

Phone: 203-798-5545

Fax: 203-791-6262

From: Miranda Raggio, RN, BSN, MA
Regulatory Health Project Manager
Division of Pulmonary and Allergy Products

Phone: 301-796-2109

Subject: Spiriva Meta-Analysis Information Request

# of Pages: 4

Comments: Please call with any questions. Thanks, miranda

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We are currently reviewing your NDA submission received November 17, 2008, for Spiriva HandiHaler. As discussed in our teleconference on March 3, 2009, we are planning to conduct meta-analyses of tiotropium and ipratropium clinical trial data. In order to plan for these analyses, we have the following requests for information:

1. Provide the following tables of tiotropium studies completed* as of July 30, 2008:
   a. Studies having the following characteristics:
      - Randomized, double-blind, placebo controlled
      - Any tiotropium dose
      - Either parallel group or crossover design
      - Patient population in any indication, excluding studies involving only healthy volunteers
      - Any study duration
   b. Studies not having the characteristics above. State the reason the study does not meet the criteria

   For each study provide the following information:
      - Study number
      - Date of completion
      - Design
      - Treatment groups (all)
      - Indication
      - Duration of protocol-specified double-blind treatment
      - Number of patients randomized to each arm of treatment
      - Number of deaths (excluding vital status) in each arm of treatment
      - Whether or not study was included in the pooled analysis (30 studies) provided in your November 17, 2008, submission

2. Provide the following tables of ipratropium studies completed* as of July 30, 2008:
   a. Studies having the following characteristics:
      - Randomized, double-blind, placebo controlled
      - Any ipratropium dose
      - Either parallel group or crossover design
      - Patient population in any indication, excluding studies involving only healthy volunteers
      - Any study duration

      Exclude studies only containing ipratropium combination therapy (i.e. Combivent)

   b. Studies not having the characteristics above. State the reason the study does not meet criteria

For each study provide the following information:

- Study number
- Date of completion
- Design
- Treatment groups (all)
- Indication
- Duration of protocol-specified double-blind treatment
- Number of patients randomized to each arm of treatment
- Number of deaths (excluding vital status) in each arm of treatment

Include all studies containing at least an ipratropium arm and placebo, even if the study was designed to evaluate a different drug (i.e. inclusion of ipratropium as an active control in a tiotropium trial). Placebo-controlled studies containing both tiotropium and ipratropium arms will be included on more than one list.

3. Provide the clinical study report synopsis or each study listed in requests 1 (a and b) and 2 (a and b) above.

*Completed studies include both studies that met enrollment and studies which were terminated prior to full enrollment. Completed studies do not include those for which no patients were randomized. The cut-off date of July 30, 2008, is arbitrary, intending to capture all studies for which the database has been locked and unblinded. You may choose to use a later cut-off date.

Please fax your response to my attention at 301-796-9728 by close of business on March 20, 2009. An official copy of your response must subsequently be submitted to the NDA.

If you have any questions, please contact Miranda Raggio, Regulatory Project Manager, at 301-796-2109.

NDA 21-395 S029

Drafted by Miranda Raggio/3-3-09
Initialed by Sandy Barnes/ 3-6-09
Terri Michele/3-6-09
Finalized by Miranda Raggio/3-6-09

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/s/

Miranda Raggio
3/6/2009 11:07:45 AM
CSO

MEMORANDUM OF TELECON

DATE: March 3, 2009

APPLICATION NUMBER: NDA 21-395 S-029

BETWEEN:

Name: Jeff Snyder, Executive Director, DRA
Chris Corsico, M.D., VP, DRA
Tacy Pack, Director, DRA

Phone: 1-866-606-4717, Passcode (b) (4)
Representing: Boehringer Ingelheim (BI)

AND

Name: Sally Seymour, M.D., DPAP, HFD-570
Theresa Michele, M.D., DPAP, HFD-570
Miranda Raggio, RN, MA, RPM, DPAP, HFD-570

SUBJECT: UPLIFT Supplement to NDA 21-395, S-029: Status Update

A teleconference was arranged for March 3rd to inform BI of the general path that the Division is taking in the review of the UPLIFT trial data. The Division made the following points:

1. The Division feels that the three safety signals (stroke, potential cardiovascular issues noted in the Singh JAMA article, and potential mortality/Respimat) need to be addressed as a global issue.

2. The Division and collaborative biostaticians will be performing a meta-analysis of BI's tiotropium studies.

3. The Division will evaluate the safety of ipratropium concurrently for a potential overall class effect.

4. The Division will be requesting information from BI related to the tiotropium and ipratropium studies during the course of the review

BI acknowledged understanding of all of the points discussed. The meeting was concluded with the Division and BI agreeing to continue to communicate in a timely and transparent fashion.

Miranda Raggio, RN, BSN, MA
TITLE: Regulatory Project Manager

Created by Miranda Raggio/3-4-09
Initialed by Sally Seymour and Terri Michelle/3-4-09
Finalized by Miranda Raggio/3-4-09

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/s/

Miranda Raggio
3/4/2009 09:47:49 AM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Drug Evaluation II

FACSIMILE CORRESPONDENCE

Date: February 24, 2009

To: Tacy Pack, Director/DRA

Company: Boehringer Ingelheim

Phone: 203-798-5545

Fax: 203-791-6262

From: Miranda Raggio, RN, BSN, MA
Regulatory Health Project Manager
Division of Pulmonary and Allergy Products

Phone: 301-796-2109

Subject: N21-395, S-029 Information Request

# of Pages: 3

Comments: Please call with any questions. Thanks, miranda

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NDA 21-395 S029

We are currently reviewing your NDA submission dated November 17, 2008, received November 17, 2008, for SPIRIVA HandiHaler. We have the following request for information:

> In reference to the following paragraph on page 22 of the Statistical Analysis Plan for UPLIFT:
>
> **"Fraudulent PFT data:** a BI audit revealed the lack of data integrity at one of the investigator sites. The PFT data for the following patients and visits are deemed as fraudulent, and will be removed from the analyses: patient 18956 visits 9 and 10, patient 18933 visit 9, patient 18974 visits 7 and 9, patient 18932 visits 3 and 5".
>
> Provide the following information:
>
> 1. The audit report for Site #1106 (Dr. Kemmerich, Germany)
> 2. The rationale for excluding only these particular data points, while including others from this site in the analyses

Please fax your response to my attention at 301-796-9728 by close of business on March 12, 2009. An official copy of your response must subsequently be submitted to the NDA.

If you have any questions, please contact Miranda Raggio, Regulatory Project Manager, at 301-796-2109.

NDA 21-395 S029

Drafted by Miranda Raggio/2-19-09
Initialed by Sandy Barnes/ 2-23-09
Terri Michele/2-24-09
Sally Seymour/2-24-09
Finalized by Miranda Raggio/2-24-09

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/s/

Miranda Raggio
2/24/2009 09:30:24 AM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: OSE/DEPI: Attention: Solomon Iyasu, Division Director	FROM (*Name, Office/Division, and Phone Number of Requestor)*: Miranda Raggio, RPM, DPAP/ODEII/OND 301-796-2109

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
2-19-09	46,487	21-395 S029	SE8	21-395 S02911-17-09

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Sprivia(titropium bromide)	Standard	Respiratory	as soon as possible

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☒ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☒ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: The results of a four year, 6000 patient, placebo controlled clinical trial with tiotropium (UPLIFT) were submitted in November 2008. We plan to discuss this study at an Advisory Committee in 2009 with regards to three potential safety signals with tiotropium:
- stroke - identified from a pooled analysis of 29 studies with tiotropium
- mortality - identified from two phase 3 studies with tiotropium Respimat
- cardiovascular events - identified from two analyses of tiotropium and ipratropium from literature - Singh et al, JAMA, September 2008 - Vol 300(12): 1439-1450 and Lee et al, Ann Intern Med, September 2008 - Vol 149(6): 380-390

Please provide input as to whether you think UPLIFT is adequate to address these safety concerns or whether other analyses are needed, e.g. meta-analysis. If further analysis are needed, we request your input as to the design of these additional analyses. We also request input as to the strengths and limitations of the meta-analyses in the literature with tiotropium/ipratropium. This input will be helpful to frame the safety signals generated from these analyses. Please contact us if you have questions.

Links: \\FDSWA150\NONECTD\N21395\S_029\2008-11-17 for NDA 21-395 S029 and \\FDSWA150\NONECTD\I46687\O_312\2008-04-17 for the UPLIFT trial data(IND 46687)	
SIGNATURE OF REQUESTOR Miranda Raggio, RN, BSN, MA	METHOD OF DELIVERY (Check one) ☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Miranda Raggio
2/23/2009 03:42:44 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Drug Evaluation II

FACSIMILE CORRESPONDENCE

Date: January 7, 2009

To: Jeff Snyder

Company: Boehringer Ingelheim

Phone: 203-778-7727

Fax: 203-837-4928

From: Miranda Raggio, RN, BSN, MA
Regulatory Health Project Manager
Division of Pulmonary and Allergy Products

Phone: 301-796-2109

Subject: NDA 21-395 S029 Information Request

# of Pages: 3

Comments: Please call with any questions. Thanks, miranda

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2109. Thank you.

NDA 21-395 S029

We are currently reviewing your NDA dated November 17, 2008, received November 17, 2008, for SPIRIVA HandiHaler. We have the following requests for information:

1. Provide summary tables and data listings by investigative site for the following:
   a. Protocol violations
   b. Deaths

2. Provide subgroup analyses for the following endpoints, using the same subgroups as per your subgroup analyses for mortality and FEV1.
   a. Time to first COPD exacerbation
   b. Time to first COPD exacerbation leading to hospitalization
   c. Number of COPD exacerbations per patient year
   d. Adverse events: individual, serious, cardiovascular events, stroke events

3. Provide the following documents:
   a. Data Safety Monitoring Board Charter and meeting minutes
   b. Mortality Adjudication Committee Charter and meeting minutes
   c. Data Handling Guidelines
   d. Clinical Data Monitoring Plan

Submit a response to #1 via telephone facsimile to me at 301-796-9728 by COB on January 26, 2009, and to #2 & 3 by COB on February 16, 2009. This information will also need to be submitted officially to the NDA, either in hard copy or electronically.

If you have any questions, please contact me at 301-796-2109.

Miranda Raggio, RN, BSN, MA
Regulatory Project Manager
Division of Pulmonary and Allergy Products
ODEII/OND/CDER
Miranda.Raggio@fda.hhs.gov

NDA 21-395 S029

Drafted by Miranda Raggio/1-7-09
Initialed by Sandy Barnes/ 1-7-09
Theresa Michele/1-7-09
Sally Seymour/1-7-09
Finalized by Miranda Raggio/1-7-09

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/s/

Miranda Raggio
1/7/2009 04:10:47 PM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Division of Drug Marketing, Advertising, and Communications (DDMAC)

FROM (*Name, Office/Division, and Phone Number of Requestor)*: Division of Pulmonary and Allergy Products: Miranda Raggio, 301-796-2109

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
11-21-08		21-395 S029	Efficacy Supplement S08	11-17-2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Spiriva HandiHaler(tiotropium bromide inhalation powder)	Standard	Respiratory	7-17-08

NAME OF FIRM: Boehringer Ingelheim

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☒ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: BI submitted an efficacy supplement which proposes new language to reflect the p outcomes of the HandiHaler UPLIFT clinical trial (205.224). Please review the labeling (PI, Patient's Instructions for Use) in this submission. The EDR link is: \\FDSWA150\NONECTD\N21395\S_029\2008-11-17

SIGNATURE OF REQUESTOR
Miranda Raggio, RN, BSN, MA

METHOD OF DELIVERY (Check one)
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/s/

Miranda Raggio
12/2/2008 12:30:05 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
CDER OSE CONSULTS

FROM: Miranda Raggio, Regulatory Project Manager, Division of Pulmonary and Allergy Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
11-21-08		21-395 S-029	Efficacy Supplement S08	11-17-08

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Spiriva HandiHaler (tiotropium bromide inhalation powder)	Standard	Respiratory	7-17-09

NAME OF FIRM: Boehringer Ingelheim

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☒ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*: **Trade name review**

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

- ☐ TYPE A OR B NDA REVIEW
- ☐ END OF PHASE II MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):

STATISTICAL APPLICATION BRANCH

- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: BI submitted an efficacy supplement which proposes new labeling language to reflect the outcomes of the HandiHaler UPLIFT clinical trial (205.235) . Please review the labeling (PI, Patient's Instructions for Use) in this submission. The EDR link is: \\FDSWA150\NONECTD\N21395\S_029\2008-11-17

PDUFA DATE:
ATTACHMENTS: Draft Package Insert, Container and Carton Labels
CC: Archival IND/NDA
HFD- /Division File
HFD- /RPM
HFD- /Reviewers and Team Leaders

NAME AND PHONE NUMBER OF REQUESTER
Miranda Raggio,Regulatory Project Manager

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/s/

Miranda Raggio
12/2/2008 12:32:12 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-395/S-029 **PRIOR APPROVAL SUPPLEMENT**

Boehringer Ingelheim
900 Ridgebury Road
PO Box 368
Ridgefield, CT 06877-0368

Attention: Tacy Pack, Director
Drug Regulatory Affairs

Dear Ms. Pack:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: SPIRIVA® HandiHaler® (tiotropium bromide inhalation powder)

NDA Number: 21-395

Supplement number: 029

Review Priority Classification: Standard (S)

Date of supplement: November 17, 2008

Date of receipt: November 17, 2008

This supplemental application proposes revisions to the package insert including adding new language to the CLINICAL STUDIES and ADVERSE REACTIONS sections, reflecting the results of Clinical Trial U08-3718-03 (205.235).

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 16, 2009, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be September 17, 2009.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We acknowledge receipt of your request for a waiver of pediatric studies for this application. Once the application has been filed we will notify you whether we have waived the pediatric study requirement for this application.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any question, call Miranda Raggio, Regulatory Project Manager, at (301) 796-2109.

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Supervisory CPMS
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Miranda Raggio
11/25/2008 12:24:14 PM
Signing for Sandy Barnes

Miranda Raggio
11/25/2008 12:24:14 PM
Signing for Sandy Barnes

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]		
NDA # 21-395 BLA #	NDA Supplement # S-29 BLA STN #	If NDA, Efficacy Supplement Type: SE8
Proprietary Name: Spiriva HandiHaler Established/Proper Name: tiotropium bromide Dosage Form: inhalation powder		Applicant: Boehringer Ingelheim Agent for Applicant (if applicable):
RPM: Miranda Raggio		Division: DPAP

NDAs: NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☒ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: **Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.** ☐ No changes ☐ Updated Date of check: **If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.** **On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.**

❖ User Fee Goal Date Action Goal Date (if different)	December 17, 2009
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None
❖ Promotional Materials *(accelerated approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance www.fda.gov/cder/guidance/2197dft.pdf). If not submitted, explain _____	☐ Received

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application[2] Characteristics	
Review priority: ☒ Standard ☐ Priority Chemical classification (new NDAs only): ☐ Fast Track ☐ Rolling Review ☐ Orphan drug designation ☐ Rx-to-OTC full switch ☐ Rx-to-OTC partial switch ☐ Direct-to-OTC NDAs: Subpart H ☐ Accelerated approval (21 CFR 314.510) ☐ Restricted distribution (21 CFR 314.520) Subpart I ☐ Approval based on animal studies BLAs: Subpart E ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 601.42) Subpart H ☐ Approval based on animal studies ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC Comments: _____	
❖ Date reviewed by PeRC *(required for approvals only)* If PeRC review not necessary, explain: _____	2-25-09
❖ BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM *(approvals only)*	☐ Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☐ No
• Press Office notified of action (by OEP)	☐ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	Yes
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) 12/17/09
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	11-17-08
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☒ Instructions for Use ☐ None

[3] Fill in blanks with dates of reviews, letters, etc.

• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date at upper right of first page of each submission)*	
• Most-recent division proposal for (only if generated after latest applicant submission)	
• Most recent applicant-proposed labeling	
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM 1/21/09 ☒ DMEDP 10/29/09 ☒ DRISK 12/11/09 ☒ DDMAC 11/2/09 ☐ CSS ☐ Other reviews
❖ Proprietary Name • Review(s) *(indicate date(s))* • Acceptability/non-acceptability letter(s) *(indicate date(s))*	NA
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	4/23/09
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ 12-17-09
❖ Application Integrity Policy (AIP) Status and Related Documents www fda.gov/ora/compliance_ref/aip_page html	
• Applicant in on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatric Page *(approvals only, must be reviewed by PERC before finalized)*	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Postmarketing Requirement (PMR) Studies	☒ None
• Outgoing communications *(if located elsewhere in package, state where located)*	
• Incoming submissions/communications	
❖ Postmarketing Commitment (PMC) Studies	☒ None
• Outgoing Agency request for postmarketing commitments *(if located elsewhere in package, state where located)*	

[4] Filing reviews for other disciplines should be filed behind the discipline tab.

• Incoming submission documenting commitment	
❖ Outgoing communications *(letters (except previous action letters), emails, faxes, telecons)*	1-7-09, 2/24/09, 3-4-09, 3-6-09, 3-10-09, 7-21-09, 7-30-09, 9-3-09, 9-14-09, 9-18-09, 10-6-09, 11-5-09, 12/3/09, 12/11/09, 12-15-09, 12/16/09
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• PeRC *(indicate date; approvals only)*	☐ Not applicable
• Pre-Approval Safety Conference *(indicate date; approvals only)*	☐ Not applicable
• Regulatory Briefing *(indicate date)*	☐ No mtg
• Pre-NDA/BLA meeting *(indicate date)*	☐ No mtg
• EOP2 meeting *(indicate date)*	☐ No mtg
• Other (e.g., EOP2a, CMC pilot programs)	
❖ Advisory Committee Meeting(s)	☐ No AC meeting
• Date(s) of Meeting(s)	11/19/09
• 48-hour alert or minutes, if available	11/19/09
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☒ None
Cross-Discipline Team Leader Review *(indicate date for each review)*	☒ None 12-17-08
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	
• Clinical review(s) *(indicate date for each review)*	1/16/09, 12/1/09
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Safety update review(s) *(indicate location/date if incorporated into another review)*	
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	Clinical Review of 12-9-09, page 22
❖ Clinical reviews from other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not needed
❖ Risk Management • Review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)* • REMS Memo *(indicate date)* • REMS Document and Supporting Statement *(indicate date(s) of submission(s))*	☒ None
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to*	☐ None requested 7/21/09.

[5] Filing reviews should be filed with the discipline reviews.

investigators)	9/14/09
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None 12/4/09
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None 12/4/09
Statistical Review(s) *(indicate date for each review)*	☐ None 12/4/09
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 12-1-09
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None 7-30-09 Memo
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 12/1/09
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
CMC/Quality ☐ None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ None
• CMC/product quality review(s) *(indicate date for each review)*	☐ None 12/1/09
• BLAs only: Facility information review(s) *(indicate dates)*	☐ None
❖ Microbiology Reviews • NDAs: Microbiology reviews (sterility & pyrogenicity) *(indicate date of each review)* • BLAs: Sterility assurance, product quality microbiology *(indicate date of each review)*	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	

☐ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout) *(date completed must be within 2 years of action date)*	Date completed: n/a ☐ Acceptable ☐ Withhold recommendation
• BLAs: o TBP-EER o Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) *(date completed must be within 60 days prior to AP)*	 Date completed: ☐ Acceptable ☐ Withhold recommendation Date completed: ☐ Requested ☐ Accepted ☐ Hold

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE’s ADRA.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21395	SUPPL-29	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	SPIRIVA HANDIHALER

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MIRANDA B RAGGIO
12/17/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: George Rochester, Team Leader, OTS/OB/DBVI	FROM (*Name, Office/Division, and Phone Number of Requestor)*: Miranda Raggio, RPM, DPAP/ODEII/OND 301-796-2109

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
1-23-09	46,487	21-395 21-936		See below in comments

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Sprivia(titropium bromide)	Standard	Respiratory	April 30, 2009

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☒ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☒ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: DPAP requests input on how to address the stroke, mortality, and cardiovascular event safety signals with Spiriva, which are described in the attached reviews/articles. The UPLIFT trial, a large four year, 6000 patient study with Spiriva HandiHaler, was received on November 14, 2008 (IND 46,687, paper only). Applicable NDAs are NDA 21-395 029(Spiriva HandiHaler) and NDA 21-936 024(Spiriva Respimat). Respective EDR links for the original submissions are: \\FDSWA150\NONECTD\N21395\S_029\2008-11-17 and \\CDSESUB1\N21395\S_024\2008-01-11.
Note 1: Medical Officer is Dr. Theresa Michele; CDTL is Dr. Sally Seymour. Please contact Miranda Raggio, RPM, with any questions(301-796-2109).
Note2: (b) (4) (b) (4)

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Miranda Raggio, RN, BSN, MA	☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER