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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:	207930
Applicant Name:	Novartis
Date of Submission:	December 29, 2014
PDUFA Goal Date:	October 29, 2015
Proprietary Name:	Utibron Neohaler
Established Name:	Glycopyrrolate and indacaterol
Dosage form:	Inhalation Powder in Capsule
Strength:	Glycopyrrolate 15.6 mcg and indacaterol 27.5 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 Utibron Neohaler (glycopyrrolate 15.6 mcg and indacaterol 27.5 mcg inhalation powder per capsule) for long-term maintenance (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.

Utibron Neohaler is a new inhalation product comprised of the long-acting anticholinergic glycopyrrolate and the long-acting beta-2 adrenergic agonist (LABA)

indacaterol. There are two combination products containing long-acting antichoinergic and LABA approved for marketing in the U.S. Anoro Ellipta, containing the long-acting anticholinergic umeclidinium and the LABA vilanterol, was approved in November 2013. Stiolto Respimat, containing the long-acting anticholinergic tiotropium and the LABA olodaterol, was approved in May 2015. During review of this NDA for Utibron Neohaler, an NDA for the single component glycopyrrolate in a Neohaler device (Seebri Neohaler, NDA 207923) was also reviewed and approved for COPD. The NDA for single component indacaterol at a dose of 75 mcg once daily in a Neohaler device was approved for COPD in July 2011 (Arcapta Neohaler, NDA 22383). To support the twice-daily dosing of indacaterol to match the twice daily dosing of glycopyrrolate for the Utibron NDA, Novartis conducted dose-ranging studies for indacaterol and decided 27.5 mcg twice-daily as the appropriate dose (discussed further in Section 7 below).

The anticholinergic glycopyrrolate has been in clinical use for many years as tablets (Robinul 6 mg), intra-operatively as an injectable (Robinul 100 mcg/injection), and as 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 concurrent NDA 207923 for Seebri Neohaler) and as a combination product with indacaterol (subject of this NDA).

In subsequent sections of this review, safety concerns with anticholinergics and LABAs are discussed, followed by a discussion of key 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 NDA 207923 for Seebri Neohaler) and as a combination product with indacaterol (subject of this NDA). 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]

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[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

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.

Indacaterol:

Indacaterol is a LABA, and currently marketed at a dose of 75 mcg once daily in the Neohaler device for the maintenance treatment of COPD (Arcapta Neohaler, NDA 22383, approved in July 2011). Other LABAs currently marketed in the United States for the treatment of COPD include salmeterol, formoterol, and arformoterol. Arformoterol and indacaterol are marketed as single-ingredient products, while salmeterol and formoterol are marketed individually and in combination with inhaled corticosteroids (fluticasone propionate and mometasone furoate, respectively). 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.[4, 5, 6, 7, 8] This has also been discussed at various FDA Advisory Committee meetings,[9] and has led to publications expressing concerns on safety,[10, 11, 12] and establishment of a safe use strategy outlined by the FDA.[13] 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.[14] 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 the development of all LABAs, including indacaterol, which was addressed during development of Arcapta Neohaler.

J Med 2013; 369:1491-501.

[4] Benson RL, Perlman F. Clinical effects of epinephrine by inhalation. J Allergy 1948; 19:129-140.
[5] 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.
[6] 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.
[7] 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.
[8] US Product Labels of salmeterol and formoterol containing products.
[9] 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.
[10] Martinez FD. Safety of long-acting beta-agonists—an urgent need to clear the air. New Eng J Med 2005; 353:2637-2639.
[11] 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.
[12] Drazen JM, O'Byrne PM. Risks of long-acting beta-agonists in achieving asthma control. New Eng J Med 2009; 360:1671-1672.
[13] 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.
[14] Chowdhury BA, Seymour SM, Levenson MS. Assessing the safety of adding LABAs to inhaled corticosteroids for treating asthma. New Eng J Med 2011; 364:2473-2475.

Regulatory interaction between the Agency and Novartis:

Novartis conducted the program for glycopyrrolate and indacaterol combination product concurrently with the development of the glycopyrrolate single ingredient product, so many of the regulatory interactions included discussion of both the combination product and the single ingredient product. Key regulatory interaction for the glycopyrrolate and indacaterol combination product included a Pre-IND meeting on May 11, 2007, End-of-Phase 2 (EOP2) meeting on September 27, 2011, follow-up to EOP2 meeting on March 7, 2012, and Pre-NDA meeting on March 19, 2014. The main topics for discussion at these meetings were selection of the optimum dose and dosing regimen for the two drug components. Novartis initially studied only once-daily dosing regimens for glycopyrrolate (b) (4) On the Division's recommendation, Novartis studied more frequent dosing interval and lower nominal doses and ultimately decided on the 15.6 mcg twice daily dosing, which the Division accepted (discussed in Section 7 below). With respect to the indacaterol component, Novartis conducted appropriate studies to identify a nominal dose for twice-daily dosing to match with the 75 mcg once daily dose that is already approved for COPD (Arcapta Neohaler, NDA 22383, approved in July 2011). Novartis ultimately decided on the 27.5 mcg twice daily dosing, which the Division accepted (discussed in Section 7 below).

3. Chemistry, Manufacturing, and Controls

The product Utibron Neohaler (glycopyrrolate and indacaterol inhalation powder) is comprised of a formulation of glycopyrrolate 15.6 mcg (equivalent to 12.5 mcg glycopyrronium) and indacaterol 27.5 mcg blended with approximately 24.9 mg of lactose monohydrate and 0.04 mg of magnesium stearate in hypromellose capsules for inhalation via the Neohaler inhaler. Utibron 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 Utibron capsules. The 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 Utibron 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 16 months.

The drug substances are 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 full nonclinical pharmacology and toxicology programs for glycopyrrolate under NDA 207923 (Seebri Neohaler) that is under concurrent review with this NDA, and for indacaterol under NDA 22383 (Arcapta Neohaler) that was approved in July 2011. The nonclinical program for the current program was, therefore, focused on the nonclinical safety assessment of the combination of glycopyrrolate and indacaterol. In a 13-week inhalation study in dogs, the toxicity of combination product containing glycopyrrolate and indacaterol was evaluated and compared to the monocomponent products. There were no dose limiting histopathological findings in the dog study. There was no evidence of additive or synergistic toxicity. In an inhalation embryo-fetal development (EFD) study in rats, the maternal and embryo-fetal toxicity of the combination product was evaluated and compared to its monoproduct constituents. There was no evidence of the combination product related maternal or fetal toxicity in this study. The glycopyrrolate and indacaterol combination product will be designated as Pregnancy Category C, similar to the monocomponent products.

5. Clinical Pharmacology and Biopharmaceutics

Novartis conducted a comprehensive clinical pharmacology program for glycopyrrolate under NDA 207923 (Seebri Neohaler) that is under concurrent review with this NDA, and for indacaterol under NDA 22383 (Arcapta Neohaler) that was approved in July 2011. There is no pharmacokinetic drug-drug interaction resulting from the concomitant administration of inhaled indacaterol and inhaled glycopyrrolate based on steady-state exposure. Therefore, the relevant findings and conclusions for the mono-therapies can be extrapolated to the combination.

6. Clinical Microbiology

The manufacturing process for Utibron 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 and indacaterol combination product 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 – Asthma and 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 96 87	FEV_1 trough at day 28	US (22%), Belgium, Germany, Hungary, India, Netherlands, Poland, Romania, Spain
A2210 [11/13 to 3/14]	- ≥ 18 yr - Asthma - XO - Single dose	Ind 37.5 mcg QD Ind 55 mcg QD Ind 75 mcg QD Ind 150 mcg QD Ind 27.5 mcg BID Placebo	84 85 86 84 87 86	FEV_1 AUC 0-24 hr	US (100%)
Pivotal bronchodilator (or lung function) efficacy and safety studies -- COPD patients					
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, Gutemala, France, Egypt, Columbia
Supportive Safety and bronchodilator (or lung function) efficacy -- COPD patients					
A2340 [10/12 to 6/14]	- ≥ 40 yr - COPD - PG - 52 weeks	GP/Ind 12.5/27.5 BID GP/Ind 25/27.5 BID Ind 27.5 mcg BID	204 204 207	1^o: Safety 2^o: ΔFEV_1 trough response	US (58%), Bulgaria, Finland, Hungary, Romania, Spain

* 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, A2210):

Dose-ranging studies A2208 and A2210 were designed to characterize the dose-response for glycopyrrolate and indacaterol as monotherpies. The study design, treatment arms, and primary efficacy variables 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 (A2336, A2337):

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 (69%) had no exacerbation in the previous year and was classified as having moderate COPD GOLD 2 (61%). 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 study (A2340):

This study enrolled patients similar in disease characteristics and demographics to the studies A2336 and A2337. The study was designed primarily to assess safety and tolerability of two doses of the glycopyrrolate and indacaterol combination product compared to the marketed single ingredient indacaterol 75 mcg QD (Arcapta Neohaler). The study also secondarily assessed efficacy using trough FEV_1.

c. Efficacy findings and conclusions

The clinical program is adequate to support the efficacy of Utibron Neohaler (glycopyrrolate 15.6 mcg and indacaterol 27.5 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 indacaterol, and then demonstrates the benefit for Utibron Neohaler for the claimed benefits of bronchodilation over the single ingredients glycopyrrolate and indacaterol.

Dose selection for glycopyrrolate and indacaterol:

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 more frequent dosing interval and lower nominal doses 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 at day 28, 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				

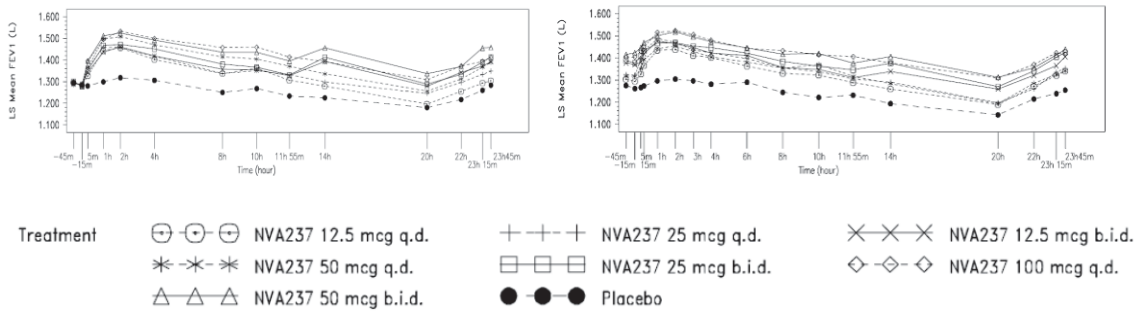
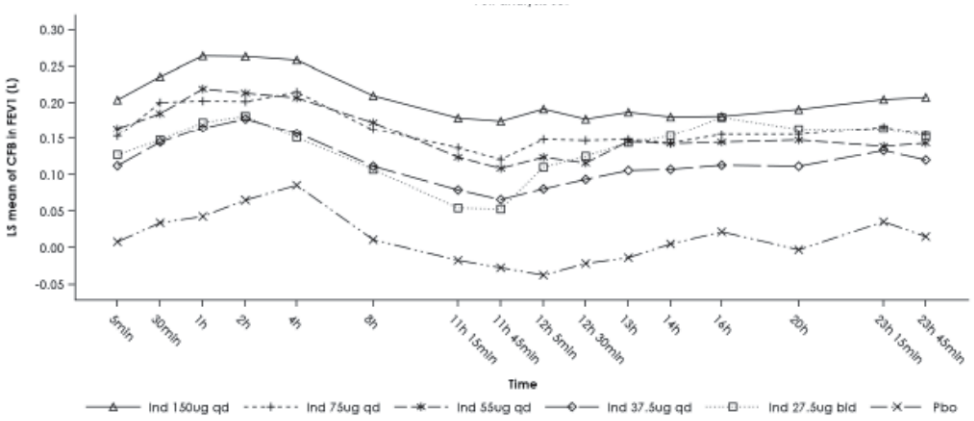


Figure 1. LS Mean FEV_1 24-hour profile at day 1 (left panel) and day 28 (right panel), Study A2208

Indacaterol dose selection was based on Study A2210 (Table 1). The results of Study A2210 are shown in Table 3 and Figure 3. As the proposed combination product of Utibron Neohaler (glycopyrrolate and indacaterol inhalation powder) uses glycopyrrolate that is dosed twice-daily, Novartis used the currently marketed indacaterol 75 mcg once-daily (Arcapta Neohaler) as a benchmark to identify the appropriate twice-daily dose on indacaterol. Overall, the results of Study A2210 supported further investigation of indacaterol 27.5 mcg twice-daily in confirmatory studies.

Table 3. LS Mean change from baseline in trough FEV_1 $AUC_{0\text{-}24hr}$ in L, Study A2210

Treatment	n	Mean	Comparison	Treatment difference	
				Mean (95% CI)	p-value
Ind 150 mcg QD	84	0.21	Ind 75 mcg QD	0.04 (0.01, 0.07)	0.004
			Ind 37.5 mcg QD	0.09 (0.06, 0.12)	<0.001
			Placebo	0.19 (0.16, 0.22)	<0.001
Ind 75 mcg QD	86	0.17	Ind 55 mcg QD	0.01 (-0.02, 0.04)	-
			Ind 37.5 mcg QD	0.05 (0.02, 0.07)	0.003
			Ind 27.5 mcg BID	0.02 (-0.01, 0.06)	-
			Placebo	0.14 (0.11, 0.17)	<0.001
Ind 55 mcg QD	85	0.15	Placebo	0.13 (0.10, 0.16)	<0.001
Ind 37.5 mcg QD	84	0.12	Placebo	0.10 (0.07, 0.13)	<0.001
Ind 27.5 mcg BID	87	0.14	Placebo	0.12 (0.09, 0.15)	<0.001
Placebo	86	0.02			-
Ind = indacaterol					



LMM: CFB in FEV1 = treatment + period + overall mean baseline FEV1 + period adjusted baseline correction + random effect of subject.
The overall mean baseline FEV1 is the average of the 6 period baselines. Each period baseline FEV1 is the mean of the -45 min and -15 min FEV1 values taken on Day 1 prior to first dose in the respective period. The period adjusted baseline correction is the deviation of a subject's period baseline for a given period from the overall mean baseline FEV1 of the subject.
Source: Table 14.2-1.13
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Figure 2. LS mean change from baseline in FEV1 24 hour profile, Study A2210

Utibron Neohaler, bronchodilator effects:

Studies conducted to support combination products typically compare the combination to each active component to show the contribution of each component present in the combination, and also to show that the combination provides clinically meaningful benefit over each single ingredient present in the combination that would justify the use of the combination product by patients. Studies A2336 and A2337 compared Utibron Neohaler (glycopyrrolate and indacaterol inhalation powder) to the respective doses of the single ingredient products (Table 1). Results of efficacy variables of mean FEV_1 0-12 hours for Studies A2336 and A2337 are shown in Table 4. The differences between Utibron Neohaler to the two active ingredients at the corresponding doses were statistically significant (Table 4). Glycopyrrolate and indacaterol were both effective in

these studies as both were also statistically significant over placebo (Table 4). These efficacy conclusions were the same in a sensitivity utility analysis that considered that 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 curves for Studies A2336 and A2337 also showed consistent efficacy over time with the Utibron Neohaler over the single ingredient products, and the single ingredient products also showed consistent efficacy over placebo (Figure 3).

Table 4. Change from baseline in FEV_1 $AUC_{0\text{-}12\ hr}$ in L at week 12, Study A2336 and Study A2337

Treatment *	N †	Change	Difference from Pbo (95% CI)	Difference from GP (95% CI)	Difference from Ind (95% CI)
Study A2336					
GP/Ind 12.5/27.5 mcg BID	258	0.21	0.23 (0.19, 0.27)‡	0.10 (0.06, 0.14)‡	0.09 (0.06, 0.13)‡
GP 12.5 mcg BID	261	0.11	0.13 (0.09, 0.17)‡	-	-
Ind 27.5 mcg BID	260	0.12	0.14 (0.10, 0.18)‡	-	-
Placebo	260	-0.02	-	-	-
Study A2337					
GP/Ind 12.5/27.5 mcg BID	249	0.23	0.26 (0.22, 0.30)‡	0.08 (0.04, 0.12)‡	0.11 (0.07, 0.15)‡
GP 12.5 mcg BID	250	0.16	0.18 (0.15, 0.22)‡	-	-
Ind 27.5 mcg BID	251	0.12	0.15 (0.11, 0.19)‡	-	-
Placebo	246	-0.03	-	-	-

* GP = glycopyrrolate; Ind = Indacaterol
† N=number of observations used in the analysis; all randomized patients who received at least one dose of study drug.
‡ p-values for comparison = < 0.001
Analyzed using a mixed model for repeated measures (MMRM) with treatment, baseline FEV_1, smoking status at baseline, baseline ICS use, region, visit, treatment-by-visit interaction, and baseline FEV_1-by-visit interaction

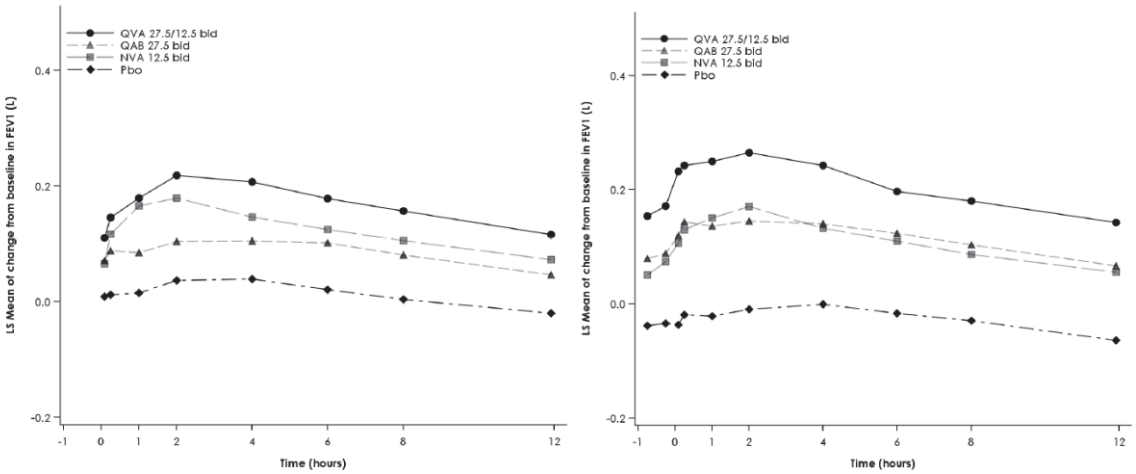

Figure 3. Adjusted mean change from baseline in FEV1 in liters over 12 hours on day 1 (left panel) and day 85 (right panel), Study A2336

The supporting study A2340 was primarily designed to evaluate long-term safety of Utibron Neohaler, but also provided supportive efficacy data. Utibron Neohaler demonstrated a difference in trough FEV_1 compared to indacaterol 75 mcg QD (Table 5). This improvement supports the demonstration of benefit of the Utibron Neohaler combination product over the marketed indacaterol 75 mcg QD (Arcapta Neohaler).

Table 5. Change from baseline in FEV_1 trough in L, Study A2340

Treatment *	N †	Change Day 29	Difference from Ind Mean (95% CI)	Change Day 365	Difference from Ind Mean (95% CI)
Study A2336					
GP/Ind 12.5/27.5 mcg BID	192	0.16	0.06 (0.02, 0.09)‡	0.12	0.08 (0.03, 0.13)‡
Ind 75 mcg QD	199	0.11	-	0.04	

* GP = glycopyrrolate; Ind = Indacaterol
† N=number of observations used in the analysis; all randomized patients who received at least one dose of study drug.
‡ p-values for comparison = < 0.05
Analyzed using a mixed model for repeated measures (MMRM) with treatment, baseline FEV_1, smoking status at baseline, baseline ICS use, region, visit, treatment-by-visit interaction, and baseline FEV_1-by-visit interaction

The mean peak FEV_1 improvement for both Studies (Studies A2336 and A2337) was sustained over the duration of treatment. For Study A2336, mean improvement in FEV_1 was 0.15 L and 0.26 L on day 1 and day 85, respectively. For Study A2337, mean improvement in FEV1 was 0.19 and 0.29 on day 1 and day 85, respectively. The median time to onset on day 1 for FEV_1, pre-specified as 100 mL increase from baseline for Studies A2336 and A2337 was 16 minutes and 12 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. There is prior precedence of including such information in product labels of other products, such as Anoro Ellipta, which is also an inhaled combination product containing a long-acting beta agonist and long-acting anticholinergic.

Utibron 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.[15] SGRQ is designed to measure health impairment in patients with asthma and COPD.[16]

SGRQ was assessed in Studies A2336 and A2337. Results are shown in Table 5. In both studies, the proportions of patients with benefits in SGRQ larger than the Minimal Clinical Important Difference or MCID of 4 were statistically significantly greater in Utibron Neohaler treatment arms than placebo. Utibron Neohaler also tended to have numerically greater response compared to the single ingredient products, and the single

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

ingredient products also tended to have numerically greater response compared to placebo. Some of the latter differences reached nominal statistical significance.

Table 6. Responder (proportion of patients with an improvement of at least 4 units in the SGRQ total score) analysis at week 12, Study A2336 and Study A2337

Treatment *	N †	Responder	Odds Ratio to Pbo (95% CI)	Odds Ratio to GP (95% CI)	Odds Ratio to Ind (95% CI)
Study A2336					
GP/Ind 12.5/27.5 mcg BID	246	57%	2.2 (1.5, 3.2)‡	1.6 (1.1, 2.3)‡	1.5 (1.1, 2.2)‡
GP 12.5 mcg BID	243	46%	1.4 (0.9, 2.0)	-	-
Ind 27.5 mcg BID	244	48%	1.4 (0.98, 2.1)	-	-
Placebo	223	39%	-	-	-
Study A2337					
GP/Ind 12.5/27.5 mcg BID	238	59%	2.9 (1.9, 4.2)‡	1.4 (0.96, 2.0)	1.1 (0.8, 1.7)
GP 12.5 mcg BID	237	52%	2.0 (1.4, 3.0)‡	-	-
Ind 27.5 mcg BID	234	57%	2.5 (1.7, 3.7)‡	-	-
Placebo	226	35%	-	-	-

* 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 Utibron Neohaler is based on the studies shown in Table 1, and the safety of single ingredient indacaterol (Arcapta Neohaler) that is approved for use in patients with COPD. The safety database for Utibron Neohaler was adequate.

b. Safety findings and conclusion

The submitted data support the safety of Utibron 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[17]), common adverse events (AEs), and assessment for areas of interest such as cardiovascular safety, anticholinergic and adrenergic effects.

A total of 7 deaths were reported in the COPD program, 3 in the glycopyrrolate or indacaterol single ingredient treatment groups (causes were reported as sudden death, COPD, and suicide) and 1 in the placebo group (causes were reported as myocardial infarction). There was no death in the Utibron Neohaler treatment group. Death was rare in the program, with causes that are typical of older COPD patients with multiple

[17] 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.

comorbid conditions. Reporting of SAEs was also infrequent in the clinical program, and balanced in the treatment groups (3.2% for Utibron Neohaler, 3.5% for indacaterol, 3.9% for glycopyrrolate, and 4.1% for placebo). The events reported as SAEs were typical and expected in COPD patients. COPD exacerbation was the commonest causes of SAEs reported, and other SAEs were reported in less than 2 patients in each treatment arm. AEs leading to discontinuations were also rare. Common adverse events typical of LABAs and anticholinergic classes of medications also occurred infrequently in the 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 nasopharyngitis, hypertension, oropharyngeal pain, and influenza. There were no clinically meaningful changes in laboratory parameters, vital signs, and or ECGs.

Cardiovascular safety events were of interest because of historical safety concerns with anticholinergics and LABA 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 (Utibron Neohaler: 0.6%, indacaterol: 0.6%, glycopyrrolate: 0.4%, placebo: 0.2%). Adjudicated atrial fibrillation/atrial flutter events also occurred infrequently (Utibron Neohaler: 1.6%, indacaterol 0.8%, glycopyrrolate: 1.2%, placebo: 0.6%). None of the patients with adjudicated new onset atrial fibrillation/flutter had adjudicated MACE events. In this setting, these small numerical imbalances are unlikely to be clinically significant.

c. REMS/RiskMAP

Novartis submitted a Risk Management Plan for Utibron Neohaler, which consists of routine pharmacovigilance practices. A REMS is not necessary for Utibron Neohaler. The product will have a Medication Guide to inform patients about the risk of asthma-related deaths with LABAs.

9. Advisory Committee Meeting

An Advisory Committee meeting was not held to discuss this application because the safety and efficacy for inhaled anticholinergics and inhaled LABAs as single ingredient products and as combination products are well understood. There were no unique findings in the Utibron Neohaler program that would warrant a discussion at an Advisory Committee meeting.

10. Pediatric

Novartis is requesting a claim for Utibron 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 two clinical sites which enrolled patients for both confirmatory trials A2336 and A2337, due to the relatively large number of patients enrolled at these sites. 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 Utibron 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 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

Utibron Neohaler will carry safety warnings typical of this class 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 Utibron Neohaler (glycopyrrolate 15.6 mcg and indacaterol 27.5 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 Utibron Neohaler (glycopyrrolate 15.6 mcg and indacaterol 27.5 mcg inhalation powder per capsule) for maintenance (b) (4) treatment of airflow obstruction in patients with COPD at a dose of one capsule by inhalation twice daily. The safety findings seen in the clinical program were consistent with that seen for similar products of the anticholinergic and LABA classes, and there were no unique safety signals seen for Utibron Neohaler combination product. The efficacy findings showed that the Utibron Neohaler provided a statistically significant bronchodilator effect that was superior to the single ingredient glycopyrrolate and indacaterol products at the corresponding doses. There was also a numerical benefit in SGRQ score with Utibron Neohaler over single ingredient glycopyrrolate and indacaterol and over placebo that places the bronchodilatory effect in context.

c. Post-marketing Risk Management Activities

Utibron Neohaler will carry safety warnings typical of the class 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
10/29/2015