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APPLICATION NUMBER:

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SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date:	July 1, 2011
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA
Subject:	Division Director Summary Review
NDA Number:	22-383
Applicant Name:	Novartis Pharmaceuticals Corporation
Date of Submission:	December 15, 2008 (original) October 1, 2010 (complete response)
PDUFA Goal Date:	July 1, 2011
Proprietary Name:	Arcapta Neohaler
Established Name:	Indacaterol maleate
Dosage form:	Inhalation Powder (Dry powder for oral inhalation)
Strength:	75 mcg and 150 mcg
Proposed Indications:	Chronic Obstructive Pulmonary Disease
Action:	Approval 75 mcg; Complete Response 150 mcg

1. Introduction

Novartis originally submitted this 505(b)(1) new drug application for use of Arcapta Neohaler (indacaterol maleate 150 mcg and 300 mcg dry powder for oral inhalation) for once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. The proposed dose was one inhalation of a 150 mcg capsule once daily; with a qualifier that administration of a 300 mcg capsule once daily has been shown to provide additional clinical benefit in some patients. A Complete Response action for the original submission was taken on October 16, 2009, because of clinical deficiencies. The clinical review concluded that the doses proposed for marketing were high and not supported by the submitted efficacy and safety data. There were higher frequencies of cardiovascular and cerebrovascular adverse events compared to placebo and formoterol in patients with COPD, and possible asthma-related deaths compared to salmeterol in patients with asthma. The submitted data did not show meaningful efficacy differences between the proposed doses and a lower dose of 75 mcg. The submitted data also did not provide substantial evidence to support use of two different doses in patients with COPD with no demonstrated clinically meaningful advantage of the 300 mcg dose over the 150 mcg dose. Novartis was asked to explore the efficacy and establish the safety of lower doses and various dosing frequencies, to provide replicate data showing a clinically meaningful advantage of a higher dose compared to a lower dose, and to provide balancing safety data to show that there was no unacceptable safety disadvantage with the higher dose.

Novartis submitted this complete response on October 1, 2010, with results from additional clinical studies to address these deficiencies. The proposed dose of indacaterol

is lowered to 75 mcg or 150 mcg once daily based on data from additional clinical studies. Two doses are proposed with the reasoning that the higher dose will provide additional benefit in patients with more severe bronchial obstruction; the proposed advantage of the 150 mcg dose over the 75 mcg is based on pharmacodynamic modeling analysis and results of the St George's Respiratory Questionnaire (SGRQ).

During review of the submission, on FDA's request in December 2010, Novartis submitted an additional comprehensive safety analysis evaluating respiratory-related endpoints of death, intubation, and hospitalization related to asthma, COPD, or pneumonia. This analysis was submitted within the last 3 months of review and resulted in extension of the PDUFA time clock.

This summary review will provide an overview of the application. Major discussion points in this review are dose selection, safety, risk-benefit assessment, and the dose and dosing frequency proposed for marketing.

2. Background

There are several drug classes available for the relief of airflow obstruction in patients with COPD. These include beta-2 adrenergic agonists, anticholinergic agents, combination products containing beta-2 adrenergic agonists and anticholinergic agents, combination of long-acting beta-2 adrenergic agonists and corticosteroids, and methylxanthines.

Indacaterol is a new molecular entity that belongs to the class called beta-2 adrenergic agonists. Due to its possible longer duration of action, indacaterol belongs to the subclass called long-acting beta-2 adrenergic agonists (LABAs). Inhaled LABAs are widely used in the United States and worldwide to treat bronchospasm in patients with asthma and COPD. LABAs currently marketed in the United States include salmeterol, formoterol, and R,R formoterol. These are marketed either as single ingredient products or as combination products with inhaled corticosteroids. All are dosed twice daily, and all are marketed at one dose level. Indacaterol is proposed to be dosed once daily and proposed to be marketed at two dose levels, 75 mcg and 150 mcg.

Inhaled beta-2 adrenergic agonists, particularly inhaled LABAs, have a safety concern of severe asthma exacerbations and asthma-related deaths in patients who use these drugs to treat the symptoms of asthma. Severe asthma exacerbations and asthma-related deaths have been described with short-acting inhaled beta-2 adrenergic agonists over the last 50 years.[1, 2, 3, 4] More recently, inhaled LABAs have also been linked to severe asthma

[1] Benson RL, Perlman F. Clinical effects of epinephrine by inhalation. J Allergy 1948; 19:129-140.
[2] Lowell FC, Curry JJ, Schiller IW. A clinical and experimental study of isoproteronol in spontaneous and induced asthma. N Eng J Med 1949; 240:45-51.
[3] Grainger J, Woodman K, Pearce N, Crane J, Burgess C, Keane A, et al. Prescribed fenoterol and death from asthma in New Zealand, 1981-1987: a further case-control study. Thorax 1991; 46:105-111.
[4] Spitzer WD, Suissa S, Ernst P, Horwitz RI, Habbick BH, et al., The use of beta-agonist and the risk of death and near death from asthma. N Eng J Med 1992; 326:501-506.

exacerbations and asthma-related deaths.[5] This has been discussed at various FDA Advisory Committee meetings,[6] has led to publications expressing concerns on safety,[7, 8, 9] and establishment of a safe use strategy outlined by the FDA.[10] To further assess the safety of LABAs in asthma, the FDA has asked all manufacturers of LABAs that are marketed in the United States for asthma to conduct controlled clinical trials to assess the safety of a regimen of LABAs plus inhaled corticosteroids as compared with inhaled corticosteroids alone.[11] The mechanisms by which inhaled beta-adrenergic agonists cause severe asthma exacerbations and asthma-related deaths are not known. Controlled studies and epidemiological studies suggest that higher doses of inhaled beta-adrenergic agonists are a contributing factor. In the United States, a higher dose of inhaled formoterol was not approved because the higher dose caused more severe asthma exacerbation compared to the approved lower dose.[12] Unlike patients with asthma, patients with COPD do not appear to carry a similar signal of worsening disease. Nevertheless, the selection of an appropriate and safe dose is an important consideration for development of all LABAs, including indacaterol, which is proposed to be marketed for COPD. Most of the U.S. marketed beta-adrenergic agonists carry both asthma and COPD indications, and the dose and dosing frequency in both indications are the same.

The indication claims of short-acting beta-adrenergic agonists, such as albuterol (Proventil HFA Inhalation Aerosol, Ventolin HFA Inhalation Aerosol, ProAir HFA Inhalation Aerosol, Proventil Inhalation solution) are for general bronchodilation ("treatment or prevention of bronchospasm with reversible obstructive airway disease"). The albuterol product labels do not mention a specific disease, such as asthma or COPD, in the indication section. Clinical studies supporting approval of these products were conducted in patients with asthma. Nevertheless, albuterol is used in patients with asthma and COPD. The indication claims of long-acting beta-adrenergic agonists, such as salmeterol (Serevent Diskus, Serevent Inhalation Aerosol) and formoterol (Foradil Aerolizer) are also for general bronchodilation, but the product labels mention asthma and COPD as specific diseases in the indication section. Clinical trials supporting the dose and dosing frequency for these two long-acting beta agonists were also conducted in patients with asthma, and the same bronchodilatory dose was carried forward to studies in COPD. The regulatory precedence of performing dose ranging and dose regimen studies

[5] US Product Labels of salmeterol and formoterol containing products.
[6] Pulmonary-Allergy Drugs Advisory Committee Meeting, July 13, 2005; and Pulmonary-Allergy Drugs, Drug Safety and Risk Management, and the Pediatric Advisory Committee Meeting, December 10-11, 2008.
[7] Martinez FD. Safety of long-acting beta-agonists—an urgent need to clear the air. New Eng J Med 2005; 353:2637-2639.
[8] Kramer JM. Balancing the benefits and risks of inhaled long-acting beta-agonists—the influence of values. New Eng J Med 2009; 360:1952-1955.
[9] Drazen JM, O'Byrne PM. Risks of long-acting beta-agonists in achieving asthma control. New Eng J Med 2009; 360:1671-1672.
[10] Chowdhury BA, DalPan G. The FDA and safe use of long-acting beta-agonists in the treatment of asthma. New Eng J Med 2010; 362:1169-1171.
[11] Chowdhury BA, Seymour SM, Levenson MS. Assessing the safety of adding LABAs to inhaled corticosteroids for treating asthma. New Eng J Med 2011 (in press).
[12] Mann M, Chowdhury B, Sullivan E, Nicklas R, Anthracite R, Meyer RJ. Serious asthma exacerbation in asthmatics treated with high-dose formoterol. Chest 2003; 124:70-74.

for bronchodilators in asthma patients has been established in order to demonstrate a large separation between doses, because the range of response is greatest in a bronchoresponsive population, such as patients with asthma. A COPD population, with some degree of fixed obstruction, has a smaller response range to a bronchodilator.

Some regulatory history relevant to the current application is described below.

Novartis studied three different inhalation indacaterol products. These were the single-dose dry powder inhaler (IND 48,649), an HFA-propelled inhalation aerosol (IND 66,337), and a multi-dose dry powder inhaler using the Certihaler device (IND 69,754). IND 48,649 was submitted on February 13, 2004, and IND 69,754 was submitted on April 27, 2004, both to study persistent asthma. An end-of-phase 2 meeting was held on August 1, 2005, to discuss the development of indacaterol multi-dose dry powder product for asthma and COPD. Most of the questions and ensuing discussions were regarding the asthma program. Novartis later suspended the development of the HFA-propelled inhalation aerosol product for technical reasons. The multi-dose dry powder inhaler using the Certihaler was also suspended due to a potential device-related problem of excessive dose delivery. Due to the suspension of development of these preferred multiple dose delivery devices, the development of the single-dose dry powder product was continued. A second end-of-phase 2 meeting was held on October 10, 2006, to discuss the development of the indacaterol single-dose dry powder product for COPD. There was some discussion surrounding asthma, but most of the questions and ensuing discussions were related to COPD. Novartis proposed a COPD study (Study 2335, discussed further in section 7 below) with an adaptive design to build dose ranging assessment and determination into a pivotal efficacy and safety study. The Division cautioned that initiation of such a study was risky with limited prior information and Agency review of relevant data of the single-dose dry powder product. On December 20, 2006, Novartis submitted the COPD study with adaptive design for Special Protocol Assessment (SPA). In a letter dated February 1, 2007, the Division expressed various concerns with the study, such as the role of the data monitoring committee (DMC), use of open-label tiotropium as an active comparator, selection of the non-inferiority margin to compare to tiotropium, definition of secondary endpoint of days of COPD exacerbation, and emphasis on trough FEV1 as the dose selection criterion. On February 21, 2007, Novartis submitted questions in a Type A meeting request to seek clarification on the Division's response to the SPA questions. On March 12, 2007, the Division sent responses to Novartis's clarification questions in preparation for the meeting. Upon receiving the Division's response, Novartis cancelled the Type A meeting. While several discussions occurred between the Division and Novartis on the study, there were no formal SPA agreements. There were no agreements on dose selection criteria.

3. Chemistry, Manufacturing, and Controls

The product Arcapta Neohaler (indacaterol) Inhalation Powder is comprised of a formulation of indacaterol maleate with lactose contained in gelatin capsules for inhalation via the Neohaler Inhaler. Arcapta capsules, which are packaged in (b) (4) aluminum blisters, (b) (4) 75 mcg (b) (4) (as free base). The

capsules are packaged as five blister cards with 6 capsules each in a box of 30. Each capsule contains a dry powder blend of either 97 mcg or (b) (4) of indacaterol maleate (equivalent to 75 and (b) (4) indacaterol, respectively) with approximately 25 mg of lactose monohydrate. The Neohaler Inhaler is a plastic device to be used for inhaling the formulation from Arcapta capsules. Neohaler Inhaler consists of a white protective cap, a base with mouthpiece, capsule chamber, and two push buttons. To deliver a dose, patients place an Arcapta capsule in the capsule chamber of the Neohaler Inhaler, press the push buttons to pierce the capsule on each end, and breathe in rapidly and steadily through the mouthpiece. Novartis has submitted adequate stability data to support expiry periods of (b) (4) 12 months for the (b) (4) 75 mcg strength Arcapta capsules, respectively.

The drug substance is manufactured by Novartis in their facilities in Ringaskiddy, Ireland and Basel, Pratteln, and Stein, Switzerland. The drug product dosage form (capsule) is manufactured by Novartis at their facility in Stein, Switzerland, and the Neohaler Inhaler is manufactured by (b) (4). All manufacturing and testing facilities associated with this drug product have acceptable establishment evaluation status. All DMFs associated with this application were also found to be acceptable.

4. Nonclinical Pharmacology and Toxicology

Novartis submitted results from a full preclinical program. The program included studies in which animals were dosed with the drug via inhalation to evaluate local and systemic toxicities. Inhalation toxicity studies were conducted in rats for up to 26 weeks and dogs for up to 39 weeks. The target organs of toxicity in the rats were the nasal cavity where the observed finding was degeneration of the olfactory epithelium, and the larynx where the observed finding was squamous metaplasia. The target organs of toxicity in the dogs were the cardiovascular system where the observed findings were increased heart rates, decreased blood pressure, and myocardial necrosis and fibrosis, and liver where the observed finding was periportal liver hepatocyte vacuolation due to glycogen deposition. The cardiovascular and liver findings are known class effects of beta-2 adrenergic agonist drugs. For all the observed findings of concern, there were adequate margins of safety for the expected human exposure.

Studies addressing genotoxicity, reproductive toxicity, and carcinogenicity did not show any findings of concern. All genotoxicity studies were negative. The reproductive toxicity study in rats did not reveal adverse effects on male and female fertility or reproductive performance. Embryo-fetal development studies in rats and rabbits did not show any teratogenic effects. The pregnancy category was determined to be Class C, similar to many other beta-2 adrenergic agonists. Carcinogenicity was assessed in a 26 week study in C6F1/TgrasH2 hemizygous mice and in a 24 month study in Sprague-Dawley rats. These studies showed increased incidences of uterine/endometrial stromal polyps and ovarian leiomyomas. These tumors have been observed with other beta-2 adrenergic agonists and are known to have no human consequence. These studies were judged to be negative by the Executive Carcinogenicity Assessment Committee (CAC).

5. Clinical Pharmacology and Biopharmaceutics

Novartis submitted results from a comprehensive clinical pharmacology program. The program addressed the key pharmacokinetic issues, including *in vitro* studies to assess protein binding and metabolism, pharmacokinetics after single and multiple does, *in vitro* and *in vivo* metabolism, effect of hepatic impairment, QTc effect, and drug-drug interaction. Studies in renal-impaired patients were not conducted since renal excretion of indacaterol is a minor route of elimination. Clinical pharmacology studies included inhalation, oral, and IV administration to fully characterize the pharmacokinetics of indacaterol maleate.

Inhaled indacaterol maleate has approximately 43% biovailability resulting from both pulmonary and intestinal absorption. Elimination is primarily through the fecal route where over 90% of the dose was recovered in a mass balance study. Approximately 54% of the drug was eliminated unchanged, and approximately 23% was excreted as a hydroxylated indacaterol metabolite. Urinary elimination is a minor route with less than 2% indacaterol excreted unchanged in the urine. Following inhalation of a single 150 mcg dose of indacaterol, Cmax values were generally reached 0.25 hours post-dose. Following multiple inhalations of 150 mcg doses, the elimination half-life of indacaterol was 49.1 hours. *In vitro* studies showed that indacaterol is a substrate for CYP3A4, and UGT1A1 can metabolize indacaterol to the phenolic O-glucoronide. Indacaterol is a low affinity substrate for the efflux pump P-gp. Population pharmacokinetic studies did not show any significant effect of age, race, gender, hepatic impairment, and presence or absence of COPD.

Novartis conducted a QT/QTc study with 150 mcg, 300 mcg, and 600 mcg of indacaterol once daily for 2-weeks, with a single dose of moxifloxacin as an active control. The mean prolongation of QTcF (QT corrected by Fridericia's method) with indacaterol was less than 5 msec with the upper limit of the 90% confidence interval below 10 msec for all time-matched comparisons to placebo. For moxifloxacin, the lower bound of the 90% confidence interval was greater than 5 msec. The QT IRT team determined that the study did not demonstrate a significant effect of indacaterol maleate on the QTcF.

6. Clinical Microbiology

Not applicable.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

Some characteristics of the relevant clinical studies that form the basis of review and regulatory decision for this application are shown in Table 1. The studies are shown in Table 1 in two groupings – those submitted with the original NDA, and those submitted with the complete response. The design and conduct of these studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in Section 8.

Table 1. Relevant clinical studies with indacaterol maleate

ID Year*	Study type	Study duration	Patient Age, yr	Treatment groups†	N (ITT)	Primary efficacy variable	Countries
Submitted with original NDA							
Dose- ranging studies in COPD patients							
B2201 [2004]	Parallel arm	4 weeks	40-75	IN SDDPI 400 mcg QD IN SDDPI 800 mcg QD Placebo	68 67 28	30 minutes post-dose FEV_1 on Day 1, 14, 28	Europe
B2205 [2004]	Parallel arm	1 week	38-75	IN MDDPI 50 mcg QD IN MDDPI 100 mcg QD IN MDDPI 200 mcg QD IN MDDPI 400 mcg QD IN SDDPI 400 mcg QD Tio 18 mcg BID Placebo	103 105 105 110 105 107	FEV_1 $AUC_{22\text{-}24\ hr}$ post-dose on Day 1	Europe, North America, South America
B2212 [2007]	Crossover	1 day treatment	43-73	IN SDDPI 150 mcg QD IN SDDPI 300 mcg QD IN SDDPI 600 mcg QD For 12 mcg BID Placebo	51	FEV_1 trough at 24 hr	Belgium
1202 [2007]	Crossover	1 day treatment	40-75	IN SDDPI 150 mcg QD IN SDDPI 300 mcg QD IN SDDPI 600 mcg QD Placebo	50	FEV_1 $AUC_{22\text{-}24\ hr}$ post-dose	Japan
Pivotal COPD studies							
B2335 [2008]	Adaptive design, dose ranging, efficacy and safety	Initial 2 weeks, Continue for 26 weeks	40-88	*Initial 2 weeks:* IN SDDPI 75 mcg QD IN SDDPI 150 mcg QD IN SDDPI 300 mcg QD IN SDDPI 600 mcg QD For 12 mcg BID Tio 18 mcg QD Placebo *Continue 6 months:* IN SDDPI 150 mcg QD IN SDDPI 300 mcg QD Tio 18 mcg QD Placebo	 107 105 110 102 112 112 104 416 416 415 418	 FEV_1 trough at 24 hr at wk 2 FEV_1 $AUC_{1\text{-}4}$ hr at wk 2 FEV_1 trough at 24 hr at wk 12	USA, Canada, W Europe, India, S Korea, Argentina, Turkey, Taiwan
B2334 [2008]	Long-term Efficacy and safety	52 weeks	40-90	IN SDDPI 300 mcg QD IN SDDPI 600 mcg QD For 12 mcg BID Placebo	437 425 434 432	FEV_1 trough at 24 hr at wk 12	W and E Europe, Russia, C/S America, Mid East, S Korea
B2346 [2008]	Efficacy and safety	12 weeks	40-89	IN SDDPI 150 mcg QD Placebo	211 205	FEV_1 trough at 24 hr at wk 12	USA, NZ, Australia, Belgium
Short-time profiling studies in COPD patients							
B2340 [2008]	Crossover 24 hr FEV	2 weeks	≥ 40	IN SDDPI 300 mcg QD Sal 50 mcg BID Placebo	68	FEV_1 trough at 24 hr at day 15	USA, Belgium, Spain
B2331 [2008]	Crossover 24 hr FEV	2 weeks	≥ 40	IN SDDPI 150 mcg QD IN SDDPI 300 mcg QD Tio 18 mcg QD Placebo	169	FEV_1 trough at 24 hr at day 15	Europe, Australia, New Zealand, South Africa
B2305 [2008]	Crossover Assess effect of	2 weeks	≥ 40	IN SDDPI 300 mcg QDAM IN SDDPI 300 mcg	96	FEV_1 trough at 24 hr at day 15	France, Germany, Spain

ID Year*	Study type	Study duration	Patient Age, yr	Treatment groups†	N (ITT)	Primary efficacy variable	Countries
	dosing time			QDPM Sal 50 mcg BID Placebo			
B2307 [2008]	Crossover Onset of effect	Single dose	≥ 40	IN SDDPI 150 mcg IN SDDPI 300 mcg Advair 500/50 mcg Albuterol 200 mcg Placebo	89	FEV_1 5 min post-dose on day 1	USA, Belgium, Germany, Hungary
Asthma studies							
A2210 [2004]	Safety	4 weeks	12-65	IN SDDPI 400 mcg QD IN SDDPI 800 mcg QD Placebo	59 59 26	None	Germany, Belgium, Canada, Czech R, Slovakia
B2338 [2008]	Safety with ICS	26 weeks	12-85	IN SDDPI 300 mcg QD IN SDDPI 600 mcg QD Sal 50 mcg BID	268 268 269	None	USA, Canada, Europe, South America
Submitted with complete response							
Dose-ranging and dose-regimen studies in asthma and COPD patients							
B2357 [2010]	Dose ranging in asthma	2 weeks	18-82	IN SDDPI 18.75 mcg QD IN SDDPI 37.5 mcg QD IN SDDPI 75 mcg QD IN SDDPI 150 mcg QD Sal 50 mcg BID Placebo	84 81 84 85 84 84	FEV_1 trough at 24 hr at day 15	US
B2356 [2010]	Dose ranging in COPD	2 weeks	40-87	IN SDDPI 18.75 mcg QD IN SDDPI 37.5 mcg QD IN SDDPI 75 mcg QD IN SDDPI 150 mcg QD Sal 50 mcg BID Placebo	89 90 94 92 91 91	FEV_1 trough at 24 hr at day 15	US
B2223 [2010]	Dose regimen in asthma	2 weeks	18-80	IN SDDPI 37.5 mcg BID IN SDDPI 75 mcg QD IN SDDPI 150 mcg QOD Placebo	48 48 48 47	FEV_1 trough at 24 hr at wk 2 and FEV1 $AUC_{0\text{-}24hr}$	US, UK, France, Jordan, Germany, Netherlands
Pivotal COPD studies							
B2336 [2009]	Efficacy and safety	26 weeks	41-89	IN SDDPI 150 mcg QD Sal 50 mcg BID Placebo	330 333 335	FEV_1 trough at 24 hr at wk 12	W and E Europe, Russia, India, Peru, Taiwan, Canada, Columbia, Iceland
B2354 [2010]	Efficacy and safety	12 weeks	40-90	IN SDDPI 75 mcg QD Placebo	163 160	FEV_1 trough at 24 hr at wk 12	US
B2355 [2010]	Efficacy and safety	12 weeks	40-86	IN SDDPI 75 mcg QD Placebo	159 159	FEV_1 trough at 24 hr at wk 12	US

* Year study subject enrollment ended

† IN SDDPI = Indacaterol single dose dry powder inhaler, Arcapta Neohaler (Indacaterol single dose dry powder inhaler); IN MDDPI = Indacaterol multiple dose dry powder inhaler; For = Foradil Aerolizer (formoterol fumarate inhalation powder); Tio = Spiriva Handihaler (tiotropium bromide inhalation powder); Sal = Serevent Diskus (salmeterol xinafoate inhalation powder)

As mentioned in section 2 above, Novartis studied three different inhalation indacaterol products – a single dose dry powder inhaler, which is the subject of this application, a multiple dose dry powder inhaler, and an HFA-propelled inhalation aerosol. Table 1 above lists relevant studies that used both the single dose dry powder inhaler and the multiple dose dry powder inhaler. The applicability of the clinical data generated with the multiple dose dry powder inhaler and the HFA propelled inhalation aerosol are of limited value for the single dose dry powder inhaler because the *in vitro* delivery characteristics for the three products are substantially different.

The pivotal dose-ranging studies for the indacaterol program are: study B2335 (initial 2 weeks), study B2223, study B2357, and study B2356. The doses of indacaterol proposed in the original NDA were 150 mcg and 300 mcg once-daily. The selection of these doses was based on the initial 2 weeks dose-ranging part of the adaptive-design study B2335 in patients with COPD. Dose regimen (once-daily dosing versus other dosing frequencies) was not studied in the original application. The doses of indacaterol proposed in the complete response are 75 mcg and 150 mcg once-daily. The selection of the doses and dose regimen are based on the dose-ranging part of study B2335 (initial 2 weeks) in patients with COPD, dose-ranging study B2357 in patients with asthma, dose-regimen study B2223 in patients with asthma, and dose-ranging study B2356 in patients with COPD. Patients with asthma were studied based on Agency recommendation that patients with asthma are more responsive to the bronchodilator effect of beta-agonists and therefore more likely to show a separation between doses.

The pivotal phase 3 efficacy and safety studies submitted with the original NDA and with the complete response to support various doses of indacaterol are listed below:

- Indacaterol 300 mcg once daily: study B2335 (latter part), and study B2334. *Novartis does not seek approval of this dose in the current submission.*
- Indacaterol 150 mcg once daily: study B2335 (latter part), study B2336, and study B2346.
- Indacaterol 75 mcg once daily: study B2354 and study B2355.

In subsequent sections, design and conduct of the studies are described following the order in which the studies appear in Table 1. Thus, studies submitted with the original NDA are described first, followed by studies submitted later with the complete response. Efficacy and safety findings are described after the description of the design and conduct of these studies.

b. Design and conduct of the studies

Studies submitted with the original NDA

Short-term dose ranging studies (B2201, B2205, B2212, B1202):

These were the early studies conducted by Novartis to gather dosing information for indacaterol. These studies used doses ranging from 50 mcg to 800 mcg in different formulations and delivery devices. The results did not provide useful dose and dosing

frequency information because the studies were limited in duration, used different devices and formulations, and some had small sample sizes. Since dose selection information was limited, Novartis designed the first pivotal COPD study (Study B2335) to have an adaptive design to build dose-ranging investigation into a pivotal efficacy and safety study. In these short-term dose-ranging studies, and in other studies, dosing frequency other than once daily was not explored.

Pivotal COPD studies (B2335, B2334, B2346):

Study B2335, the adaptive design study, was a randomized, double-blind (except for the tiotropium arm, which was open label), parallel group in design conducted in patients with moderate-to-severe COPD. Patients were required to be 40 years of age and older, have a clinical diagnosis of COPD, post-bronchodilator FEV1/FVC <70%, post-bronchodilator FEV1 ≤80% predicted (post-bronchodilator refers to 30 minutes post-inhalation of 400 mcg albuterol), and be a current or previous smoker with a smoking history of ≥20 pack years. The study had a 2-week run-in period, followed by an initial 2-week double-blind treatment period. There were seven treatment arms in this period as shown in Table 1. An independent data monitoring committee (DMC) was chartered to review the 2-week interim data and make a decision on dose selection. [*The guideline given to DMC for dose selection was as follows: 1. The selected dose needed to be 0.12 L greater than placebo for trough FEV1, and should also have higher trough FEV1 than tiotropium and formoterol. 2. The dose needed to have higher FEV1 AUC 1-4 hours than tiotropium and formoterol. 3. The lowest dose that fulfilled the above two criteria and the next highest dose were to be selected.*]. Based on these criteria, indacaterol 150 mcg and 300 mcg were selected to move forward for the remainder of the study. After the dose selection, patients continued on a double-blind treatment period for a total of 26 weeks. There were four treatment arms in this period as shown in Table 1. Patients in all treatment arms were permitted to continue on baseline inhaled corticosteroids (ICS) and all received as needed short-acting beta-agonists (SABA). The primary efficacy variable was 24-hour post-dose trough FEV1 after 12 weeks of treatment. The 24-hour post-dose trough FEV1 was defined as the average of two FEV1 measurements taken in the clinic 23 hours 10 minutes and 23 hours 40 minutes after the previous dose. All patients had serial spirometry covering the first 1 hour after dosing (time points 5 minutes, 30 minutes, and 1 hour) and last 1 hour (time points 23 hours 10 minutes and 23 hours 40 minutes) after dosing at clinic visit days 2, 15, 85, and 183. In a subset (about 30 to 40 patients in each treatment arm) 12-hour serial spirometry (time points 2 hours, 4 hours, 6 hours, 8 hours, 10 hours, and 11 hours 45 minutes) were done on day 1, and after 2, 12, and 26 weeks of treatment. Other efficacy variables included days of poor control, COPD exacerbation, other spirometry variables, peak expiratory flow measures, SGRQ at baseline and at weeks 4, 8, 12, and 26, dyspnea assessed by baseline dyspnea index (BDI) and transitional dyspnea index (TDI) score at weeks 4, 8, 12, and 26, and BODE (body mass, airflow obstruction, dyspnea, and exercise capacity) index at weeks 12 and 26, MMRC dyspnea score, and 6 minute walk at baseline and at weeks 12 and 26. Safety assessments included adverse event recording, vital signs, physical examination, clinical laboratory and hematology measures, ECGs in all patients, and Holter monitoring in a subgroup of patients. Blood samples were also collected for sparse sampling

pharmacokinetic (PK) analysis at baseline and weeks 2, 12, and 26.

Studies B2334 and B2346 were randomized, double-blind, parallel-group in design conducted in patients with moderate-to-severe COPD. The patient population, design and conduct of the study, efficacy variables, and safety variables were similar to study B2335 with some minor differences, such as Holter monitoring was not conducted in either study and 6-minute walk test was not conducted in study B2346. The study duration and treatment arms were different as shown in Table 1.

Short-term crossover studies (B2340, B2305, B2307):

Studies B2340, B2331, B2305, and B2307 were randomized, double-blind, crossover in design conducted in patients with predominately moderate-to-severe COPD. Studies B2340 and B2331 were designed to collect data to construct a 24-hour spirometry profile. Study B2305 was designed to compare the efficacy of morning and evening indacaterol doses. Study B2307 was designed to assess the onset of action of indacaterol. These studies were relatively small and not germane to the major issues for discussion. Therefore, these studies will not be described further in this document.

Asthma safety studies (A2210, B2338):

Study A2210 was randomized, double-blind, placebo controlled, parallel group in design conducted in patients with stable asthma who were receiving treatment with inhaled beta-agonist with or without inhaled corticosteroids (ICS). The study had a 14-day run-in period, followed by 28-day double-blind treatment period. There were three treatment arms as shown in Table 1. The objective of the study was to assess safety and tolerability of 28 days treatment with indacaterol and to measure pharmacokinetics. For the assessment of safety, particular attention was paid to serum potassium, blood glucose, heart rate, blood pressure, QTc, FEV1, and adverse events such as tremor, headache, and nervousness.

Study B2338 was randomized, double-blind, active-controlled, parallel group in design conducted in patients with moderate-to-severe persistent asthma. The intent of the study was to evaluate the safety of indacaterol compared to salmeterol in patients with asthma using ICS as background treatment. The study had a 14-day run-in period, followed by 26-week double blind treatment period. There were three treatment arms as shown in Table 1. All enrolled patients were on ICS (study required daily ICS of at least 100 mcg beclomethasone or equivalent for at least 1 month prior to enrollment), had mean baseline post-bronchodilator (SABA) FEV1 of 94.6% (study required FEV1 of $\geq$50%), had mean FEV1 reversibility of 22.3% (study required an increase of $\geq$12% and $\geq$200 mL in FEV1 over pre-bronchodilator value within 30 minutes after inhaling a total of 180 mcg of albuterol), and had no emergency room treatment or hospitalization for asthma in the 6 months prior to study entry (study requirement). Safety assessments included collection of adverse events, serious adverse events, vital signs, clinical blood chemistry and hematology, urinalysis, ECG, and Holter monitoring in a subset of patients. Key safety variables identified for the study were serum potassium and glucose, heart rate, blood

pressure, and QTc measure on ECG. The main efficacy variable was 24-hour post-dose trough FEV1 over 26 weeks with end of week 12 as the time point of interest. Other efficacy measures were PEFR, daytime symptoms, nighttime awakenings, rescue medication use, and quality of life measurements. Blood samples were also collected for sparse sampling PK analysis at weeks 1 and 12.

Studies submitted later with complete response

Dose ranging (B2357, B2356) and dose regimen (B2223) studies:

Study B2357 was randomized, double-blind, parallel group in design conducted in patients with persistent asthma 18 years of age and older. The study had a 14-day run-in period, followed by 2-week double blind treatment period. There were six treatment arms in this period as shown in Table 1. All enrolled patients were on inhaled corticosteroids (study requirement), had mean screening FEV1 ranging from 2.23 to 2.40 L in different treatment groups (study required FEV1 ≥50% and ≤90% of predicted normal), and mean screening FEV1 reversibility ranging from 20.5% to 24.5% in different treatment groups (study required an increase of ≥12% and ≥200 mL in FEV1 over pre-bronchodilator value within 30 minutes after inhaling a total of 360 mcg of albuterol via an inhalation aerosol). The primary efficacy variable was 24-hour post-dose trough FEV1 on day 15. The 24-hour post-dose trough FEV1 was defined as the average of two FEV1 measurements taken in the clinic 23 hours 10 minutes and 23 hours 40 minutes after the previous dose. All patients had serial spirometry at time points -50 minutes, -25 minutes, -15 minutes, 5 minutes, 15 minutes, 30 minutes, 1 hour, 2 hour, 4 hour, 8 hour, 11 hour 10 minutes, and 11 hour 45 minutes relative to study drug dosing on days 1 and 15. In a subset of patients (ranging from 44 to 49 patients in different treatment arms) additional time points were added at 14 hours, 20 hours, and 22 hours relative to dosing on day 15. The secondary efficacy variables were 24-hour post-dose trough FEV1 on day 1, peak FEV1 on day 1, FEV1 AUC on days 1 and 14, morning and evening PEFR over 14 days, and use of rescue medication. Safety assessments included adverse event recording including asthma exacerbation, vital signs, physical examination, clinical laboratory and hematology measures, and ECGs.

Study B2356 was similar to study B2357 in design and conduct with the notable difference that patients in this study were required to have moderate-to-severe COPD, with post-bronchodilator FEV1/FVC <70% and post-bronchodilator FEV1 ≤80% and ≥30% predicted, and a smoking history of at least 10 pack years. Study treatment arms are shown in Table 1. Enrolled patients had a mean duration of COPD for 6.9 years, mean screening FEV1 ranging from 1.22 to 1.37 L in different treatment groups, and mean screening FEV1 reversibility to albuterol ranging from 14.2% to 16.7% in different treatment groups. Efficacy and safety assessments were the same as study B2357 with one difference of additional blood sampling on the last day of dosing for indacaterol pharmacokinetic analysis.

Study B2223 was randomized, double blind, parallel group in design conducted in patients with persistent asthma 18 years of age and older. The design and conduct of this

study was similar to study B2357, but with 3 treatments arms with different dose regimens of the same total daily dose of indacaterol 75 mcg as shown in Table 1. All enrolled patients were on inhaled corticosteroids (study requirement), had mean screening FEV1 ranging from 2.51 to 2.84 L in different treatment groups (which was higher than study B2357), and mean screening FEV1 reversibility ranging from 20.4% to 22.5% in different treatment groups (same as study B2357). Efficacy and safety assessments were the same as study B2357 with one difference of additional blood sampling on the first and last day of dosing for indacaterol pharmacokinetic analysis.

Pivotal COPD studies (B2354, B2355, B2336):

Study B2336 was randomized, double-blind, parallel group in design. This study was ongoing at the time of original NDA submission and subsequently completed and submitted later with the complete response. Patients enrolled in the study were required to be 40 years of age and older, have a clinical diagnosis of COPD, moderate-to-severe by GOLD guideline criteria, smoking history of at least 20 pack-years, post-bronchodilator FEV1 <80% and ≥30% of predicted, and post-bronchodilator FEV1/FVC <70% (post-bronchodilator refers to 10-15 minutes post-inhalation of 400 mcg albuterol). The study had a 2-week run-in period, followed by a 26-week double-blind treatment with indacaterol 150 mcg QD, salmeterol 50 mcg BID, or placebo (Table 1). The primary efficacy variable was 24-hour post-dose trough FEV1 after 12 weeks of treatment. The 24-hour post-dose trough FEV1 was defined as the average of two FEV1 measurements taken in the clinic after 23 hours 10 minutes and 23 hours 40 minutes after the previous dose. The primary comparison was between indacaterol and placebo. On the first day and after weeks 12 and 26 of treatment, serial spirometry was done at time points -50 minutes, -25 minutes, -15 minutes, 5 minutes, 30 minutes, 1 hour, 2 hours, and 4 hours (time points 2 hours and 4 hours were done in subgroup of approximately 300 patients) relative to study drug dosing. Other efficacy variables included other additional spirometry measures at various time points, rescue medication use, nighttime awakenings, daytime symptoms, dyspnea assessed by baseline dyspnea index (BDI) and transitional dyspnea index (TDI) score after 4, 8, 12 and 26 weeks of treatment, one month recall version SGRQ score at baseline, and after 4, 12, and 26 weeks of treatment, 6 minute walk test at baseline, and after 12 and 26 weeks of treatment, BODE index (composite of % predicted FEV1, distance walked in 6 min, MMRC dyspnea scale, and body mass index) at baseline and after 12 and 26 weeks of treatment, and COPD exacerbation frequency. Safety assessments included adverse event recording, vital signs, physical examination, clinical laboratory and hematology measures, and ECGs. In a subset of patients, blood samples were collected at the end of week 12 for indacaterol pharmacokinetic analysis.

Studies B2354 and B2355 were randomized, double-blind, parallel group in design. Patients were required to be 40 years of age and older, have a clinical diagnosis of COPD, moderate-to-severe by GOLD guideline criteria, smoking history of at least 10 pack years, post-bronchodilator FEV1 <80% and ≥30% of predicted, and post-bronchodilator FEV1/FVC <70% (post-bronchodilator refers to 10-15 minutes post-inhalation of 400 mcg albuterol). Both studies had a 2-week run-in period, followed by

12-week double blind treatment with indacaterol 75 mcg QD or placebo (Table 1). Patients were permitted to continue on baseline ICS, and all received as needed SABA. The primary efficacy variable was 24-hour post-dose trough FEV1 after 12 weeks of treatment. The 24-hour post-dose trough FEV1 was defined as the average of two FEV1 measurements taken in the clinic 23 hours 10 minutes and 23 hours 40 minutes after the previous dose. On the first day and last day of treatment, serial spirometry was done at time points -50 minutes, -25 minutes, -15 minutes, 5 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 23 hours 10 minutes, and 23 hours 45 minutes relative to study drug dosing. Other efficacy variables included additional spirometry measures at various time points, rescue medication use, nighttime awakenings, daytime symptoms, dyspnea assessed by baseline dyspnea index (BDI) and transitional dyspnea index (TDI) score after 4 and 12 weeks of treatment, one month recall version SGRQ score at baseline, and after 4 and 12 weeks of treatment, and COPD exacerbation frequency. Safety assessments included adverse event recording, vital signs, physical examination, clinical laboratory and hematology measures, and ECGs. In a subset of patients, blood samples were collected at the end of week 12 for indacaterol pharmacokinetic analysis.

c. Efficacy findings and conclusions

The clinical program supports approval of the 75 mcg once-daily dose, but not the higher 150 mcg dose. The clinical program showed that Arcapta Neohaler at 75 mcg, 150 mcg, and 300 mcg once-daily doses provided statistically significant bronchodilator effect in patients with COPD with replicate findings with these doses. There are no replicate findings comparing 75 mcg dose to 150 mcg dose in the same study to support the proposed dosing recommendation statement that the higher 150 mcg dose provides additional benefit over the 75 mcg dose in patients with more severe bronchial obstruction. Novartis' claim of advantage of the 150 mcg dose over the 75 mcg dose is based on a modeling analysis of FEV1 data from various clinical studies. In the following sections, efficacy findings from the original NDA are discussed first, followed by efficacy findings from the complete response. These are followed by discussion of the modeling analysis of FEV1 data conducted by Novartis and the SGRQ data.

Original NDA

In the original NDA submission, exploration of dose ranging was limited and primarily based on the first 2 weeks of data from the adaptive design study (Study B2335); different dosing frequencies were not explored. In the adaptive design dose-ranging study, all active treatment arms provided a statistically significant bronchodilator effect as measured by trough FEV1 compared to placebo at the interim analysis time point of 2 weeks, with no significant differences among any of the indacaterol doses (Table 2, Figure 1). Additional spirometry variables and other secondary measures went in a similar direction as trough FEV1 (data not shown in this document). Based on the DMC dose selection criteria using trough FEV1 and FEV1 AUC 1-4 hours (described in the previous section), the 75 mcg dose was considered to be suboptimal, so the 150 mcg and 300 mcg doses were carried forward for further assessment in the study. At the 2-week time point, the numerical differences between the 75 mcg and higher indacaterol doses

were small. It appears that all studied doses were on the plateau of the dose-response curve. The data show that the DMC dose selection criteria, which were geared towards selection of an indacaterol dose that would provide numerically higher efficacy versus the active comparators, may have led to the selection of higher than necessary doses.

Table 2. Study B2335, LS Mean for trough FEV1 (in L) at 2 weeks (interim analysis) and 12 weeks (primary efficacy time point)

Treatment	Trough FEV1 at Week 2	Treatment comparison	Treatment Difference at 2 weeks LS Mean (95% CI)	Treatment Difference at 12 weeks LS Mean (95% CI)
IN 75 mcg	1.46	IN 75 - Placebo	0.15 (0.09, 0.20)	
IN 150 mcg	1.49	IN 150 - Placebo	0.18 (0.12, 0.24)	0.18 (0.15, 0.21)
IN 300 mcg	1.52	IN 300 - Placebo	0.21 (0.15, 0.27)	0.18 (0.15, 0.21)
IN 600 mcg	1.51	IN 600 - Placebo	0.20 (0.14, 0.25)	
For 12 mcg	1.42	For - Placebo	0.11 (0.06, 0.17)	
Tio 18 mcg	1.45	Tio - Placebo	0.14 (0.08, 0.19)	0.14 (0.11, 0.17)
Placebo	1.31			

IN = Indacaterol single dose dry powder inhaler, Arcapta Neohaler (Indacaterol single dose dry powder inhaler); For = Foradil Aerolizer (formoterol fumarate inhalation powder); Tio = Spiriva Handihaler (tiotropium bromide inhalation powder)

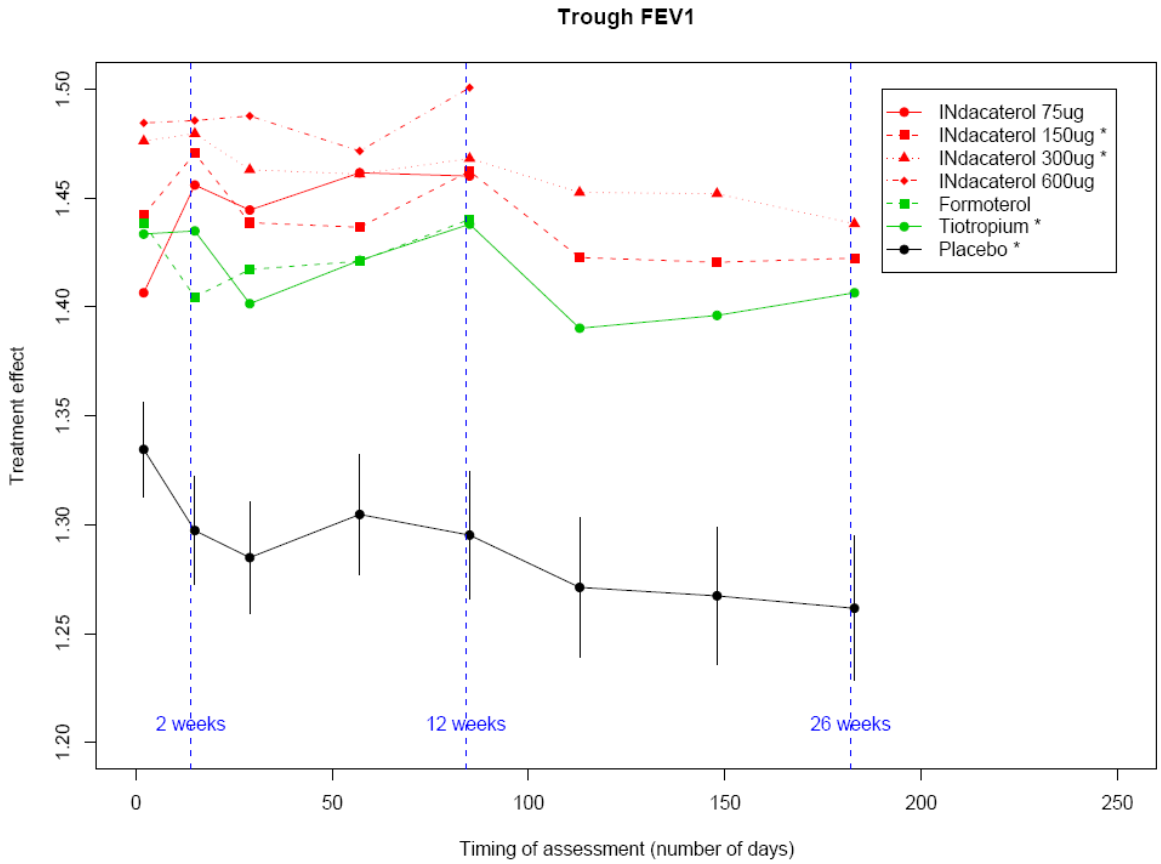

Figure 1. Study B2335, Summary of trough FEV1 in various treatment arms at different assessment times. Note: 2 weeks is interim analysis, 12 weeks is primary efficacy time point, and 26 weeks is end of the study

In the other two pivotal studies submitted with the original NDA submission (Studies B2334 and B2436), indacaterol 150 mcg, 300 mcg, and 600 mcg provided a statistically significant bronchodilator effect as measured by trough FEV1 compared to placebo (Table 3). Additional spirometry variables and other secondary measures went in a similar direction to trough FEV1 (data not shown in this review). Similar to the adaptive design study, separation between the indacaterol doses was minimal to none, but the separation between indacaterol and Foradil Aerolizer 12 mcg was numerically large.

Table 3. Studies B2334 and B2346, LS Mean for trough FEV1 (in L) at 12 weeks (primary efficacy time point)

Treatment	Trough FEV1 at week 12	Treatment comparison	Treatment Difference LS Mean (95% CI)
Study B2334			
IN 300 mcg	1.48	IN 300 – Placebo	0.17 (0.13, 0.20)
IN 600 mcg	1.48	IN 600 – Placebo	0.17 (0.13, 0.20)
For 12 mcg	1.38	For – Placebo	0.07 (0.04, 0.10)
Placebo	1.31		
Study B2346			
IN 150 mcg	1.49	IN 150 – Placebo	0.13 (0.09, 0.18)
Placebo	1.35		
IN = Indacaterol single dose dry powder inhaler, Arcapta Neohaler (Indacaterol single dose dry powder inhaler); For = Foradil Aerolizer (formoterol fumarate inhalation powder);			

Similar concerns were raised by the results of B2338, which was a 26 week study in patients with asthma comparing indacaterol 300 mcg, indacaterol 600 mcg, and salmeterol 50 mcg BID, that showed a larger trough FEV1 for both doses of indacaterol compared to salmeterol. The LS mean trough FEV1 at week 12 for indacaterol 300 mcg was superior to salmeterol with LS mean difference of 0.07 L, 95% CI 0.02- 0.12 L, and p-value of 0.006; the LS mean trough FEV1 at week 12 for indacaterol 600 mcg was superior to salmeterol with LS mean difference of 0.08 L, 95% CI 0.02- 0.13 L, and p-value of 0.004.

There were three efficacy questions that were not answered with the data submitted in the original NDA presented above: dose selection, dosing frequency, and efficacy advantages of the 300 mcg dose over the 150 mcg dose.

The first question was whether the doses of indacaterol proposed to be marketed were optimal, or whether a lower dose may be equally or similarly effective. Since Novartis did not test doses lower than 75 mcg once-daily in the original development program, this question could not be answered without further dose exploration. Based on the observation that all doses were at the plateau of the dose-response curve (Table 2, Figure 1, Table 3), it was possible that 75 mcg once-daily or even a lower dose might be equally effective. Given the general safety concerns with LABAs, specifically the dose-related finding of severe asthma exacerbations and asthma-related deaths, exploration of lower doses was deemed to be necessary. In the adaptive design study, the DMC dose selection criteria were geared towards selection of an indacaterol dose that would provide

numerically higher efficacy versus the active comparators, and likely resulted in selection of an unnecessarily high dose. Specifically, the selected 150 mcg and 300 mcg doses provided numerically higher bronchodilator responses as compared to formoterol, another LABA (Table 2, Figure 1, Table 3). It is worth noting that although a higher dose of formoterol (Foradil Aerolizer 24 mcg) provided a numerically superior bronchodilator response compared to the approved dose of formoterol (Foradil Aerolizer 12 mcg) in patients with asthma,[13] the higher dose was not approved for marketing in the United States because of safety concerns noted in the formoterol NDA studies.[14] Given the known safety issues with formoterol at higher doses, selection of indacaterol at the 150 mcg and 300 mcg doses based on numerical superiority to formoterol may not have been a safe strategy.

The second question was whether indacaterol is truly a once-daily drug, or whether it is more appropriate to dose this product twice daily or more frequently. It is possible that similar efficacy might have been achieved with twice-daily or a more frequent dosing interval, as compared to a once-daily dosing interval, with less of a total daily dose, hence with better safety. Since Novartis did not compare once-daily dosing to a more frequent dosing interval in the original NDA, this question could not be answered without further dose frequency exploration. At the other end of the dosing frequency spectrum, with the half-life of indacaterol being about 49 hours, it seemed a fair question to ask whether indacaterol could even be dosed less frequently than once-daily to prevent drug accumulation and alleviate drug accumulation-related safety concerns.

The third question was the proposed labeling statement that the 300 mcg dose provided additional clinical benefit over the 150 mcg dose in some patients. The only study that compared 300 mcg and 150 mcg dose head-to-head was the adaptive design study B2335. In that study at the interim analysis time point of 2 weeks, there was a numerical separation favoring the 300 mcg dose, but at the primary efficacy analysis time point of 12 weeks, there was no difference between the two doses (Table 2, Figure 1). Therefore, it was determined that the proposed labeling statement was not supported. It was determined that to support such a labeling statement, Novartis would need to provide efficacy data showing a clinically meaningful advantage of the 300 mcg dose over 150 mcg, and provide balancing safety data showing no unacceptable safety disadvantages that would negate the efficacy advantage.

Complete Response

These deficiencies were communicated in the Agency's Complete Response action letter of the original NDA submission that was issued on October 16, 2009, and subsequently discussed with Novartis at a meeting held in November 2009. Novartis subsequently conducted further studies (Studies B2357, B2356, and B2223) to evaluate doses of indacaterol lower than 150 mcg and regimens with dosing frequencies of less than and

[13] US Product label for Foradil Aerolizer (formoterol fumarate inhalation powder).
[14] Mann M, Chowdhury B, Sullivan E, Nicklas R, Anthracite R, Meyer RJ. Serious asthma exacerbation in asthmatics treated with high-dose formoterol. Chest 2003; 124:7-74.

more than once-daily in bronchoreactive patients, such as patients with asthma and patients with COPD responsive to the bronchodilator effect of short-acting beta-agonists (Table 1). Although indacaterol is proposed to be marketed as a bronchodilator for COPD patients, the Agency recommended that exploration of dose and dose regimen be conducted in patients with asthma who are more responsive to the bronchodilator effect of beta-agonists and more likely to show separation of doses and in patients with COPD who are tested and identified to be bronchodilator responsive. Novartis also conducted two further pivotal efficacy studies (Studies B2354 and B2355) in COPD patients with indacaterol 75 mcg once-daily dose (Table 1). Based on the results of these studies, the proposed dose of indacaterol has been lowered to 75 mcg or 150 mcg once-daily. Two doses are proposed with the reasoning that the higher dose will provide additional benefit in patients with more severe disease. New data submitted with the complete response are presented below with some comments.

In dose-ranging studies in asthma patients (Study B2357) and COPD patients (Study B2356) all indacaterol doses tested (18.75 mcg, 37.5 mcg, 75 mcg, and 150 mcg once-daily) provided a statistically significant bronchodilator effect as measured by trough FEV1 compared to placebo at day 15 (Table 4). The effect size of the 18.75 mcg once-daily dose was lower compared to other doses. The effect size did not show clear separation among the other three indacaterol doses at day 15 (Table 4). Other measures of spirometry variables and other secondary measures went in a similar direction with trough FEV1 (data not shown in this document). The FEV1 time profile curves showed some numerical dose ordering after the first dose with indacaterol 75 mcg and 150 mcg once-daily doses separating from the lower doses, but after the last dose at week 2, indacaterol doses 37.5 mcg and above did not show clear separation (Figures 2 and 3). The FEV1 time profile curve for the indacaterol 150 mcg and 75 mcg once-daily doses were essentially superimposable after the first dose in patients with asthma (Figure 2). These FEV1-based data do lend support for the 75 mcg dose, but do not show a clear efficacy advantage of the 150 mcg dose over the 75 mcg dose. The data show that 18.75 mcg dose is inferior to other doses studied and is probably near, but not at the plateau of the bronchodilator effect of indacaterol. The other doses are harder to discriminate from one another, suggesting that these are at the plateau of the bronchodilator effect of indacaterol. Given that variability of FEV1 response, some patients receiving a dose of 37.5 mcg dose will still reside on the upward slope portion of the bronchodilator effect of indacaterol, whereas with the 75 mcg dose, most patients will be above the slope of the bronchodilator effect of indacaterol (Table 4, asthma dose ranging study B2357). The totality of the dose-ranging data supports 75 mcg as the optimum dose for indacaterol.

Table 4. Studies B2357, B2223, and B2356, LS Mean for trough FEV1 (in L) at day 15 (primary efficacy time point)

Treatment	Trough FEV1 at week 2	Treatment comparison	Treatment Difference LS Mean (95% CI)
Study B2357 (asthma dose-ranging)			
IN 18.75 mcg	2.50	IN 18.75 - Placebo	0.09 (0.00, 0.17)
IN 37.5 mcg	2.52	IN 37.5 - Placebo	0.11 (0.02, 0.19)
IN 75 mcg	2.59	IN 75 - Placebo	0.17 (0.08, 0.26)

Treatment	Trough FEV1 at week 2	Treatment comparison	Treatment Difference LS Mean (95% CI)
IN 150 mcg	2.54	IN 150 - Placebo	0.12 (0.04, 0.21)
Sal 50 mcg	2.54	Sal - Placebo	0.13 (0.04, 0.21)
Placebo	2.42		
Study B2356 (COPD dose-ranging)			
IN 18.75 mcg	1.35	IN 18.75 - Placebo	0.07 (0.02, 0.12)
IN 37.5 mcg	1.38	IN 37.5 - Placebo	0.10 (0.05, 0.16)
IN 75 mcg	1.38	IN 75 - Placebo	0.10 (0.04, 0.15)
IN 150 mcg	1.40	IN 150 - Placebo	0.12 (0.07, 0.17)
Sal 50 mcg	1.39	Sal - Placebo	0.10 (0.05, 0.16)
Placebo	1.28		
Study B2223 (asthma dose-regimen)			
IN 37.5 BID		IN 37.5 BID - Placebo	0.16 (0.08, 0.23)
IN 75 QD		IN 75 QD - Placebo	0.20 (0.12, 0.27)
IN 150 QOD		IN 150 QOD - Placebo	0.20 (0.12, 0.27)
Placebo			
IN = Indacaterol single dose dry powder inhaler, Arcapta Neohaler (Indacaterol single dose dry powder inhaler); Sal = Serevent Diskus (salmeterol xinafoate inhalation powder)			

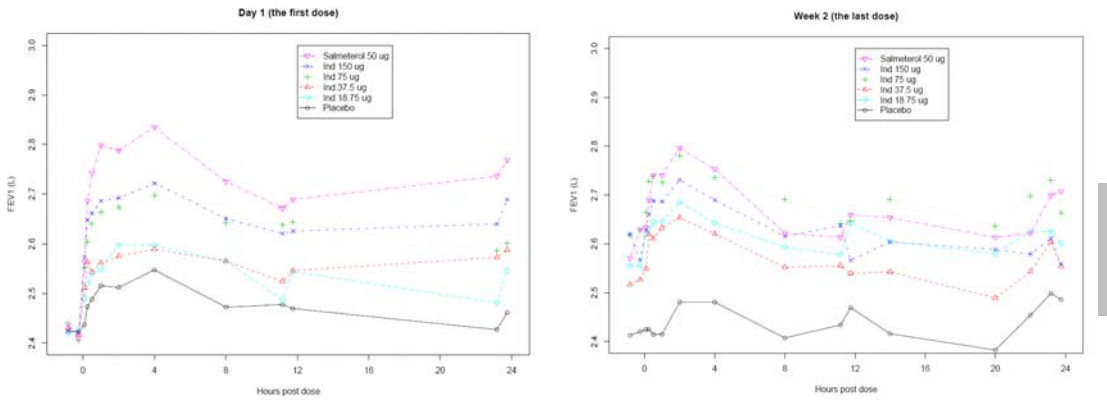

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Figure 2. LS mean FEV1 time profile curve over 24 hours after the first dose and the last dose (study B2357, asthma dose ranging)

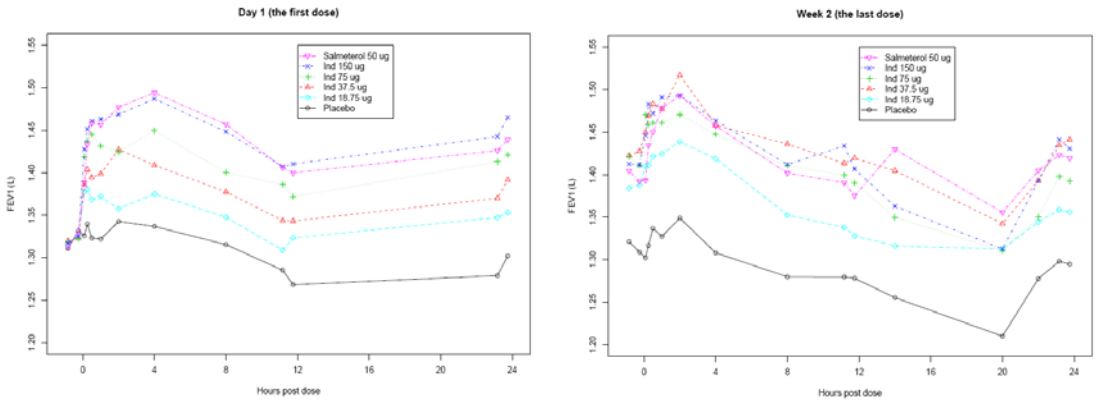

Figure 3. LS mean FEV1 time profile curve over 24 hours after the first dose and the last dose (study B2356, COPD dose ranging)

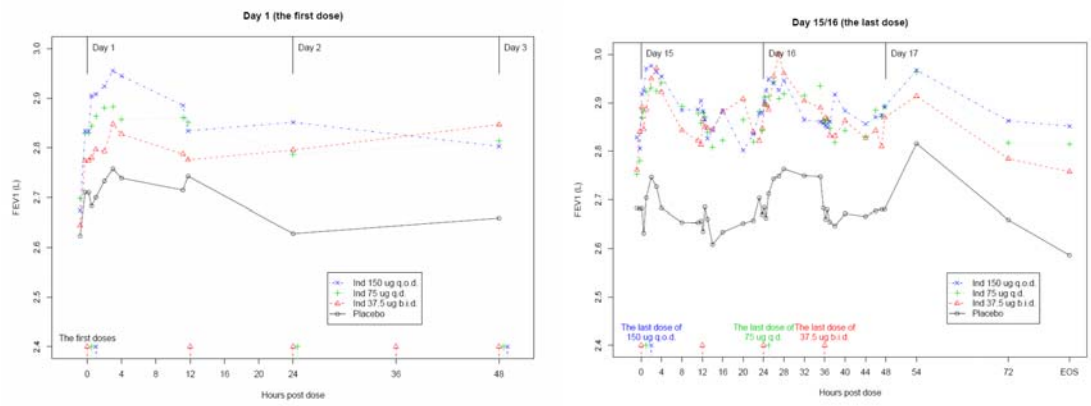

Figure 4. LS mean FEV1 time profile curve over 24 hours after the first dose and the last dose (study B2223, asthma dose regimen)

Results of study B2223, exploring three different dosing regimens of the same nominal dose are shown in Table 4 and Figure 4. Results of the study do not show clear separation of the different dosing regimens. One limitation of this study was that the screening baseline FEV1 was higher in this study compared to the asthma dose-ranging study (2.51 to 2.84 L in this study compared to 2.23 to 2.40 L in asthma dose ranging study B2357), which may make the study less sensitive to show differences among doses. Nevertheless, the three dosing regimens at day 1 showed some numerical separation (Figure 4) suggesting that even with higher baseline FEV1, the study was adequate to test different dosing regimens. Overall, this study supports a once-daily dosing regimen for indacaterol.

Results of the pivotal efficacy study (Study B2336) that was started when the original NDA was submitted but completed later, and the two pivotal efficacy studies (Studies B2354 and B2355) in COPD patients with indacaterol 75 mcg once-daily dose, are shown in Table 5 and Figure 5. The results show statistically significant bronchodilator effect as measured by trough FEV1 compared to placebo at week 12 in the three studies (Table 5). The mean peak improvement relative to baseline within the first 4 hours after the first dose (Day 1) was 0.19 L (Trial B2354) and 0.22 L (Trial B23555) and was 0.24 L (Trial B2354) and 0.27 L (Trial B23555) after 12 weeks. Because patients may reach their personal peak at different timepoints, this number was calculated based on the average of each patient's personal peak FEV1 within 4 hours of dosing. Additional spirometry variables and other secondary measures went in a similar direction with trough FEV1 (data not shown in this document).

Table 5. Studies B2336, B2354, and B2355, LS Mean for trough FEV1 (in L) at 12 weeks (primary efficacy time point)

Treatment	Trough FEV1 at week 12	Treatment comparison	Treatment Difference LS Mean (95% CI)
Study B2336			
IN 150 mcg	1.45	IN 150 – Placebo	0.17 (0.13, 0.20)
		IN 150 – Sal 50	0.06 (0.02, 0.10)
Sal 50 mcg	1.39	Sal - Placebo	0.11 (0.07, 0.14)

Treatment	Trough FEV1 at week 12	Treatment comparison	Treatment Difference LS Mean (95% CI)
Placebo	1.28		
Study B2354			
IN 75 mcg	1.38	IN 75 – Placebo	0.12 (0.08, 0.15)
Placebo	1.26		
Study B2355			
IN 75 mcg	1.49	IN 75 – Placebo	0.14 (0.10, 0.18)
Placebo	1.35		
IN = Indacaterol single dose dry powder inhaler, Arcapta Neohaler (Indacaterol single dose dry powder inhaler); Sal = Serevent Diskus (salmeterol xinafoate inhalation powder)			

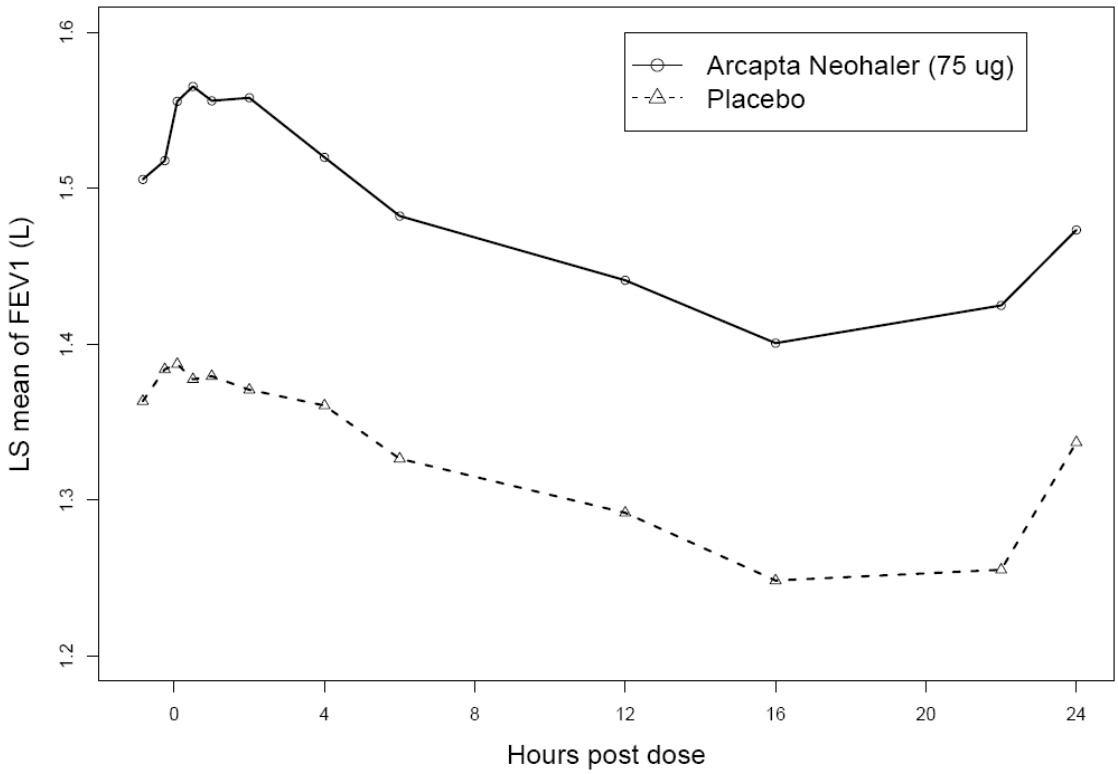

Figure 5. LS mean FEV1 time profile curve over 24 hours at week 12 for study B2355 (subset of 239 patients)

Novartis is proposing two doses of indacaterol (75 mcg and 150 mcg) with the reasoning that the higher dose will provide additional benefit in patients with more severe bronchial obstruction, partly relying on comparing the two doses across studies using pharmacodynamic modeling analysis, and SGRQ data to support the additional efficacy of the 150 mcg dose. In the Complete Response action letter to the original NDA submission, Novartis was asked to provide replicate data showing a clinically meaningful advantage of a higher dose compared to a lower dose and balancing safety data to show

no unacceptable safety disadvantage with the higher dose. Novartis's response to the efficacy component of the deficiency was the modeling analysis (discussed further below).

From an efficacy standpoint, the FEV1 data and other related efficacy data presented above do not directly provide support for the approval of two doses. There are no 12-week studies that include the 75 mcg dose and the 150 mcg dose in the same study, and therefore, there is no direct comparison of the two doses. In the FDA's COPD draft guidance, it is noted that "if more than one dose is ultimately intended to be marketed, the clinical program design should produce data that allow for a comparative assessment of efficacy and safety between the doses in addition to the usual comparison of the doses of the new drug to placebo." On cross study comparison, which has limitations, the bronchodilatory effect sizes do not show a clear efficacy advantage of the 150 mcg dose over the 75 mcg dose. Furthermore, there is no regulatory precedence for approving more than one dose of a beta-adrenergic bronchodilator. Historically, bronchodilator dosing has been assessed in bronchodilator responsive patients, such as patients with asthma, and later the same dose has been carried forward to patients with COPD. For this reason, Novartis was asked to test dosing in patients with asthma to select the appropriate dose, which they did in studies submitted with the complete response. It is possible that some patients with COPD, who have less bronchial reversibility, may not respond to a typical dose of a bronchodilator, but this does not necessarily justify using higher doses of a bronchodilator in these patients with the intent of achieving a certain level of bronchodilation, especially given the dose-related safety issues with beta-agonists.

Modeling analysis

Novartis is relying on modeling analysis to support the claim that the higher dose of 150 mcg provides additional benefit in patients with more severe bronchial obstruction. Novartis submitted results of a modeling analysis with the complete response, in the FDA Advisory Committee briefing document, as a briefing document submitted to the Agency on May 18, 2011, and also published the results[15]. On May 31, 2011, Novartis met with the Agency to present and discuss the modeling analysis to support the proposed 75 mcg and 150 mcg doses. The comments below pertain primarily to the briefing document submitted to the Agency on May 18, 2011, and the meeting with Novartis held on May 31, 2011.

Novartis conducted two different analyses to characterize dose-response to show added benefit of the 150 mcg dose over the 75 mcg dose: 1) An integrated analysis of study level data from 12 studies that included 8111 patients with COPD treated with indacaterol doses of 18.75 mcg to 600 mcg once daily. Data from 2 to 26 weeks of treatment were considered and multiple visits were included. 2) An integrated analysis of patient level data from two dose ranging studies (B2335S and B2356) that included 1835 patients with COPD treated with indacaterol doses of 18.75 mcg to 600 mcg once daily.

[15] Renard D, Looby M, Kramer B, Lawrence D, Morris, and Stanski DR. Characterization of the bronchodilatory dose response to indacaterol in patients with chronic obstructive pulmonary disease using model-based approaches. Respir Res 2011; 12:54.

Data from days 14 and 15 of treatment were included. In both the analyses, the intent was to characterize dose-response at steady state; therefore, data from time points earlier than 2 weeks were excluded. In the analyses, only trough FEV1 data were used.

A summary of the study level analysis conducted by Novartis is shown in Figure 6. Based on this analysis, Novartis concluded the following: there is a 92% probability that the 37.5 mcg dose provides less than the minimal clinically important difference (MCID) of 120 mL trough FEV1; there is a 95% probability that 75 mcg dose exceeds the MCID; 150 mcg dose has an incremental benefit over 75 mcg dose and is the lowest indacaterol dose that exceeds the average bronchodilation observed for the comparators; and 150 mcg is located mid-way between the MCID and the maximal response. It should be noted that the MCID of 120mL for trough FEV1 was defined by Novartis and there is no well-accepted definition of MCID for trough FEV1 as discussed further below.

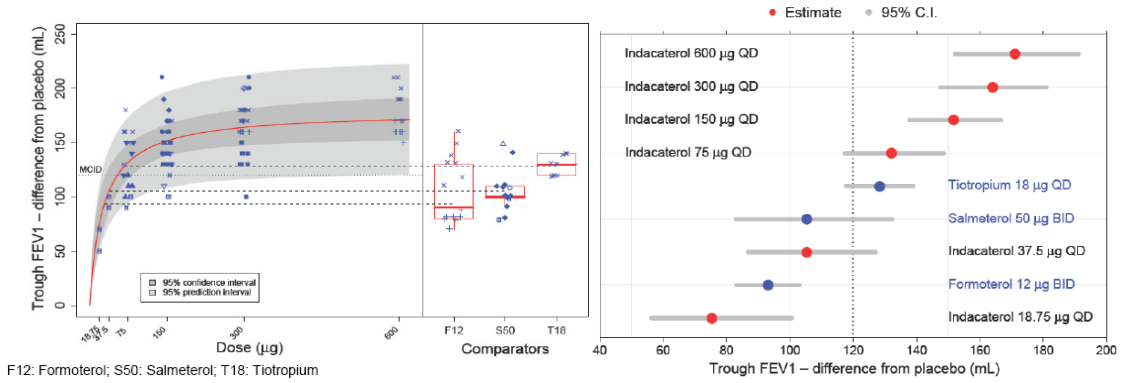

Figure 6. Study level analysis. Left Panel: Prediction of dose response for trough FEV1 at steady state in COPD patients for indacaterol and comparators. Right Panel: Ranking of predicted improvement in trough FEV1 at steady state in COPD patients for indacaterol doses and comparators.

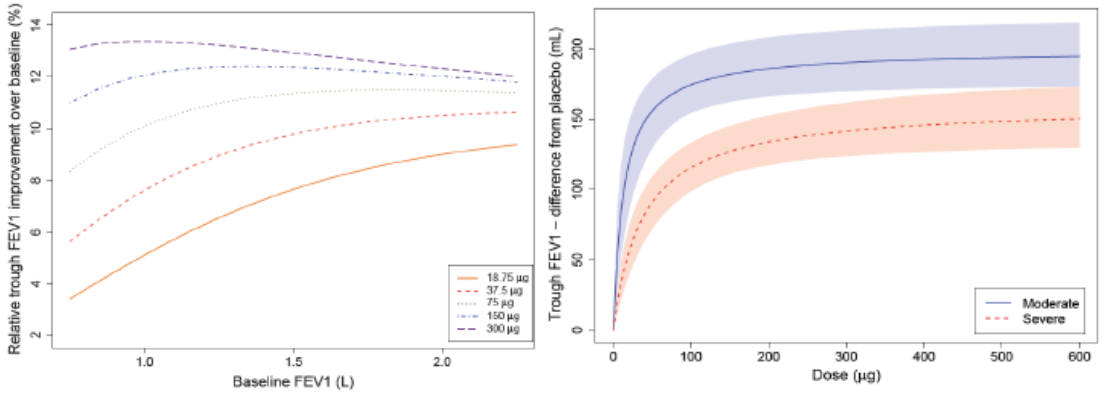

Figure 7. Patient level analysis. Left Panel: Impact of baseline FEV1 and dose on the improvement in trough FEV1 relative to baseline in COPD patients. Right Panel: Prediction of trough FEV1 at steady state in patients with moderate and severe COPD patients according to criteria defined by GOLD.

A summary of the patient level analysis conducted by Novartis is shown in Figure 7. Based on this analysis, Novartis concluded that while the 75 mcg dose provided minimum bronchodilation in most patients, the 150 mcg dose provided an incremental benefit in patients with severe COPD, and that population heterogeneity in disease status is not adequately dealt with in a "one dose fits all" approach.

There are limitations with the modeling analysis (including the methodology) conducted by Novartis that limit the utility of the analysis for dose selection and comparing doses across studies. In addition, there are concerns with the analysis from a broader clinical perspective.

FDA's Office of Clinical Pharmacology conducted independent analysis of the data and identified limitations in the Novartis analysis. FDA's analysis showed that the actual data do not fit the Novartis's model prediction (shown in Figure 8). For the study level analysis, the model prediction overestimates the incremental difference between two adjacent doses, especially for 150 mcg versus 75 mcg and 75 mcg versus 37.5 mcg. This may be due to the data not supporting a linear relationship between transformed dose and change in trough FEV1 variables presumed by the model, and undersampling at lower doses. For the patient-level analysis, although the 95% confidence intervals within each baseline FEV1 quartiles are wide, the point estimates based on the observed means or LS means from ANCOVA analysis of the true data (including day 14 and day 15 data from study B2335S and study B2356) do not support the model predicted trend.

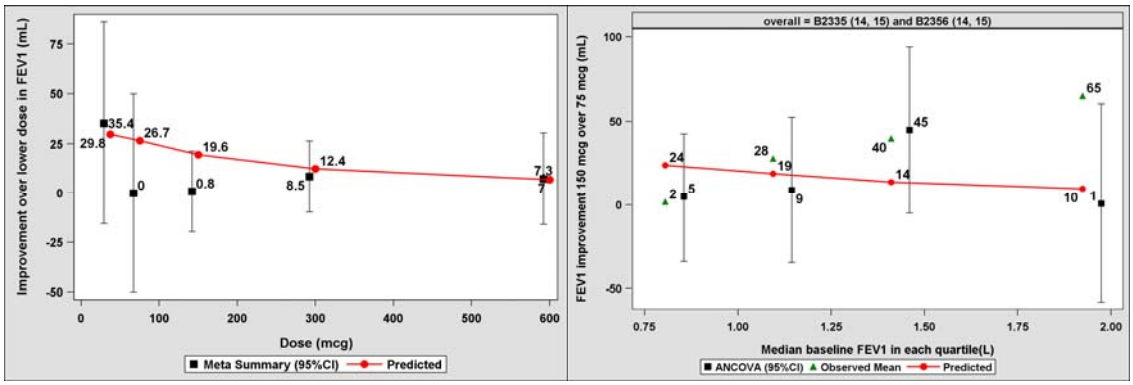

Figure 8. Novartis's model prediction versus actual data for incremental difference between doses. Left Panel: Study level analysis for trough FEV1 improvement over lower doses for doses ranging from 37.5 mcg to 600 mcg. Right Panel: Patient level analysis for trough FEV1 improvement of 150 mcg dose over 75 mcg dose.

In addition, the FDA also conducted a sensitivity analysis based on the primary endpoint day 15 data, which demonstrates a flattened dose response in the more severe patients (Figure 9), suggesting that more severe patients may not have a greater response to doses above 75 mcg, a conclusion that contradicts Novartis' model prediction.

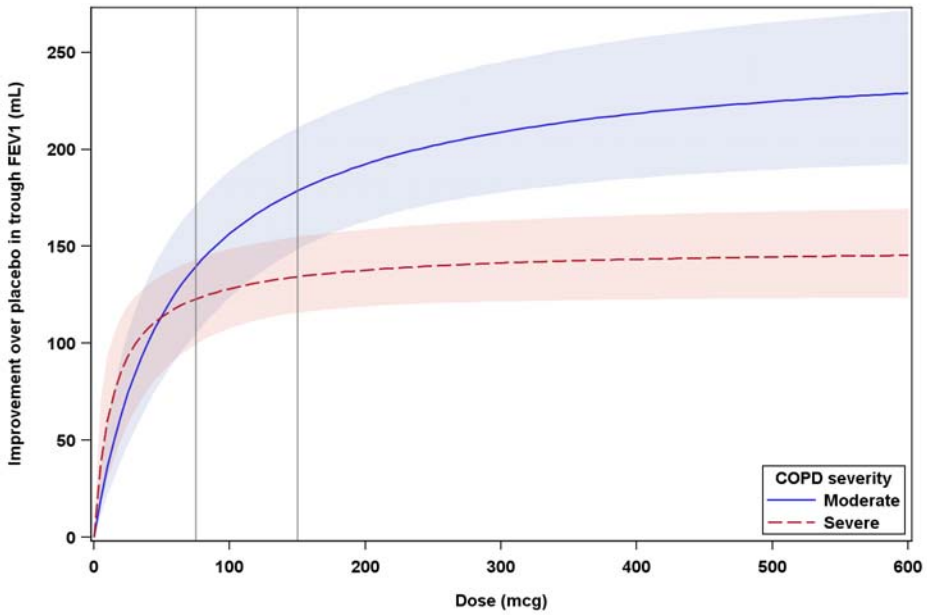

Figure 9: FDA sensitivity analysis of Novartis model

Novartis's modeling analysis raises concerns from a broader clinical perspective as well, which limit the utility of the findings. The analysis presented above only used trough FEV1 data and no FEV1 data from other time points after dosing. The peak FEV1 response and overall time profile FEV1 response after dosing are important considerations for a bronchodilator response, which the model presented above does not take into consideration. Another concern is that the model includes all available FEV1 data from 2 weeks and beyond; however, it is known that the FEV1 response to beta-adrenergic agonists changes over time. In addition, different studies may have different demographic and baseline disease characteristics, which may not be accounted for in the mode.

Furthermore, Novartis's conclusions are based on a minimal clinically important difference (MCID) of 120 ml for trough FEV1, a number that has not been determined by the scientific community and the FDA as an MCID for trough FEV1 bronchodilator response. Most currently approved bronchodilators do not reach this level, as was confirmed in the Novartis's modeling analysis (Figure 5). Yet, the currently marketed bronchodilators are clearly beneficial to patients. Benchmarking to marketed LABA products, salmeterol and formoterol, Novartis's modeling analysis presented above suggests that the 37.5 mcg dose of indacaterol would provide a similar level of bronchodilation as measured by trough FEV1 at steady state. However, this modeling analysis does not take into account bronchodilator effect at the first dose. As determined in the most sensitive population (asthma, study B2357), the 37.5 mcg dose does not provide an acceptable level of bronchodilation after the first dose (Figure 2), which is also important to patients.

Modeling analysis can be useful in providing guidance for dose selection for further evaluation, but is of limited use as a sole determinant for dose selection or to support a second higher dose. Therefore, data from the dose-ranging studies in patients with asthma (study B2357) and bronchodilator responsive COPD patients (study B2356) discussed above remain the more relevant data source to select dose. The modeling analysis does not provide substantial evidence to support that 150mcg provides a clinically meaningful benefit over the 75mcg dose.

SGRQ

SGRQ was assessed in all pivotal COPD studies as either one of the key secondary efficacy variables (B2336) or as one of the many efficacy variables (B2335, B2334, B2346, B2354, and B2355). Results of analysis based on the difference in mean total SGRQ scores between active treatment and placebo are shown in Table 6, and based on the percentage of patients with a minimally important difference (MID) of -4 units or more from baseline in SGRQ total score (defined as responder) are shown in Figure 10. The MID of -4 for SGRQ has support in the literature.[16, 17]

Table 6. ANCOVA results of SGRQ total scores in various COPD studies

Treatment	Baseline (arithmetic mean)	Week 12 (arithmetic mean)	Change from Baseline	Treatment comparison	Treatment Difference LS Mean (95% CI)
Study B2335					
IN 150 mcg	45.4	38.9	-5.6	IN 150 - Placebo	-2.8 (-4.5, -1.1)
IN 300 mcg	44.8	39.6	-5.2	IN 300 - Placebo	-2.5 (-4.2, -0.8)
Tio 18 mcg	44.6	41.0	-3.5	Tio - Placebo	-1.1 (-2.8, 0.6)
Placebo	45.7	42.7	-3.0		
Study B2334					
IN 300 mcg	44.4	38.6	-5.8	IN 300 - Placebo	-3.8 (-5.6, -2.1)
IN 600 mcg	44.4	38.3	-6.1	IN 600 - Placebo	-4.1 (-5.9, -2.3)
For 12 mcg	44.4	39.2	-5.2	For - Placebo	-3.2 (-5.0, -1.5)
Placebo	43.6	41.6	-2.1		
Study B2346					
IN 150 mcg	50.2	43.7	-6.5	IN 150 - Placebo	-4.8 (-7.2, -2.4)
Placebo	48.7	47.6	-1.1		
Study B2336					
IN 150 mcg	43.6	35.9	-7.7	IN 150 - Placebo	-6.3 (-8.2, -4.3)
Sal 50 mcg	43.2	37.8	-5.4	Sal - Placebo	-4.2 (-6.1, -2.2)
Placebo	43.6	42.4	-1.2		
Study B2354					
IN 75 mcg	48.4	42.7	-5.8	IN 75 - Placebo	-3.8 (-6.2, -1.4)
Placebo	49.5	47.6	-2.0		
Study B2355					
IN 75 mcg	51.2	46.2	-4.9	IN 75 - Placebo	-3.6 (-6.4, -0.9)
Placebo	50.1	49.2	-0.9		

[16] Jones PW. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. Eur Respir J 2002; 19:398-404.
[17] Jones PW. St. George's Respiratory Questionnaire: MCID. J of COPD 2005; 2:75-79.

Treatment	Baseline (arithmetic mean)	Week 12 (arithmetic mean)	Change from Baseline	Treatment comparison	Treatment Difference LS Mean (95% CI)
IN = Indacaterol single dose dry powder inhaler, Arcapta Neohaler (Indacaterol single dose dry powder inhaler); For = Foradil Aerolizer (formoterol fumarate inhalation powder); Sal = Serevent Diskus (salmeterol xinafoate inhalation powder); Tio = Spiriva Handihaler (tiotropium bromide inhalation powder)					

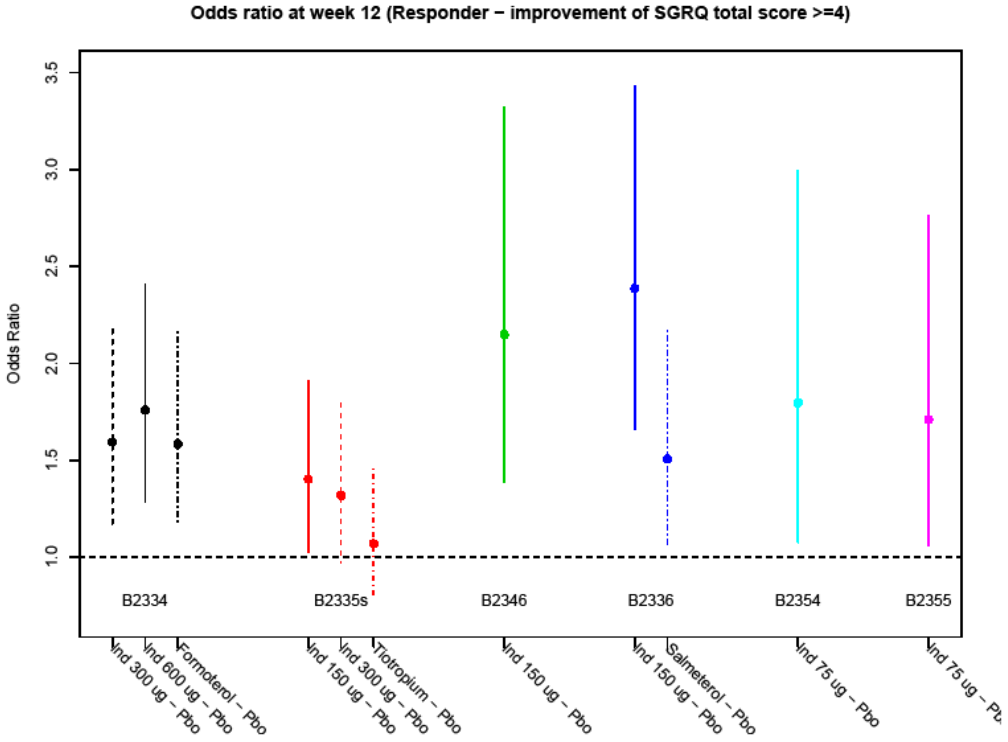

Figure 10. Summary of SGRQ responder analysis in controlled COPD studies.

Other than tiotropium, all active treatments, including indacaterol 75 mcg, 150 mcg, 300 mcg, and 600 mcg showed statistically significant separation from placebo. The difference in means between the indacaterol 150 mcg dose and placebo in studies B2336 and B2346 crossed the MID of -4, and the difference in means between the indacaterol 75 mcg dose and placebo did not cross the MID of -4 in studies B2354 and B2355 (Table 6). It is worth noting that the numerical difference for SGRQ scores between indacaterol 150 mcg dose and 75 mcg dose is small, and the difference in the mean scores between indacaterol 300 mcg dose and placebo did not cross the MID of -4 in studies B2335 and B2334. Based on the analysis of the COPD three-month efficacy population pooled data, comparing to placebo, the improvement of SGRQ total scores after 12 weeks of treatment was -3.8 [95% CI :-5.3, -2.3] for indacaterol 75 mcg, -4.6 with a [95% CI:-5.5, -3.6] for indacaterol 150 mcg, and -3.8 [95% CI:-4.9, -2.8] for indacaterol 300 mcg. Confidence intervals for the three doses overlap considerably. The percentage of patients who had an improvement of SGRQ total score crossing the MID of -4 from baseline was 49% for indacaterol 75 mcg, 52% for indacaterol 150 mcg, 52% for indacaterol 300 mcg, and

40% for placebo (Figure 5). There was no statistically significant difference among different doses. Considering the evidence collectively, the SGRQ results do not support a clinically meaningful advantage of the 150 mcg dose over the 75 mcg dose. Likewise, the SGRQ results do not support a specific labeling claim, although the overall data are sufficient to permit description in the clinical trials section of the label.

8. Safety

a. Safety database

The safety assessment of Arcapta Neohaler is based primarily on studies shown in Table 1. The safety database is reasonably large with approximately 15,000 patients exposed to indacaterol across various development programs. Novartis defined the COPD safety population as patients in all COPD studies with treatment duration of at least 3 months. At the time of the data lock for the submission of the complete response, there were a total of 9441 patients in this COPD safety population of whom 4764 received indacaterol in the following dose groups: 449 for the 75 mcg dose, 2611 for the 150 mcg group, 1157 for the 300 mcg dose, and 547 for the 600 mcg dose, with duration of exposure varying for different groups.

b. Safety findings and conclusion

The major safety concern with indacaterol is linked to selection of an appropriate dose, because beta-2 adrenergic bronchodilators, particularly at high doses, have the safety concerns of severe asthma exacerbations and asthma-related deaths in patients who use these drugs to treat the symptoms of asthma. Although such a risk of worsening disease has not been shown in COPD, it is nevertheless important to select an appropriate and safe dose for all bronchodilators, including indacaterol, which is proposed to be marketed for COPD. Marketing an unnecessary and unreasonably high dose has safety concerns.

The safety database for indacaterol shows possible asthma exacerbation and asthma-related death at 300 mcg dose in patients with asthma, and a potential for a dose-related increase in beta-adrenergic effects, such as cardiovascular and cerebrovascular effects at doses of 300 mcg and higher in patients with COPD. The 75 mcg once daily dose of indacaterol is an appropriate and safe dose because it is considerably lower (4-fold) than the dose of 300 mcg that has concerning safety findings. The exposure database for the 75 mcg dose is relatively small compared to the 150 mcg dose (Section 8a above). The safety conclusion for the 75 mcg dose is based on findings from this dose, and also from findings from the 150 mcg, which by itself appears reasonably safe. Also relevant to safety conclusion is the efficacy conclusion that shows lack of appreciable and clinically meaningful efficacy advantage of doses higher than 75 mcg once daily (discussed in section 7 above).

The safety findings of indacaterol are discussed further in the following sections: asthma studies, COPD studies, FDA requested meta-analysis of respiratory-related events conducted by Novartis during the review period of this application, and finally a review of post-marketing safety of indacaterol.

Asthma Studies

There were a total of 13 studies in patients with asthma conducted with indacaterol; the majority were either short duration or conducted with a product or a formulation different than the proposed to-be-marketed formulation. The important asthma studies from safety perspective are A2210 and B2338 (Table 1). Design and conduct of these studies are described in section 7b above.

The asthma studies raise safety concerns for indacaterol as a bronchodilator due to the occurrence of serious asthma events. A particular safety concern were the 2 deaths seen in the asthma safety study B2338 (26-week study involving about 268 patients per treatment arm), both occurring in patients treated with indacaterol 300 mcg once-daily while they were receiving concurrent ICS.

The first death occurred in a 60-year-old male with a seven-year history of asthma with no other active medical problems. On day 165 of treatment, the patient was hospitalized for one day with "asthmatic crisis" and treated with oral corticosteroid and nebulized medication. Four days later, on day 169, he again developed an acute asthma exacerbation and died on his way to the hospital. This patient was on inhaled beclomethasone 500 mcg twice daily for approximately the first six months of the study, and then on inhaled budesonide 400 mcg twice daily for the rest of the study until death.

The second death occurred in a 75-year-old woman with a two-year history of asthma, allergic rhinitis, osteoporosis, and past history of respiratory arrest and anaphylactic reaction. On day 119 of treatment the patient experienced a cardiac arrest at home. The patient was resuscitated, intubated, and admitted to the hospital. On evaluation, significant findings were a small pneumothorax and pulmonary hyperinflation consistent with asthma. There were no findings consistent with myocardial infarction or other cardiovascular diseases. Life support was withdrawn on day 11 of hospitalization on family request and the patient expired. The patient was on inhaled mometasone 220 mcg once daily for the entire duration of the study.

Serious Adverse Events (SAEs) related to asthma exacerbation or respiratory events seemed to be more common in patients treated with indacaterol in various asthma studies. In the asthma safety study B2338 (26-week study involving about 268 patients per treatment arm) where two deaths were seen (described above), SAEs related to asthma exacerbation were reported for 2 patients in the indacaterol 300 mcg group, 3 patients in indacaterol 600 mcg group, and for no patients in the salmeterol group. In the other asthma safety study (Study A2210, 4-week study involving 59 patients per active treatment arm) there were more respiratory-related SAEs in the indacaterol treated group compared to placebo (4 in indacaterol versus 0 in placebo). In the 2-week asthma dose regimen study (B2223, 2-week crossover study involving 48 patients) there was one SAE of asthma exacerbation possibly due to viral influenza and pollen exposure reported in one patient while receiving indacaterol 150 mcg every other day.

Although the submitted application for indacaterol is for COPD, the two deaths in patients with asthma while receiving indacaterol with background of concurrent ICS

treatment is concerning. The deaths are reminiscent of asthma-related deaths seen with other LABAs. Both the deaths occurred in patients on the 300 mcg dose, which is not very far removed from the 150 mcg dose proposed to be marketed as a bronchodilator. Asthma-related deaths in typical LABA programs for asthma to support NDA submission, even when LABAs were used alone in such studies without concomitant ICS, are very rare to nonexistent. In the indacaterol program, two possible asthma-related deaths occurred in patients receiving indacaterol in a study where there was a salmeterol active comparator and in which the LABAs were administered concomitantly with ICS. The possible imbalance of SAEs related to asthma exacerbation further supports the safety concerns for indacaterol.

COPD Studies

The safety assessment of Arcapta Neohaler is based primarily on studies shown in Table 1. The safety database is reasonably large.

Deaths and SAEs[18] occurred in the COPD program as would be expected in the relatively older and sicker patient population studied. There were 7 deaths out of 4764 patients in the COPD safety population who received indacaterol, and 23 deaths out of 4677 patients in the control group. Exposure adjusted death rates did not show any concerning imbalances raising safety concerns for indacaterol. In the COPD safety population, there were 325 SAEs (fatal and non-fatal) in indacaterol-treated patients. Review of the SAEs does not show any concerning imbalances or unexpected trends against indacaterol.

In the COPD studies, the adverse event profile was typical for COPD patients, with respiratory disorders and cardiac disorders being most common. Adverse events leading to discontinuations and commonly reported adverse events did not raise any specific or unique safety concerns for indacaterol in COPD patients. Adverse events relating to beta-adrenergic effects, such as those in the cardiovascular system, cerebrovascular system, and muscle spasm were seen in indacaterol-treated patients, some occurring more frequently than in placebo-treated patients. These were was more prominent in the original NDA review where a higher dose was proposed.

There were no unique or findings of concerns with indacaterol on analysis of clinical laboratory values, ECGs, and Holter monitoring.

During review of the original NDA, analysis of the cardiac and cerebrovascular adverse events was done to assess effects of beta-2 adrenergic stimulation of the 150 mcg and 300 mcg doses proposed at that time. The intent of the analysis was to assess the appropriateness of the proposed indacaterol doses, and not as a safety assessment in isolation. Novartis conducted a pooled analysis of the phase 3 COPD database available

[18] Serious Adverse Drug Experience is defined in 21 CFR 312.32 as any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience (defined in the same regulation as any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred), inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

at the time of the original NDA. Results of that analysis are shown in Table 7. In general, the tiotropium arm had the highest frequency of adverse effects, and the placebo arm had the lowest frequency. Indacaterol arms had higher frequencies compared to formoterol. There was no dose ordering for the indacaterol doses and the number of patients with serious adverse events was small. The increased frequencies of serious adverse events with indacaterol compared to placebo and to formoterol, particularly at later time points, suggested that the indacaterol doses proposed for marketing in the original NDA were high.

Table 7. Percentage of patients in various treatment groups from pooled COPD studies presenting with ≥1 cardiac or cerebrovascular (CCV) adverse events (AE) or serious adverse events (SAE) [from original NDA submission]

	IN 150 mcg	IN 300 mcg	IN 600 mcg	For 12 mcg	Tio 18 mcg	Placebo
AE at 3 months	3.03	3.52	2.01	1.98	4.34	2.46
SAE at 3 months	0.96	0.94	0.55	0.18	1.45	0.66
AE at 6 months	5.77	5.04	3.29	3.96	5.78	3.65
SAE at 6 months	2.16	1.41	1.28	0.54	2.17	1.06
AE at 12 months	-	6.6	6.1	6.5	-	3.90
SAE at 12 months	-	3.4	2.6	1.4	-	0.9
IN = Indacaterol single dose dry powder inhaler, Arcapta Neohaler (Indacaterol single dose dry powder inhaler); For = Foradil Aerolizer (formoterol fumarate inhalation powder); Tio = Spiriva Handihaler (tiotropium bromide inhalation powder);						
From Novartis original submission: Summary of Clinical Safety, pages 187-195						

The exposure database is now larger, particularly at lower doses, with new studies conducted by Novartis and submitted with the complete response. At lower doses, particularly at 150 mcg, higher frequencies of these cardiac and cerebrovascular serious adverse events are not evident at 12 month time point (Table 8).

Table 8. Percentage of patients in various treatment groups from pooled COPD studies presenting with ≥1 cardiac or cerebrovascular (CCV) adverse events (AE) or serious adverse events (SAE) [from complete response submission]

	IN 75 mcg	IN 150 mcg	IN 300 mcg	IN 600 mcg	For 12 mcg	Tio 18 mcg	Placebo
AE at 3 months	2.00	2.37	3.11	2.01	1.98	2.22	2.58
SAE at 3 months	0.45	0.92	0.69	0.55	0.18	0.91	0.65
AE at 6 months	4.72	5.57	4.80	3.29	3.96	5.78	4.08
SAE at 6 months	2.36	1.71	1.15	1.28	0.54	2.17	1.24
AE at 12 months	-	9.72	8.58	6.12	6.45	-	5.40
SAE at 12 months	-	0.62	3.09	2.59	1.38	-	1.44
IN = Indacaterol single dose dry powder inhaler, Arcapta Neohaler (Indacaterol single dose dry powder inhaler); For = Foradil Aerolizer (formoterol fumarate inhalation powder); Tio = Spiriva Handilaler (tiotropium bromide inhalation powder);							
From Novartis original submission: Summary of Clinical Safety, pages 187-195 Novartis complete response: Summary of Clinical Safety, pages 230-242							

The primary medical officer reviewing the complete response submission initially concluded that there were safety concerns with cardiovascular adverse events even with the proposed lower doses of indacaterol and recommended a large safety trial (primary medical officer review addendum filed on April 5, 2011) - a recommendation that the primary medical officer later rescinded (primary medical officer review addendum filed on June 8, 2011). The clinical team leader and statistical team were not in agreement with the primary medical officer's initial concerns regarding cardiovascular safety with the proposed lower doses of indacaterol. The initial conclusion reached by the primary medical officer was probably due to over interpretation of small numbers of adverse events (considered often as composite, and often combining adverse events and serious adverse events) influencing overall rates, not considering lack of consistency across various indacaterol doses for adverse events, and wide confidence intervals around the small number of these events.

Meta-analysis of respiratory related events

In the Agency's Complete Response action letter to the original NDA submission, Novartis was asked to provide replicate data showing a clinically meaningful advantage of a higher dose compared to a lower dose and balancing safety data to show no unacceptable safety disadvantage with the higher dose. Based on review of the complete response, it was determined that further analyses of the existing data would help in the assessment and balancing of the safety risk of the two proposed doses of indacaterol. On December 16, 2010, Novartis was asked to conduct a blinded adjudicated analysis (by a committee external to Novartis) comparing indacaterol-treated patients to controls by evaluating adverse events of interest (all cause death, asthma-related death, asthma-related intubation, asthma-related hospitalization, COPD-related death, COPD-related intubation, COPD-related hospitalization, pneumonia-related death, pneumonia-related intubation, pneumonia-related hospitalization) for all parallel-arm controlled trials 7 days or more in duration that used the proposed to-be-marketed product for the treatment of COPD and asthma. Analyses of various study sets were requested - all studies, COPD only studies, asthma only studies, and COPD studies subgroups of bronchodilator responsive patients compared to non-bronchodilator responsive patients.

Analyses of the COPD studies are more important and relevant for this review and regulatory decision because the asthma studies were small in number and the safety findings from the asthma studies were relatively simple and straightforward (discussed in 8c above). Meta-analysis findings from the COPD are studies are discussed below.

The all-treated COPD safety population included in the meta-analysis consisted of 11,755 patients from 23 studies. The majority of the studies was greater than 12 weeks in duration and was conducted with the to-be-marketed Neohaler device. Of the 11,755 COPD patients, 6863 were treated with indacaterol, 2482 with placebo, and 2408 with one of three active controls (formoterol n=556, tiotropium n=842, and salmeterol n =1010). In the all-treated COPD safety population, a total of 239 of 11,755 patients were identified as having had a respiratory-related event. Of these 239 patients, there were 219 patients who had an acute respiratory-related hospitalization or intubation. There were no

acute respiratory-related deaths in this population. The incidence of total and acute respiratory-related events and exposure adjusted total and acute respiratory-related events are shown in Table 8. "Total" refers to any respiratory related event (e.g. pulmonary embolus, lung cancer), while "acute" includes only those respiratory-related deaths which were adjudicated to be asthma-, COPD-, or pneumonia-related.

The meta-analysis data needs to be viewed cautiously because the numbers of events are small, exposure to different doses of indacaterol and active comparators are variable, and it is not known whether the event rates are related to duration of exposure. Nevertheless, there does appear to be a dose-related increase in the composite and hospitalization rates for indacaterol with a break point at the 300 mcg dose. The dose relationship is not consistent because the numbers of events are low in the 600 mcg group. The data provides safety assurance for the 75 mcg dose in the COPD population as the events with 75 mcg dose are lower than other doses of indacaterol and comparable or less than placebo and active comparators. The data provides reasonable safety assurance for the 150 mcg dose as well. Long-term safety data with the 75 mcg dose is limited, and the safety assurance of the 150 mcg dose, which has large long-term exposure, is supportive of long-term safety of the 75 mcg dose. However, the safety data with the 150 mcg dose does not justify approval over a lower dose with similar efficacy (75 mcg) given the known dose response relationship of beta-agonist adverse effects.

Table 9. Total and acute respiratory-related events in all-treated COPD safety population

	Indacaterol treatment groups (mcg)						**Active comparators**			
	75	150	150+Tio	300	600	All	For	Tio	Sal	Pbo
	n=543	n=2754	n=1142	n=1422	n=584	n=6863	n=556	n=842	n=1010	n=2484
Events shown as number (frequency)										
Composite, n (%)										
Total	6 (1.1)	43 (1.6)	16 (1.4)	54 (3.8)	15 (2.6)	134 (2.0)	32 (5.8)	7 (0.8)	14 (1.4)	52 (2.1)
Acute	6 (1.1)	37 (1.3)	15 (1.3)	47 (3.3)	15 (2.6)	120 (1.8)	31 (5.6)	6 (0.7)	12 (1.2)	50 (2.0)
Hospitalizations, n (%)										
Total	6 (1.1)	43 (1.6)	16 (1.4)	53 (3.7)	15 (2.6)	133 (1.9)	32 (5.8)	7 (0.8)	14 (1.4)	50 (2.0)
Acute	6 (1.1)	37 (1.3)	15 (1.3)	46 (3.2)	15 (2.6)	119 (1.7)	31 (5.6)	6 (0.7)	12 (1.2)	47 (1.9)
Intubations, n (%)										
Total	0	1 (<0.1)	1 (<0.1)	2 (0.1)	0	4 (0.1)	3 (0.5)	0	1 (<0.1)	1 (<0.1)
Acute	0	1 (<0.1)	0	1 (0.1)	0	2 (<0.1)	3 (0.5)	0	0	1 (<0.1)
Events shown as exposure-adjusted for 1000 patient-years										
Composite										
Total	109	865	258	747	395	2394	396	179	280	941
Acute	55	54	78	80	38	62	106	45	50	63
Hospitalizations										
Total	55	53	70	78	38	60	93	45	50	63
Acute	55	46	66	68	38	54	91	39	43	60

Intubations										
Total	0	1	4	3	0	2	10	0	0	1
Acute	0	1	0	1	0	1	8	0	0	1

Lower dose groups and dosing regimens for which no respiratory related events were reported are not included in this table [e.g. 18.75 mcg (n=173), 37.5 mcg QD/BID (n=219), 150 mcg QOD (n= 48), 400 mcg QD (n=7)]; all dosing regimens are QD unless otherwise noted
Total: Includes those patients who had any respiratory related event
Acute: Includes those events that were deemed COPD/pneumonia related;
For: formoterol; Tio: tiotropium; Sal: salmeterol

Post-marketing safety

Indacaterol is marketed in over 50 countries around the world for COPD. The worldwide sales reported by Novartis during the review period of this submission are approximately 57,000 patient years. Post-marketing adverse event reports do not raise any new safety concerns. There were a number of deaths reported with indacaterol worldwide post-marketing, which is not atypical for COPD population. There were higher numbers of deaths reported from a patient support program in Mexico. The majority of patients enrolled in the program in Mexico had severe COPD. There was one death from acute worsening of asthma reported in a 44-year-old female with a diagnosis of asthma and COPD. Details of the report are scant, but this death seems reminiscent of LABA-related asthma death.

c. REMS/RiskMAP

Novartis submitted a REMS for Arcapta Neohaler consisting of a Medication Guide and a communication plan regarding LABA safety of asthma related death. The communication plans included a Health Care Professional Letter, information posted on a website, and notification of professional societies.

Per the February 2011, Draft Guidance for Industry: Medication Guides – Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS), in most cases FDA expects to include a Medication Guide as part of a REMS only when the REMS includes elements to assure safe use. Thus, while a Medication Guide is required to communicate the potential risks of Arcapta Neohaler, a Medication Guide as part of REMS is not necessary. Therefore, the REMS will consist of a communication plan and timetable for assessments.

9. Advisory Committee Meeting

A Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting was held on March 8, 2011, for this application. The major issues for discussion at the PADAC meeting were: a) whether the proposed doses of 75 mcg and 150 mcg and the once-daily dosing frequency are supported by submitted data, b) whether the second higher dose of 150 mcg is necessary and supported by submitted efficacy data and balancing safety data, c) whether the SGRQ benefit claim is supported, and whether the SGRQ data provide supportive evidence of efficacy for any of the doses, and finally, d) the safety of the

proposed dose and dosing regimen of indacaterol. The Committee by majority voting concluded that efficacy for 75 mcg dose was demonstrated, that the 75 mcg was safe for use in COPD patients, and recommended approval of the 75 mcg dose (votes were 13 yes and 4 no). Regarding the 150 mcg dose, the Committee concluded that added benefit of the 150 mcg dose was not demonstrated, and balancing the overall efficacy and safety data, recommended against approval of the 150 mcg dose (votes were 5 yes and 12 no). The Committee was split as to whether or not the SGRQ data provide supportive evidence of efficacy for the 75 mcg dose [votes were 10 yes and 7 no].

In the open public forum of the PADAC meeting, the consumer advocacy group Public Citizen raised issues with Novartis's involvement in a "series of unethical, placebo-controlled clinical trials testing the experimental drug indacaterol in human subjects with moderate to severe COPD that were conducted at multiple US institutions." The specific ethical concerns raised include the use of placebo control group in the clinical trials, failure to minimize risk to participants, and inadequate informed consent. The Public Citizen group later followed their presentation with written concerns in a letter sent to the FDA and other parts of the US Government. The Public Citizen group identified four studies conducted in the United States (B2335, B2346, B2354, and B2355) and two studies conducted outside the United States (B2334, and B2336) in its complaint.

At the PADAC meeting, the Committee did not discuss or address the Public Citizen issues raised with some Novartis studies. Comments regarding the Public Citizen complaint are made in this review in Sections 11a and 11c below.

10. Pediatric

COPD is an adult disease, therefore, specific pediatric studies would not be required that relate to this action specific to COPD. Prior to the scheduled August 26, 2009, PeRC meeting, the Committee agreed that a full waiver should be granted because studies would be impossible or highly impractical since the disease does not exist in pediatric patients. The program was not discussed at the PeRC meeting.

11. Other Relevant Regulatory Issues

a. DSI Audits

No DSI audit was conducted for the original NDA application. DSI audits were conducted at representative sites from three clinical studies (B2354, B2355, and B2357). The DSI audit did not identify data and scientific integrity issues at the sites inspected. All studies were conducted in accordance with accepted ethical standards.

In light of the Public Citizen issues discussed in Section 9 above, the DSI was asked to review the informed consents for the trials identified by Public Citizen. The DSI reviewed the original informed consent templates, which could have been modified subsequently to suit the individual studies and sites. The informed consent documents informed patients of the chance of being assigned to placebo, and that their current medications may be stopped or changed. The exact risks of these changes were not described in detail. The risks of use of placebo and change of medication (such as switch

from LABA to SABA) are known and unlikely to result in substantial harm or injury in these short-term COPD studies.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. Five investigators had significant financial interest in Novartis. The number of subjects that these investigators enrolled was not 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, DMEPA, or from other groups in CDER.

In light of the Public Citizen issues discussed in section 9 above, the review team further reviewed the ethical aspects of the studies in question in consultation with the Office of Good Clinical Practice in the Office of the Commissioner. The overall conclusion after further review was that the conduct of the studies in question was ethically acceptable. This conclusion was based on the following observations: a) Patients in the placebo arms of these trials were not untreated, they were allowed to use short-acting beta-agonists (SABA) as needed, and the studies had escape criteria for patients to discontinue the study; b) Stopping a LABA that patients may have been taking before enrollment and replacing that with either placebo (use of SABA allowed as needed) or indacaterol would not result in substantial harm or injury because SABA is an acceptable alternate to LABA for relatively short-term treatment of COPD as was the case for patients enrolled in these studies; c) Two of the three drugs currently approved for COPD exacerbation (Spiriva HandiHaler and Daliresp) that patients could theoretically have used in these indacaterol studies were not approved at the time these studies were conducted; and d) One of three drugs approved for COPD exacerbation (Advair Diskus) that patients could have used in these indacaterol studies was not allowed, but not allowing Advair in these relatively short term indacaterol studies would not place patients in substantial harm or injury because patients were allowed to use ICS, which in effect would change a LABA plus ICS (Advair Diskus) to SABA (as needed use) and ICS.

12. Labeling

a. Proprietary Name

Novartis initially submitted Arcapta (b) (4) as the proposed proprietary name. The DMEPA rejected this proposed name Best Available Copy Novartis subsequently submitted Arcapta Neohaler as the proposed proprietary name, which was accepted by the DMEPA.

b. Physician Labeling

Novartis submitted a label in the Physician Labeling Rule format. The label was reviewed by various disciplines of this Division, DRISK, DMEPA, and DDMAC. During labeling review, one major discussion point with Novartis was the dose to be

labeled, with Novartis wanting both the 75 mcg and 150 mcg dose to be indicated, with supporting evidence from the modeling analysis included in the product label. As discussed in various sections of this document above, the Division did not consider modeling analysis adequate to support the claim that the 150 mcg dose provides additional benefit over the 75 mcg dose, and concluded that the overall risk benefit analysis does not provide justification for the 150 mcg as an additional dose over the 75 mcg dose. Novartis and the Division finally agreed that 75 mcg would be the only recommended dose. Various sections of the proposed label from Novartis were changed to reflect the recommended dose. Various other changes to different sections of the label were made to reflect the data accurately and better communicate the findings to health care providers. The label contains efficacy data from the dose-ranging asthma and COPD studies submitted with the complete response of the NDA, all other COPD studies relevant for the approved doses, and the asthma safety study that had findings of asthma-related death and serious asthma exacerbations. Asthma-related safety warnings are described in the label, including in a Boxed Warning. The Division and Novartis have agreed on the final label language.

c. Carton and Immediate Container Labels

These were reviewed by various disciplines of this Division and DMEPA, and found to be acceptable.

d. Patient Labeling and Medication Guide

Arcapta Neohaler will carry an asthma-related safety warning that will be part of the Medication Guide.

13. Action and Risk Benefit Assessment

a. Regulatory Action

Novartis has submitted adequate data to support approval of Arcapta Neohaler for long term once daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including bronchitis and emphysema, at the dose of 75 mcg once daily. The recommended regulatory action on this application is Approval.

The comment below is for the 150 mcg dose Complete Response.

1. The submitted data do not provide substantial evidence to support marketing of two different doses of Arcapta Neohaler in patients with COPD. The submitted data do not show a clinically meaningful bronchodilator efficacy advantage or other clinically meaningful efficacy advantage of the 150 mcg once daily dose over the 75 mcg once daily dose. There is also the potential for a safety disadvantage with administration of a higher dose.

   To support approval of a 150 mcg once daily dose in addition to the 75 mcg once daily dose, provide substantial evidence from a clinical program directly comparing the 150 mg dose to the 75 mcg dose. This program will need to demonstrate a clinically meaningful bronchodilator or other efficacy advantage of the 150 mcg once

daily dose compared to the 75 mcg once daily dose without an unacceptable safety disadvantage of the higher dose.

b. Risk-Benefit Assessment

The overall risk-benefit assessment supports approval of Arcapta Neohaler at 75 mcg once daily for long-term once daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including bronchitis and emphysema. The proposed claim that the higher 150 mcg dose will provide additional benefit in patients with more severe bronchial obstruction is not supported.

The major safety concern with indacaterol is linked to selection of appropriate dose, because beta-2 adrenergic bronchodilators, particularly at high doses, have the safety concerns of severe asthma exacerbations and asthma-related deaths in patients who use these drugs to treat the symptoms of asthma. Although such a risk of worsening disease has not been shown in COPD, it is nevertheless important to select an appropriate and safe dose for all bronchodilators, including indacaterol, which is proposed to be marketed for COPD. The safety database for indacaterol shows possible asthma exacerbation and asthma-related death at the 300 mcg dose in patients with asthma, and a potential for dose-related increase in beta-adrenergic effects. The 75 mcg once daily dose of indacaterol is an appropriate and safe dose because it is reasonably removed from the dose of 300 mcg that has concerning safety findings.

From an efficacy standpoint, the clinical program showed that Arcapta Neohaler at 75 mcg, 150 mcg, and 300 mcg once-daily doses provided statistically significant bronchodilator effect in patients with COPD with replicate findings with these doses. There are no replicate findings comparing the 75 mcg dose to the 150 mcg dose in the same study to support the proposed dosing recommendation statement that the higher 150 mcg dose provides additional benefit over the 75 mcg dose in patients with more severe bronchial obstruction. Novartis primarily relied on modeling analysis of trough FEV1 data from various clinical studies to support the claim that the higher dose provides additional benefit in patients with more severe bronchial obstruction. There are concerns with the methodology of the analysis, and concerns from a broader clinical perspective, which limit the utility of the analysis for dose selection and comparing doses across studies.

Data from the dose-ranging studies in patients with asthma and bronchodilator responsive COPD patients are a more relevant data source from which to select dose. These data support 75 mcg as the appropriate dose and do not show clinically meaningful incremental bronchodilator benefit with higher doses.

c. Post-marketing Risk Management Activities

Arcapta Neohaler will carry an asthma-related safety warning that will be part of the Medication Guide. No other post-marketing risk management activities are required.

d. Post-marketing Study Commitments

None.

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/s/

BADRUL A CHOWDHURY
07/01/2011
Div Dir Summary Review