CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date:	October 29, 2015
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA
Subject:	Division Director Summary Review
NDA Number:	207923
Applicant Name:	Novartis
Date of Submission:	December 29, 2014
PDUFA Goal Date:	October 29, 2015
Proprietary Name:	Seebri Neohaler
Established Name:	Glycopyrrolate
Dosage form:	Inhalation Powder in Capsule
Strength:	Glycopyrrolate 15.6 mcg per capsule
Proposed Indications:	Maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD)
Action:	Approval

1. Introduction

Novartis submitted this 505(b)(1) new drug application for use of Seebri Neohaler (glycopyrrolate 15.6 mcg inhalation powder per capsule) for long-term maintenance [redacted] (b) (4) treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD). The proposed dose is one capsule by inhalation twice daily. The application is based on clinical efficacy and safety studies. This summary review will provide an overview of the application, with a focus on the clinical efficacy and safety studies.

2. Background

There are several drug classes available for the relief of airflow obstruction in patients with COPD. These include short- and long-acting beta-2 adrenergic agonists, short- and long-acting anticholinergics, combination products containing short- and long-acting beta-2 adrenergic agonists and short- and long-acting anticholinergics, combination products containing long-acting beta-2 adrenergic agonists and corticosteroids, and products containing methylxanthines, and phosphodiesterase-4 (PDE4) inhibitors. There are a smaller number of drug classes available for reducing exacerbations in COPD. These include long-acting anticholinergics, combination products containing long-acting beta-2 adrenergic agonists (LABA) and inhaled corticosteroids (ICS), and PDE inhibitors. With the exception of methylxanthines and PDE-4 inhibitors, all others are inhalation products.

Seebri Neohaler is a new inhalation product comprised of the long-acting anticholinergic glycopyrrolate. Glycopyrrolate has been in clinical use for many years as tablets

(Robinul 6 mg), and intra-operatively as an injectable (Robinul 100 mcg/injection), and an oral solution (Cuvposa) for severe drooling in pediatric patients with neurologic conditions. Novartis developed glycopyrrolate for use in COPD patients as a single entity product (subject of this NDA) and as a combination product with indacaterol (subject of concurrent NDA 207930 for Utibron Neohaler).

In subsequent sections of this review, safety concerns with anticholinergics are discussed, followed by a discussion of regulatory interaction between the Agency and Novartis related to this application.

Glycopyrrolate:

Glycopyrrolate has been available in oral and injectable formulations for multiple years. Novartis has now formulated glycopyrrolate as a dry powder formulation for inhalation use in COPD patients as a single entity product (subject of this NDA) and as a combination product with indacaterol (subject of NDA 207930 for Utibron Neohaler). Inhaled anticholinergics are widely available in the U.S. and worldwide for the treatment of COPD. In the US, one short-acting anticholinergic, ipratropium bromide, and three long-acting anticholinergics, tiotropium bromide (Spiriva HandiHaler, Spiriva Respimat), aclidinium bromide (Tudorza Pressair), and umeclidinium (in combination with vilanterol as Anoro Ellipta, and as single ingredient Incruse Ellipta) are currently available.

In the past, safety concerns of stroke and cardiovascular death have been raised with the use of these drug products in patients with COPD, and thus have been the subject of previous FDA advisory committee meetings. [1] These concerns have been alleviated based on data from large studies with Spiriva HandiHaler and Spiriva Respimat. [2, 3] Nevertheless, it is important to select an appropriate dose and dose regimen for any anticholinergic in a COPD program to limit high systemic exposure and potential safety concerns.

Regulatory interaction between the Agency and Novartis:

Novartis conducted the program for glycopyrrolate single ingredient product concurrently with the development of the glycopyrrolate and indacaterol combination product, so many of the regulatory interactions included discussion of both the single ingredient product and the combination product. Key regulatory interactions for the glycopyrrolate single ingredient product included an End-of-Phase 2 (EOP2) meeting on July 15, 2008, Type A meetings on May 4, and July 13, 2009, a second EOP2 meeting on January 29,

[1] FDA Early Communication about Ongoing Safety Review of Tiotropium. http: //ww fda.gov/cder/drug/early_comm/tiotropium htm

[2] Tashkin DP, Celli B, Senn S. et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Eng J Med 2008; 359: 1543-54.

[3] Wise RA, Anzueto A, Cotton D, et al. Tiotropium Respimat inhaler and the risk of death in COPD. N Eng J Med 2013; 369:1491-501.

2010, and a Pre-NDA meeting on September 28, 2011. The main topics for discussion at these meetings were selection of the optimum dose and dosing regimen for glycopyrrolate. Novartis initially studied only a once-daily dosing regimen for glycopyrrolate (b) (4) . On the Division's recommendation, Novartis studied a more frequent dosing interval and lower nominal dose and ultimately decided on the 15.6 mcg twice daily dosing, which the Division accepted (discussed in Section 7 below).

3. Chemistry, Manufacturing, and Controls

The product Seebri Neohaler (glycopyrrolate inhalation powder) is comprised of a formulation of glycopyrrolate 15.6 mcg (equivalent to 12.5 mcg glycopyrronium) blended with approximately 25 mg of lactose monohydrate and 0.04 mg of magnesium stearate in hypromellose capsules for inhalation via the Neohaler Inhaler. Seebri capsules are packaged in aluminum blister cards in a box of 60 (10 blister cards with 6 capsules each). The Neohaler Inhaler is a plastic device to be used for inhaling the formulation from Seebri 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 a Seebri 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 an expiry period of 18 months.

The drug substance is manufactured by Novartis in their facilities in Ringaskiddy, Ireland 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 conducted a full nonclinical pharmacology and toxicology program for glycopyrrolate. The program included general chronic toxicology studies, genetic toxicology studies, carcinogenicity assessments, reproductive and developmental toxicity studies, and pre- and post-natal development studies.

General chronic toxicology studies included a 26-week inhalation toxicology study in rats, and a 39-week inhalation toxicology study in beagle dogs. In the rat, the target organs of toxicity were the eyes, lungs (epithelial hypertrophy), seminal vesicles (inflammation), and urinary bladder (inflammation). In the dog, the targets organs of toxicity were the eyes, pharynx (inflammation, ectasia of the ducts and/or alveoli), lacrimal gland (hypertrophy), and mandibular salivary glands (hypertrophy). Increased heart rate was noted, but this is an expected pharmacological effect of the drug, which is

clinically monitorable. Most findings reversed after the recovery period. Glycopyrrolate caused eye findings in both rats (anterior capsular opacity, anterior prominent suture line, anterior slight cataract) and dogs (conjunctival hyperemia, corneal opacity, focal nuclear opacity). Eye findings were partially reversible in the rat, and fully reversible in the dog. Based upon eye findings in both species, these findings were noted in the label. There were adequate safety margins for the proposed clinical dose for both local and systemic toxicity. Glycopyrrolate was found to be non-genotoxic, non-carcinogenic, and non-teratogenic. Glycopyrrolate impaired fertility in the rat fertility study, and the labeling language reflects this result. Glycopyrrolate will carry a Pregnancy Category C designation because there are no adequate and well-controlled studies in pregnant women.

5. Clinical Pharmacology and Biopharmaceutics

Novartis submitted results from a comprehensive clinical pharmacology program that included studies to assess the pharmacokinetics and metabolism of the drug product.

The absolute bioavailability of glycopyrrolate is approximately 40% after oral inhalation of which 90% is from lung absorption and 10% is from gastrointestinal absorption. Cmax of glycopyrronium is reached by 5 minutes following inhalation. Renal elimination of parent drug accounts for ~60-70% of systemic clearance, and metabolism and bile excretion accounts for non-renal elimination. The apparent elimination half-life of glycopyrronium following oral inhalation was ~33-53 hours. Glycopyrronium is a substrate for the cationic SLC transporter OCT2 and MATE1. Glycopyrronium does not significantly inhibit or induce CYP450 enzymes, transporters or solute carriers at therapeutic concentrations, suggesting the potential of relevant drug-drug interactions to be low.

The total daily dose and dosing frequency of glycopyrrolate has been adequately explored. Prior to the confirmatory trials, 2 dose ranging trials were conducted in patients with COPD exploring total daily doses from 12.5 mcg to 200 mcg administered once daily (QD) or twice daily (BID). A dose-response relationship was observed for glycopyrrolate 12.5 mcg QD, 25 mcg QD, 12.5 mcg BID, 50 mcg QD, 25 mcg BID, 100 mcg QD, and 50 mcg BID. Based on the data (as discussed in Section 7 below), 12.5 mcg BID was selected for confirmation in the phase 3 program.

6. Microbiology

The manufacturing process for Seebri Neohaler was reviewed by the microbiology team and determined that adequate validation data for (b) (4) manufacturing environment have been provided to demonstrate that the manufacturing process is capable of producing (b) (4) drug product

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 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 glycopyrrolate in COPD

ID Year*	**Study Characteristics †** **- Patient age** **- Patient characteristics** **- Study design, objective** **- Study duration**	**Treatment groups ‡**	**N §**	**Efficacy variables ¶**	**Regions and Countries //**
Dose-response studies – COPD patients					
A2208 [4/10 to 12/10]	- ≥ 40 yr - COPD - PG - 4 weeks	GP 12.5 mcg QD GP 25 mcg QD GP 50 mcg QD GP 100 mcg QD GP 12.5 mcg BID GP 25 mcg BID GP 50 mcg BID Placebo	89 96 92 96 96 96 87 91	FEV_1 trough	US (22%), Belgium, Germany, Hungary, India, Netherlands, Poland, Romania, Spain
Pivotal bronchodilator (or lung function) efficacy and safety studies -- COPD patients					
A2317 [11/12 to 10/13]	- ≥ 40 yr - COPD - PG - 12 weeks	GP 12.5 mcg BID Placebo	222 219	1^o: ΔFEV_1 0-12 hr response at wk 12 2^o: SGRQ at wk 12	US (100%)
A2318 [11/12 to 12/13]	- ≥ 40 yr - COPD - PG - 12 weeks	GP 12.5 mcg BID Placebo	216 216	1^o: ΔFEV_1 0-12 hr response at wk 12 2^o: SGRQ at wk 12	US (100%)
Supportive bronchodilator (or lung function) efficacy and safety studies -- COPD patients					
A2319 [10/12 to 6/14]	- ≥ 40 yr - COPD - PG - 52 weeks	GP 12.5 BID Ind 75 mcg QD	251 256	1^o: ΔFEV_1 0-12 hr response at wk 12 2^o: SGRQ at wk 12	US (100%)
A2336 [11/12 to 2/14]	- ≥ 40 yr - COPD - PG - 12 weeks	GP/Ind 12.5/27.5 BID GP 12.5 mcg BID Ind 27.5 mcg BID Placebo	260 260 261 261	1^o: ΔFEV_1 0-12 hr response at wk 12 2^o: SGRQ at wk 12	US (51%), Canada, Spain, Philippines, Poland, Romania, Ukraine, Vietnam
A2337 [12/12 to 2/14]	- ≥ 40 yr - COPD - PG - 12 weeks	GP/Ind 12.5/27.5 BID GP 12.5 mcg BID Ind 27.5 mcg BID Placebo	250 251 251 249	1^o: ΔFEV_1 0-12 hr response at wk 12 2^o: SGRQ at wk 12	US (58%), Slovenia, Slovakia, Panama, Hungary, France, Guatemala, Egypt, Columbia

* Study ID shown (top to bottom) as Novartis's study number, and [month year study started-completed]
† XO=cross over, PG=parallel group
‡ GP = glycopyrrolate; Ind = Indacaterol
§ Intent to treat
¶ The primary endpoint in pivotal studies was change from baseline in FEV_1 AUC 0-12 hr post morning dose at week 12. Baseline FEV_1 was defined as the mean of the pre-dose FEV_1 measured at -45 minutes and -15 minutes at day 1.
// Shown as countries.

b. Design and conduct of the studies

Dose ranging studies (A2208):

Dose-ranging study A2208 was designed to characterize the dose-response for glycopyrrolate as monotherapy. The study design, treatment arms, and primary efficacy variable are shown in Table 1. In addition there was another dose-ranging study with glycopyrrolate, Study A2205 (discussed further below).

Pivotal bronchodilator (or lung function) studies (A2317, A2318):

These studies were identical in design (Table 1). Patients eligible for the studies were required to have a diagnosis of moderate-to-severe COPD with post-bronchodilator FEV_1 of ≤80% predicted, a post-bronchodilator FEV_1/FVC ratio of ≤0.70, and a smoking history of >10 pack-years. Eligible patients entered a 2-week single-blind placebo run-in period, and the patients who remained eligible entered the 12-week double-blind treatment period. These studies allowed background treatment with inhaled corticosteroids, and short-acting beta-agonists as needed. The majority of the patents (78%) had no exacerbation in the previous year and the majority was classified as having moderate COPD GOLD 2 (63%). Study treatment arms and efficacy variables are shown in Table 1. Safety assessments included adverse event recording, vital signs, physical examination, clinical laboratory and hematology measures, and ECGs.

Supportive studies (A2336, A2337):

These studies were identical in design conducted primarily to support the glycopyrrolate and indacaterol combination product (Table 1). Patients eligible for the studies were required to have a diagnosis of moderate-to-severe COPD with post-bronchodilator FEV_1 of ≤80% predicted, a post-bronchodilator FEV_1/FVC ratio of ≤0.70, and a smoking history of >10 pack-years. Eligible patients entered a 2-week single-blind placebo run-in period, and the patients who remained eligible entered the 12-week double-blind treatment period. These studies allowed background treatment with inhaled corticosteroids, and short-acting beta-agonists as needed. Majority of the patents (69%) had no exacerbation in the previous year and majority was classified as having moderate COPD GOLD 2 (61%). Study treatment arms and efficacy variables are shown in Table 1. Relevant arms for the studies for this application are the glycopyrrolate and placebo treatment arms. Safety assessments included adverse event recording, vital signs, physical examination, clinical laboratory and hematology measures, and ECGs.

c. Efficacy findings and conclusions

The clinical program is adequate to support the efficacy of Seebri Neohaler (glycopyrrolate 15.6 mcg inhalation powder per capsule) at a dose of one capsule by inhalation twice daily for long-term maintenance (b) (4) treatment of airflow obstruction in patients with COPD. The efficacy demonstration builds on the selection of

appropriate dose and dosing regimens for glycopyrrolate, and then demonstrates the benefit for Seebri Neohaler for the claimed benefits of bronchodilation over placebo.

Dose selection for glycopyrrolate:

Glycopyrrolate dose selection was based on two studies, A2205 and A2208. Study A2205 assessed the efficacy of glycopyrrolate 12.5, 25, 50, and 100 mcg, all dosed once daily, in an active- (tiotropium) and placebo-controlled 7-day study in COPD patients. (b) (4) On the Division's recommendation, Novartis studied a more frequent dosing interval and lower nominal dose in Study A2208 (Table 1), and ultimately decided on the 15.6 mcg twice-daily dosing, which the Division accepted. Results of Study A2208 are shown in Table 2 and Figure 1. All glycopyrrolate doses showed statistically significant improvements in trough FEV_1 when compared to placebo at Day 28. In comparison of glycopyrrolate doses, the same total daily dose generally resulted in numerically higher changes in trough $FEV_1$when administered twice-daily versus once-daily. Overall, the results of Study A2208 demonstrated that the glycopyrrolate 12.5 mcg BID dose was a safe and effective dose and supported further investigation of this dosing regimen in the confirmatory studies.

Table 2. LS Mean change from baseline in trough FEV_1 in L, Study A2208

Treatment	n	Mean	Treatment difference vs plalcebo	
			Mean (95% CI)	p-value
GP 12.5 mcg QD	81	1.33	0.08 (0.03, 0.14)	0.002
GP 25 mcg QD	88	1.34	0.09 (0.05, 0.15)	<0.001
GP 12.5 mcg BID	90	1.39	0.14 (0.09, 0.19)	<0.001
GP 50 mcg QD	88	1.34	0.09 (0.04, 0.14)	<0.001
GP 25 mcg BID	87	1.41	0.17 (0.12, 0.22)	<0.001
GP 100 mcg QD	90	1.42	0.18 (0.13, 0.22)	<0.001
GP 50 mcg BID	81	1.42	0.18 (0.13, 0.22)	<0.001
Placebo	82	1.25		
GP = glycopyrrolate				

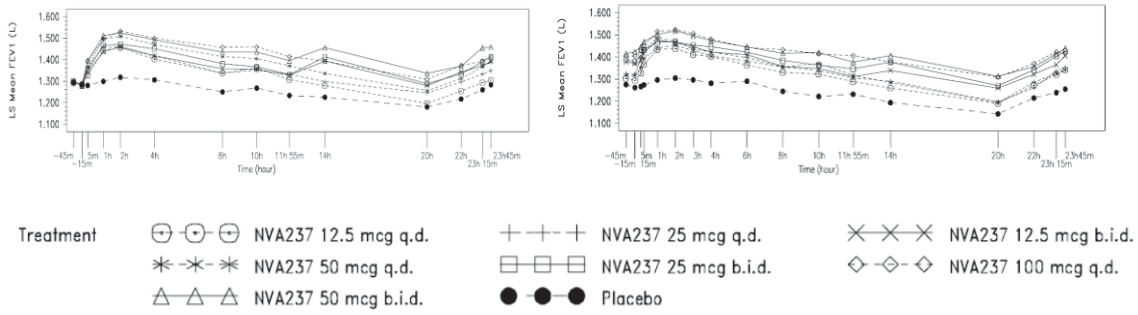

Figure 1. LS Mean FEV_1 24-hour profile at day 1 (left panel) and day 28 (right panel), Study A2208

Seebri Neohaler (glycopyrrolate inhalation powder), bronchodilator effects:

Studies A2317 and A2318 were the primary studies (b) (4) for Seebri Neohaler, and studies A2319, A2336, and A 2337 provide supporting evidence. Results from the primary efficacy variable analysis from the two primary studies showed statistically significant differences between Seebri Neohaler and placebo (Table 3). These efficacy conclusions were confirmed in a sensitivity utility analysis that considered the study therapy failed for patients who had missing data. Efficacy was consistent across demographic subgroups including gender, race, geographical region, smoking status, BMI, inhaled ICS use at baseline, inhaled SABA use at baseline, etc. FEV_1 time profile curved for Studies A2317 and A2318 also showed consistent efficacy over time with the Seebri Neohaler over placebo (Figure 2).

The three supportive studies also provided positive data to support the bronchodilatory effect of Seebri Neohaler. In Studies A2336 and A2337 (primary studies submitted to support the glycopyrrolate and indacaterol combination product), single entity glycopyrrolate provided statistically significant FEV_1 $AUC_{0\text{-}12\ hr}$ response compared to placebo, with treatment differences of 0.13L (95% CI: 0.09, 0.17) and 0.18L (95% CI: 0.15, 0.22), for Studies A2336 and A2337, respectively.

Table 3. Mean change from baseline in FEV_1 AUC $_{0\text{-}12\ hr}$ in Liters at week 12, Studies A2317, A2318

	Study A2317		Study A2318	
	GP 12.5 mcg BID N=222	Placebo N=216	GP 12.5 mcg BID N=215	Placebo N=213
Mean at week 12	0.125	-0.014	0.115	-0.008
Difference vs Placebo	0.139		0.123	
95% CI	0.095, 0.184		0.081, 0.165	
p-value	< 0.001		< 0.001	
GP = glycopyrrolate				

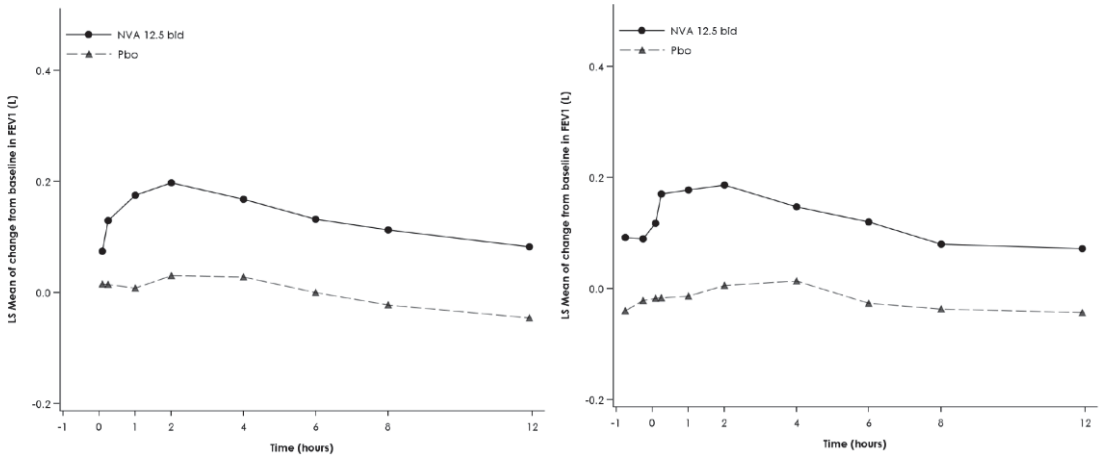

Figure 2. Adjusted mean change from baseline in FEV_1 in Liters over 0-12 hours on day 1 (left panel) and day 85 (right panel), Study A2317

The mean peak FEV_1 improvement for both Studies (Studies A2317 and A2318) was sustained over the duration of treatment. For Study A2336, mean improvement in peak FEV_1 was 0.14 L and 0.16 L on day 1 and day 85, respectively. For Study A2318, mean improvement in FEV1 was 0.14 and 0.15 on day 1 and day 85, respectively. The median time to onset on day 1 for FEV_1, as pre-specified as 100 mL increase from baseline for Studies A2317 and A2318 was 19 minutes and 21 minutes, respectively. These results will be displayed in the product label as they are clinically relevant because they inform the health care provider about sustained benefit over time, and also the expected benefit after first dosing. While there is no prior precedence of including such information in product labels of single entity inhaled anticholinergic drug products, it is reasonable to include this information for Seebri Neohaler because combination products containing an inhaled anticholinergic with a long-acting beta agonist, such as Anoro Ellipta, have such information. Also Utibron Neohaler, which is a combination product containing glycopyrrolate and indacaterol (reviewed concurrently with this application), will have such information in its product label.

Seebri Neohaler, St. George's Respiratory Questionnaire (SGRQ)

SGRQ is designed to measure impact on overall health, daily life, and perceived well-being in patients with obstructive airway disease.[4] SGRQ is designed to measure health impairment in patients with asthma and COPD.[5]

SGRQ was assessed in Studies A2317 and A2318. Results are shown in Table 4. In one study, the proportions of patients with benefits in SGRQ larger than the Minimal Clinical Important Difference or MCID of 4 were statistically significantly greater in the Seebri Neohaler treatment arm than placebo. In the other study, Seebri Neohaler had a numerically greater response compared to placebo (Table 4).

The supportive studies also provided useful data. In Studies A2336 and A2337 (primary studies submitted to support the glycopyrrolate and indacaterol combination product), the odds ratio of proportion of patients with benefits in SGRQ larger than MCID for glycopyrrolate compared to placebo was 1.4 (95% CI: 0.9, 2.0) and 2.0 (95% CI 1.4, 3.0), for Studies A2336 and A2337, respectively.

Table 4. Responder (proportion of patients with an improvement of at least 4 units in the SGRQ total score) analysis at week 12, Study A2317 and Study A2318

[4] St. George's Respiratory Questionnaire (SGRQ), at ATS website:
http://www.thoracic.org/members/assemblies/assemblies/srn/questionaires/sgrq.php
[5] St George's Respiratory Questionnaire Manual, at:
http://www.healthstatus.sgul.ac.uk/SGRQ_download/SGRQ%20Manual%20June%202009.pdf

Treatment *	N †	Responder	Odds Ratio to placebo (95% CI)
Study A2317			
GP 12.5 mcg BID	210	49%	1.43 (0.95, 2.15)
Placebo	192	41%	-
Study A2318			
GP 12.5 mcg BID	193	55%	1.78 (1.17, 2.71)
Placebo	194	42%	-

* GP = glycopyrrolate; Ind = Indacaterol
† N=number of patients with a SGRQ score
‡ p-values for comparison = < 0.05

8. Safety

a. Safety database

The safety assessment of Seebri Neohaler is based on studies shown in Table 1. The safety database for Seebri Neohaler was adequate.

b. Safety findings and conclusion

The submitted data support the safety of Seebri Neohaler for use as maintenance treatment of airflow obstruction in patients with COPD.

Novartis conducted a comprehensive safety analysis of the available data. Safety analysis included evaluation of deaths, serious adverse events (SAEs[6]), common adverse events (AEs), and assessment for areas of interest such as cardiovascular safety, anticholinergic and adrenergic effects.

A total of 5 deaths were reported in the COPD program, 3 in the Seebri Neohaler treatment group (causes were reported as sudden death, infection, and unknon) and 2 in the placebo group (causes were reported as myocardial infarction, and pump failure). Death was rare in the program, but when it occurred, was typical of older COPD patients with multiple comorbid conditions. Reporting of SAEs was also infrequent in the clinical program, and balanced in the treatment groups (4.2% for Seebri Neohaler, 4.1% for placebo). The events reported as SAEs were typical and expected in COPD patients. COPD exacerbation and pneumonia were common causes of SAEs with reporting in more than 2 patients in each treatment arm. AEs leading to discontinuations were also rare. Common adverse events typical of anticholinergic class of medications also occurred infrequently in the 12-week pooled safety database. The most common adverse events in the pooled safety database that occurred with an incidence of ≥ 1% and higher than placebo were upper respiratory tract infection, nasopharyngitis, urinary tract infection, sinusitis, and oropharyngeal pain. There were no clinically meaningful changes in laboratory parameters, vital signs, and or ECGs.

[6] 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.

Cardiovascular safety events were of interest because of historical safety concerns with anticholinergics as discussed in section 2 above. Novartis included several pre-specified evaluations to assess cardiovascular safety that included adjudicated Major Adverse Cardiac Events (MACE), and adjudicated atrial fibrillation and flutter. Overall, adjudicated MACE and/or cardiovascular death occurred infrequently in the development program and were balanced between groups (glycopyrrolate: 0.5%, placebo: 0.6%). There was a small numerical imbalance of "increase in atrial fibrillation/flutter" events in the glycopyrrolate group (1.7%) compared to the placebo group (0.8%), as well as both "new onset atrial fibrillation/flutter" (0.5% vs. 0.1%) and "recurrent/persistent atrial fibrillation/flutter" (1.3% vs. 0.6%). The new onset events were considered SAEs for two of the glycopyrrolate patients and 1 of the placebo patients. None of the patients with adjudicated new onset atrial fibrillation/flutter had adjudicated MACE events and all of these patients (with the exception of 2) had at least one CV risk factor at baseline. In this setting, these small numerical imbalances are unlikely to be clinically significant.

c. REMS/RiskMAP

Novartis submitted a Risk Management Plan for Seebri Neohaler, which consists of routine pharmacovigilance practices. A REMS is not necessary for Seebri Neohaler.

9. Advisory Committee Meeting

An Advisory Committee meeting was not held to discuss this application because the safety and efficacy for inhaled anticholinergic are well understood. There were no unique findings in the Seebri Neohaler program that would warrant a discussion at an Advisory Committee meeting.

10. Pediatric

Novartis is requesting a claim for Seebri Neohaler for COPD only. Since COPD is a disease that occurs only in adults, specific pediatric studies would not be required related to this action specific to COPD. PeRC had previously agreed that for such COPD applications a full waiver should be granted because studies would be impossible or highly impracticable since the disease does not exist in pediatric patients.

11. Other Relevant Regulatory Issues

a. DSI Audits

The review team requested that DSI audit a single clinical site which enrolled patients for both confirmatory trials A2317 and A2318, due to the relatively large number of patients enrolled at this site. Audit of this site did not show any major irregularities. Review of the application did not identify any irregularities that would raise concerns regarding data integrity. No ethical issues were present. All studies were conducted in accordance with accepted ethical standards.

b. Financial Disclosure

Novartis submitted acceptable financial disclosure statements. One investigator had significant financial interest in Novartis. The number of subjects enrolled in the investigator site was not large enough to alter the outcome of any study. Furthermore, the multi-center nature of the studies makes it unlikely that the financial interest could have influenced or biased the results of these studies.

c. Others

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

12. Labeling

a. Proprietary Name

Novartis submitted Seebri Neohaler as the proposed proprietary name, which was accepted by DMEPA.

b. Physician Labeling

Novartis submitted a label in the Physician Labeling Rule format. The label was reviewed by various disciplines of this Division, the Division of Medical Policy Programs (DMPP), DRISK, DMEPA, and by OPDP. Revisions were made to various sections of the label were done to reflect the data accurately and to better communicate the findings to healthcare providers. The Division and BI 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

Novartis has proposed a Patient Information sheet and Instructions for Use for this product, which is acceptable. Seebri Neohaler will carry safety warnings typical of this class.

13. Action and Risk Benefit Assessment

a. Regulatory Action

Novartis has submitted adequate data to support approval of Seebri Neohaler (glycopyrrolate 15.6 mcg inhalation powder per capsule) at a dose of one capsule by inhalation twice daily for long-term maintenance (b) (4) treatment of airflow obstruction in patients with COPD. The regulatory action on this application is Approval.

b. Risk-Benefit Assessment

The overall risk-benefit assessment supports approval of Seebri Neohaler (glycopyrrolate 15.6 mcg inhalation powder per capsule) for maintenance (b) (4) treatment of airflow obstruction in patients with COPD at a dose of one capsule by inhalations twice

daily. The safety findings observed in the clinical program were consistent with that observed for similar products of the anticholinergic class, and there were no unique safety signals seen for Seebri Neohaler. The efficacy findings showed that the Seebri Neohaler provided a statistically significant bronchodilator effect that was superior to placebo. There was also a numerical benefit in SGRQ score with Seebri Neohaler over placebo that places the bronchodilatory effect in context.

c. Post-marketing Risk Management Activities

Seebri Neohaler will carry safety warnings typical of the class. No other post-marketing risk management activities are required.

d. Post-marketing Study Commitments

None.

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/s/

BADRUL A CHOWDHURY
10/29/2015