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APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	October 8, 2015
From	Banu A. Karimi-Shah, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 207930
Supplement#	
Applicant	Novartis
Date of Submission	December 29, 2014
PDUFA Goal Date	October 29, 2015
Proprietary Name / Established (USAN) names	Utibron Neohaler, indacaterol/glycopyrrolate inhalation powder
Dosage forms / Strength	indacaterol 27.5mcg/glycopyrrolate 15.6 mcg per capsule (= 12.5 mcg glycopyrrolate per capsule)
Proposed Indication(s)	Long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD)
Recommended:	<i>Approval</i>

1. Introduction

Novartis submitted a 505(b)(1) New Drug Application (NDA) 207930 on December 29, 2014, for indacaterol/glycopyrrolate inhalation powder (Utibron Neohaler; QVA149) indicated for the long-term maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD). Indacaterol/glycopyrrolate is formulated as a dry powder in hard capsules, to be inserted into a single dose dry powder inhalation device, the Neohaler, which was reviewed, approved, and marketed under NDA 22-383 (Arcapta Neohaler). The dry powder capsule contains 15.6 mcg glycopyrrolate/capsule, which corresponds to 12.5 mcg of the active moiety, glycopyrrolate (GP; NVA237) and 27.5 mcg of indacaterol (Ind; QAB149) per capsule. Throughout this review, the dose strength of the drug product will be referred to as the dose of the active moieties, and the combination product will be referred to as GPI (glycopyrrolate/indacaterol).

GP is an anticholinergic drug which has been in clinical use for many years as tablets (Robinul 6 mg), or intra-operatively as an injectable (Robinul 100 mcg/injection every 2-3 minutes). In the United States, an oral formulation (Cuvposa) is indicated for severe drooling in patients 3-16 years of age with neurologic conditions (initial dose 0.02 mg/kg three times daily, titrated to a maximum 0.1 mg/ three times daily). There are also multiple generic GP products. GP has also been formulated by Novartis as a dry powder for inhalation under NDA 207923 (Seebri Neohaler), which has been reviewed concurrently with this NDA, and is also recommended for Approval.

Indacaterol is long-acting beta-2 adrenergic agonist (LABA) that is approved for the once-daily maintenance treatment of airflow obstruction in patients with COPD. Indacaterol 75 mcg once

daily delivered via the Neohaler device, was reviewed under NDA 22-383 (Arcapta Neohaler), and approved in July 2011. Inhaled LABAs are widely used in the United States and worldwide to treat bronchospasm in patients with asthma and COPD.

To support the GPI 12.5/27.5 mcg twice daily (BID) dose for COPD, Novartis has conducted a clinical program that includes two dose-ranging trials (one for each of the monocomponents), two confirmatory phase 3 efficacy and safety trials, and one supportive phase 3 long-term safety/efficacy trial. This memo provides an overview of the application, reviewing the data which demonstrate the efficacy and safety of GPI 12.5/27.5 mcg BID in patients with COPD. Focus is placed on the FEV₁ AUC (0-12hours), which was the primary endpoint in the lung function studies designed to demonstrate efficacy. The memo also addresses the recommendations from each of the individual review disciplines.

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 (LABA), anticholinergic agents, combination products containing beta-2 adrenergic agonists and anticholinergic agents, combination of LABA and corticosteroids (LABA/ICS), methylxanthines, and phosphodiesterase-4 (PDE4) inhibitors. With the exception of methylxanthines and PDE-4 inhibitors, all others are inhalation products.

Glycopyrrolate

GP is an anticholinergic drug with specificity for muscarinic receptors. GP has been available in oral and injectable formulations; the Applicant has now formulated GP as a dry powder for inhalation. The single ingredient product (NDA 207923, Seebri Neohaler) has also been submitted for review. 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. All of these products have anticholinergic adverse effects, such as dry mouth, constipation, and urinary retention.

In the past, there has been a concern regarding increased risk of stroke, cardiovascular death, and myocardial infarction with the use of anticholinergics.¹ A pooled analysis of 29 studies conducted by Boehringer Ingelheim (BI) in 2007 (25 studies with Spiriva HandiHaler, and 4 studies with Spiriva Respimat) suggested an increased risk of stroke with tiotropium bromide.² In contrast, a 6,000 patient, 4-year study with Spiriva HandiHaler conducted by BI in COPD patients (The UPLIFT Study – Understanding Potential Long-term Impacts on Function with

¹ Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. JAMA 2008; 300:1439-50.

² FDA Early Communication about an Ongoing Safety Review of Tiotropium.
[Http://www.fda.gov/cder/drug/early_comm/tiotropium.htm](http://www.fda.gov/cder/drug/early_comm/tiotropium.htm)

Tiotropium) did not show increased mortality or cardiovascular safety risk with Spiriva HandiHaler.^{3,4} A more recent study conducted by BI involving 17,135 COPD patients followed for a mean of 2.3 years (The TIOSPIR study – Tiotropium Safety and Performance in Respimat) showed comparable all-cause mortality between Spiriva Respimat and Spiriva HandiHaler.⁵ Results of the TIOSPIR study were reviewed as part of NDA 21-936; analysis of this large study alleviated the safety concerns of increased mortality, stroke, and cardiovascular events with Spiriva Respimat and provided important data to inform the safety of the anticholinergic class of drugs.

Indacaterol

Indacaterol is a LABA, and currently marketed as Arcapta Neohaler 75 mcg once daily for the maintenance treatment of COPD. 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 individual and in combination with inhaled corticosteroids (fluticasone propionate and mometasone furoate, respectively). Salmeterol, formoterol, and arformoterol are dosed twice-daily.

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 asthma. Unlike patients with asthma, patients with COPD do not appear to carry a similar signal of worsening disease.

Relevant Regulatory History for GPI

Novartis conducted the program for GPI for COPD concurrently with the development of the monotherapy, GP for COPD, so many of the regulatory interactions included discussion of both the mono-components and combination product. With respect to development of the GPI combination product and the GP monocomponent , key regulatory interactions included:

Table 1. Key regulatory interactions for the glycopyrrolate and indacaterol/glycopyrrolate development programs

GP Development	GPI Development
End-of-Phase 2A Meeting: July 15, 2008	Pre-IND Meeting: May 11, 2007
Type A Meeting: May 4, 2009	End-of-Phase 2A Meeting: September 27, 2011
Type A Meeting: July 13, 2009	Type B Meeting: March 7, 2012
End-of-Phase 2A Meeting: January 29, 2010	Pre-NDA Meeting: March 19, 2014
Pre-NDA Meeting: September 28, 2011	

With respect to the GP component of the combination product, the main topic for discussion at the above-listed meetings was dose selection. The Applicant had numerous discussions with the Division regarding what the optimal dose and dosing regimen for GP should be, and how this should be investigated. Initially, the Applicant had not studied more frequent dosing regimens, (b) (4) The Division recommended that more

³ 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.

⁴ Michele TM, Pinheiro S. Iyasu S. The safety of tiotropium – The FDA conclusions. N Eng J Med 2010; 363: 1097-99.

⁵ 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.

frequent dosing regimens and those with lower nominal doses should be explored, and discussed approaches of how this could be done with the Applicant. (b) (4)

(b) (4) With respect to the indacaterol component, discussion focused on development of an indacaterol monoprotect that was pharmaceutically equivalent to the indacaterol component of the combination product.

3. CMC/Device

The recommended action from a CMC/Quality perspective is Approval pending adequate facilities inspection.

All CMC information for the two drug substances, indacaterol and glycopyrrolate, are cross referenced to other NDAs. For indacaterol maleate, all drug substance information was provided in NDA 22-383 for Arcapta Neohaler. However, in the current submission the particle size specification has been (b) (4); the new limit is supported by the updated drug substance data. The complete CMC information for glycopyrrolate is maintained and has been reviewed in NDA 207923 for Seebri Neohaler. Overall the CMC information provided in this application for the drug substances, via cross reference to other NDAs, was deemed acceptable.

The drug product consists of a dry powder formulation for delivery of a combination of indacaterol and glycopyrrolate to patients by oral inhalation. The inhalation powder is packaged in transparent yellow hypromellose capsules. The drug product consists of glycopyrrolate (15.6 mcg), indacaterol (27.5 mcg), lactose monohydrate (24.9 mg), and magnesium stearate (37.5 mcg). While the active moiety is glycopyrrolate 12.5 mcg, per previous interactions with the Division, glycopyrrolate 15.6 mcg will be used for labeling purposes.

The device used to administer the drug is the "Concept1" which is used in the currently-marketed Arcapta Neohaler (NDA 22-383). The device was reviewed as part of NDA 22-383. The Utibron Neohaler is supplied as indacaterol/glycopyrrolate inhalation powder capsules packaged in aluminum blister cards and one Neohaler device. The unit dose (blister pack) is supplied as a box of 60 capsules (10 blister cards with 6 transparent (b) (4) capsules each. The proposed shelf-life of 16 months is appropriate.

The drug product is manufactured by Novartis Pharma Stein AG (Stein, Switzerland).

4. Nonclinical Pharmacology/Toxicology

The recommended regulatory action from a Nonclinical Pharmacology/Toxicology perspective is Approval. There are no outstanding nonclinical issues at this time. The summary below is divided into sections for glycopyrrolate, indacaterol, GPI. A complete summary for the nonclinical program of QAB149 for the inhalation route of administration is available under NDA 22-383; a brief summary is provided below.

Glycopyrrolate

General chronic toxicology studies included a 26-week inhalation toxicology study in rats, and 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 pharynx (inflammation, ectasia of the ducts and/or alveoli), lacrimal gland (hypertrophy), and mandibular salivary glands (hypertrophy). All findings reversed after the recovery period. The non-clinical reviewer determined that there are adequate safety margins for the proposed clinical dose for both local and systemic toxicity. GP was found to be non-genotoxic, non-carcinogenic, and non-teratogenic. Non-clinical review did reveal the GP impaired fertility in the rat fertility study, and the recommended labeling language reflect this result.

In a 13-week inhalation study in dogs, the toxicity of combination product GPI was evaluated and compared to its monoproduct constituents, indacaterol and GP. 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 maternal or fetal toxicity in this study. With respect to teratogenic effects, GP is designated as Pregnancy Category C.

Indacaterol

The toxicological profile of indacaterol has been characterized previously under NDA 22-383 for Arcapta Neohaler, approved July 2011. A summary of the nonclinical development of indacaterol is available in a review under NDA 22-383. Pivotal general toxicology studies to support the use of indacaterol were 26 and 39 week inhalation studies in rats and dogs, respectively. NOAELs were identified in both studies. The target organs of toxicity for indacaterol in the rat are nasal cavity (degeneration of the olfactory epithelium) and larynx (squamous metaplasia). The target organs of toxicity in the dog are the cardiovascular system (increased heart rates), decreased blood pressure and myocardial fibrosis (class effects) and the liver (periportal liver hepatocyte vacuolation due to glycogen deposition; class effect). With respect to teratogenic effects, indacaterol is designated Pregnancy Category C. Indacaterol was not teratogenic following subcutaneous administration to rats and rabbits at doses up to 1 mg/kg. It is not known if indacaterol is excreted in human milk. Carcinogenicity was evaluated in a 26 week study in Tg.rasH2 mice using oral administration and in a 2 -ear rat study using inhalation administration. Indacaterol did not show statistically significant increases in tumor formation in mice or rats.

GPI

In a 13-week inhalation study in dogs, the toxicity of combination product GPI was evaluated and compared to its monoproduct constituents. 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 GPI-related maternal or fetal toxicity in this study. GPI will also be designated as Pregnancy Category C.

5. Clinical Pharmacology/Biopharmaceutics

The recommended regulatory action from a Clinical Pharmacology/Biopharmaceutics perspective is Approval. There are no outstanding clinical pharmacology issues at this time.

To support this NDA submission, the Applicant provided information from 11 clinical pharmacology studies, some of which were submitted to support NDA 207923. Highlights of the clinical pharmacology review are summarized here.

- Following oral inhalation of GPI from the Neohaler, both indacaterol and glycopyrronium were rapidly absorbed and reached peak plasma levels (C_{max}) at 15 min and 5 min, respectively.
- There is no pharmacokinetic drug-drug interaction resulting from the concomitant administration of inhaled indacaterol and inhaled glycopyrronium based on steady-state exposure. Therefore, the relevant findings and/or conclusions for the mono-therapies may be extrapolated to the combination.
- The dose ranging performed in the combination program included full characterization (dose-ranging) of the individual components and was adequate for the Phase 3 dose selection. This is further discussed in Section 7 of this memorandum.

6. Clinical Microbiology

The recommended regulatory action from a Clinical Microbiology perspective is Approval. There are no outstanding clinical microbiology issues at this time.

The drug product is not a sterile product. Manufacturing of the inhalation hard capsule takes place in (b) (4). The inhalation powder hard capsules are submitted to microbiological release testing. The microbial attributes of the drug product were assessed through development studies and as part of the long-term registration stability testing. All microbial attributes are consistently met to date on all batches.

7. Clinical/Statistical-Efficacy

Overview of the clinical program

The studies relevant to regulatory decision-making for this application are listed in Table 2. All listed studies were conducted in patients with moderate to severe COPD, except the indacaterol dose ranging study, A2210, which was a conducted in patients with asthma.

Table 2: Indacaterol/glycopyrrolate clinical development program

Trial <i>Trial period</i>	Design	Treatment (mcg)	N*	Endpoint	Sites <i>% US sites¹</i>
Dose Selection Trials					
A2210 <i>Nov 2013- Mar2014</i>	SD, R, DB, PC, XO (asthma)	Ind 37.5 QD Ind 55 QD Ind 75 QD Ind 150 QD Ind 27.5 BID Placebo BID	84 85 86 84 87 86	FEV ₁ AUC(0-24h)	12 sites in US 100%
A2208 <i>Apr 2010- Dec 2010</i>	4-wk, R, DB, PC, incomplete XO	GP 12.5 QD GP 25 QD GP 50 QD GP 100 QD GP 12.5 BID GP 25 BID GP 50 BID Placebo BID	89 96 92 96 96 96 87 91	Trough FEV ₁	50 sites (US, Belgium, Germany, Hungary, India, Netherlands, Poland, Romania, Spain) 22%
Confirmatory Trials					
A2336 <i>Nov 2012- Feb 2014</i>	12-wk, R, DB, PC, AC, PG	GP/Ind 12.5/27.5 BID GP 12.5 BID Ind 27.5 BID Placebo BID	260 260 261 261	FEV ₁ AUC(0-12h)	150 sites (US, Canada, Spain, Philippines, Poland, Romania, Ukraine, Vietnam) 51%
A2337 <i>Dec 2012 – Feb 2014</i>	12-wk, R, DB, PC, AC, PG	GP/Ind 12.5/27.5 BID GP 12.5 BID Ind 27.5 BID Placebo BID	250 251 251 249	FEV ₁ AUC(0-12h)	102 sites (US, Slovenia, Slovakia, Panama, Hungary, Guatemala, France, Egypt, Colombia) 58%
Supportive Trials					
A2340 <i>Oct 2012 – Jun 2014</i>	52-wk, R, DB, AC, PG	GP/Ind 12.5/27.5 BID GP/Ind 25/27.5 BID Ind 75 QD	204 204 207	Long-Term Safety Trough FEV ₁	88 sites (US, Bulgaria, Finland, Hungary, Romania, Spain) 58%
mcg: micrograms; R=randomized, SD=single dose, DB=double-blind, PG=parallel group, PC=placebo controlled, AC=active controlled, XO=crossover, GP: glycopyrronium, Ind: indacaterol, FEV ₁ : forced expiratory volume in 1 second, AUC: area under the curve, QD=once daily, BID=twice daily, wk=week. * number randomized 1. % of total sites that were in the United States					

The clinical development program consisted of two dose selection trials (A2208 and A2210), two confirmatory efficacy/safety trials (A2336 and A2337), and one supportive efficacy/safety trial (A2340). Trials A2336 and A2337 were replicate, 12-week lung function trials with the typical factorial design in adult patients with COPD. Trial A2340 was a 52-week long-term safety study, which also included an efficacy comparison of the combination product to the marketed indacaterol 75 mcg QD (Arcapta Neohaler). With respect to efficacy, this summary review focuses on trials A2336 and A2337, as well as the dose selection trials (A2208 and A2210). A brief overview of the efficacy of the proposed combination of GPI vs. indacaterol 75 mcg QD from trial A2340 is also provided here. The long-term safety information from trial A2340 will be briefly summarized in the safety discussion.

Dose selection for glycopyrrolate

Dose selection for GP included two trials, A2205 and A2208. A2205 was a randomized, double-blind, placebo-controlled, active-controlled, 7-day study comparing the efficacy of GP 12.5, 25, 50, and 100 mcg once daily with tiotropium 18 mcg once-daily in 83 patients with moderate to severe COPD. (b) (4)

During multiple pre-submission interactions, the Division noted that the dose/dosing frequency had not been adequately investigated (see key regulatory interactions above). As a result, the Applicant was requested to evaluate both twice daily and once daily regimens over a range total daily doses. The Applicant the conducted trail A2208, which forms the basis of later evaluation for the dose that was carried over into the pivotal U.S registration program. As a result, trial A2208 will be the focus of this review.

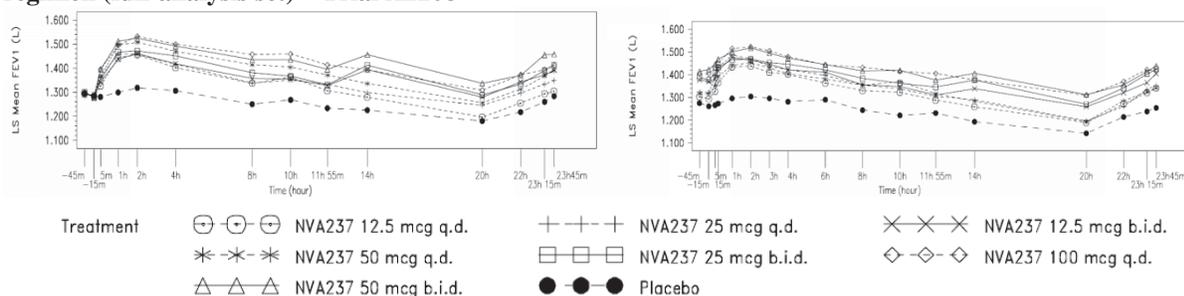
Trial A2208 was a 28-day, double-blind, randomized, dose finding trial in 385 COPD patients. Baseline demographics and disease characteristics were generally similar to the confirmatory trial population, and comparable between treatment groups. The GP doses studied were 12.5 mcg QD, 25 mcg QD, 50 mcg QD, 100 mcg QD, 12.5 mcg BID, 25 mcg BID, 50 mcg BID, and placebo. Both nominal dose and dose frequency were investigated in this trial. The primary endpoint was change from baseline in trough FEV1 at day 28. The results of trial A2208 are presented below in Table 3 and Figure 1.

Table 3: Mean change from baseline in trough FEV₁(L) - Trial A2208

Treatment	n	LS Mean (SE)	Treatment Difference vs. Placebo	
			LS Mean (95% CI)	p-value
GP 12.5 mcg QD N=89	81	1.33 (0.02)	0.08 (0.030, 0.136)	0.002
GP 25 mcg QD N=96	88	1.34 (0.02)	0.09 (0.048, 0.148)	<0.001
GP 12.5 mcg BID N=95	90	1.39 (0.02)	0.14 (0.089, 0.189)	<0.001
GP 50 mcg QD N=92	88	1.34 (0.02)	0.09 (0.038, 0.142)	<0.001
GP 25 mcg BID N=96	87	1.41 (0.02)	0.17 (0.115, 0.219)	<0.001
GP 100 mcg QD N=96	90	1.42 (0.02)	0.18 (0.132, 0.220)	<0.001
GP 50 mcg BID N=87	81	1.42 (0.02)	0.18 (0.132, 0.222)	<0.001
Placebo N=91	82	1.25 (0.02)	--	--

The model has been adjusted for the following covariates: period baseline FEV1 measurement, FEV1 prior to inhalation and FEV1 45 min post-inhalation of ipratropium bromide, smoking status, baseline ICS use, and period. Patient is included as a random effect.
 The analysis excluded values taken within 6 hours of rescue medication or 7 days of systemic corticosteroid use.
 The period baseline FEV1 is the mean of the 45 and 15 minutes pre-dose FEV1 values at each period. Trough FEV1 is defined as the mean of the FEV1 values measured at 23 hours 15 min and 23 hours 45 min post-dose.
 N = number of patients randomized, n = number of patients with available data
 Source: Module 5.3.5.3, Study A2208 CSR Addendum 2, p. 5

Figure 1: 24-hour profile of LS mean FEV₁ at Day 1 (left panel) and Day 28 (right panel) by treatment regimen (full-analysis set) – Trial A2208



The model has been adjusted for the following covariates: period baseline FEV1 measurement, FEV1 prior to inhalation, and FEV1 45 min post inhalation of ipratropium bromide, smoking status, baseline ICS use, and period. Patient is included as a random effect.
 NVA237 = Glycopyrronium = GP
 Source: Module 5.3.5.3, Trial A2208 CSR, pp. 818 and 821

All GP doses showed statistically significant improvements in trough FEV1 when compared to placebo at Day 28. In comparison of GP doses, the same total daily dose (nominal dose) generally resulted in numerically higher changes in trough FEV1 when administered twice-daily versus once-daily. Overall, the results of trial A2208 demonstrated that the GP 12.5 mcg BID dose was a safe and effective dose and supported further investigation of this dosing regimen in the confirmatory trials.

Dose selection for indacaterol

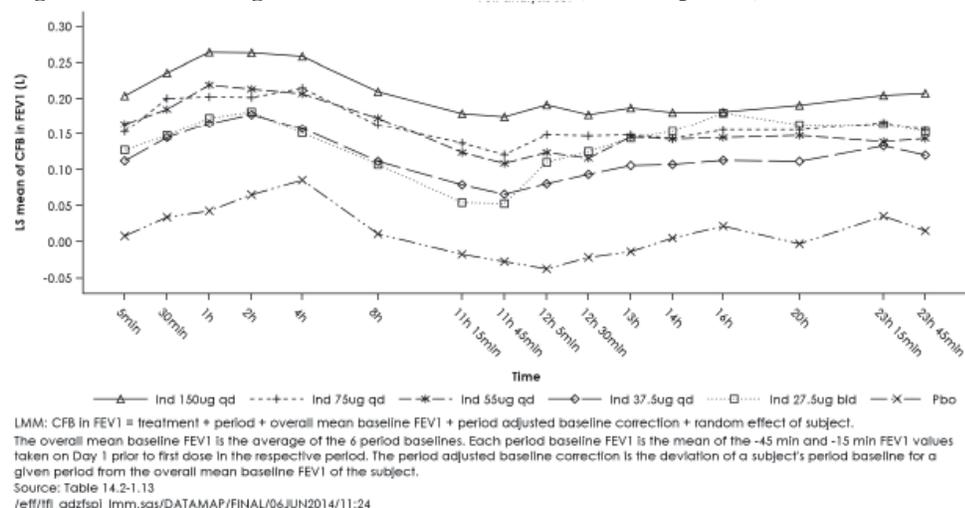
Trial A2210 was a single-dose, double-blind, placebo-controlled, crossover study in 91 patients with persistent asthma. The indacaterol dosing regimens studied were 37.5 mcg QD, 55 mcg QD, 75 mcg QD, 150 mcg QD, and 27.5 mcg BID. The primary efficacy endpoint was the change from baseline in FEV₁ AUC(0-24h). The results of trial A2210 are presented below in Table 4 and Figure 2.

Table 4. Mean change from baseline in FEV₁ AUC(0-24h) (L) - Trial A2210

Treatment	n	LS Mean (SE)	Comparison	Treatment Difference	
				LS Mean (95% CI)	p-value
Ind 150 mcg QD	84	0.21 (0.06)	Ind 75 mcg QD	0.04 (0.014, 0.073)	0.004
			Ind 37.5 mcg QD	0.09 (0.058, 0.118)	<0.001
			Placebo	0.19 (0.157, 0.216)	<0.001
Ind 75 mcg QD	86	0.17 (0.02)	Ind 55 mcg QD	0.01 (-0.018, 0.041)	-
			Ind 37.5 mcg QD	0.05 (0.015, 0.074)	0.003
			Ind 27.5 mcg BID	0.02 (-0.007, 0.051)	-
			Placebo	0.14 (0.114, 0.173)	<0.001
Ind 55 mcg QD	85	0.15 (0.03)	Placebo	0.13 (0.103, 0.162)	<0.001
Ind 37.5 mcg QD	84	0.12 (0.02)	Placebo	0.10 (0.069, 0.128)	<0.001
Ind 27.5 mcg BID	87	0.14 (0.02)	Placebo	0.12 (0.092, 0.151)	<0.001
Placebo	86	0.02 (0.02)	---	---	---

LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval, CFB = change from period baseline, Ind: indacaterol
 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 patient's period baseline for a given period from the overall mean baseline FEV₁ of the patient.
 Source: Module 5, CSR A2210, Table 4-1, page 6

Figure 2. Mean change from baseline in FEV₁(L) (24 hour profile) – Trial A2210



Source: Module 5.3.5.3, Clinical Study Report A2210, Figure 14.2.1.1, p. 256.

As this is a combination product and GP is administered BID, the Applicant used the currently marketed Arcapta (Ind 75 mcg QD) as a benchmark to identify the appropriate BID dose. Overall, the results of trial A2210 supported the further investigation of indacaterol 27.5 mcg BID in the confirmatory trials.

Confirmatory Trials: A2336 and A2337

The confirmatory trials were designed to evaluate the safety and efficacy of GPI 12.5/27.5 mcg BID on lung function in subjects with moderate to severe COPD. Patients were permitted to take inhaled corticosteroids along with study treatments. Albuterol or salbutamol were provided as rescue medication for use as necessary during the trials. The primary endpoint in both trials was change from baseline in FEV₁ AUC(0-12 hours). The baseline FEV₁ was defined as the mean of the pre-dose FEV₁ measured 45 and 15 minutes prior to dosing on Day 1.

Trials A2336 and A2337 were 12-week, randomized, placebo-controlled trials which evaluated a total of 2,043 subjects with moderate to severe COPD. Of these, 510 patients received GPI 12.5/75mcg BID, 511 patients received indacaterol 27.5 mcg BID, 512 patients received GP 12.5 mcg bid, and 510 subjects received placebo. The trials consisted of a one-week screening period, two-week run-in period, a 12-week treatment period, and a 30-day follow-up visit.

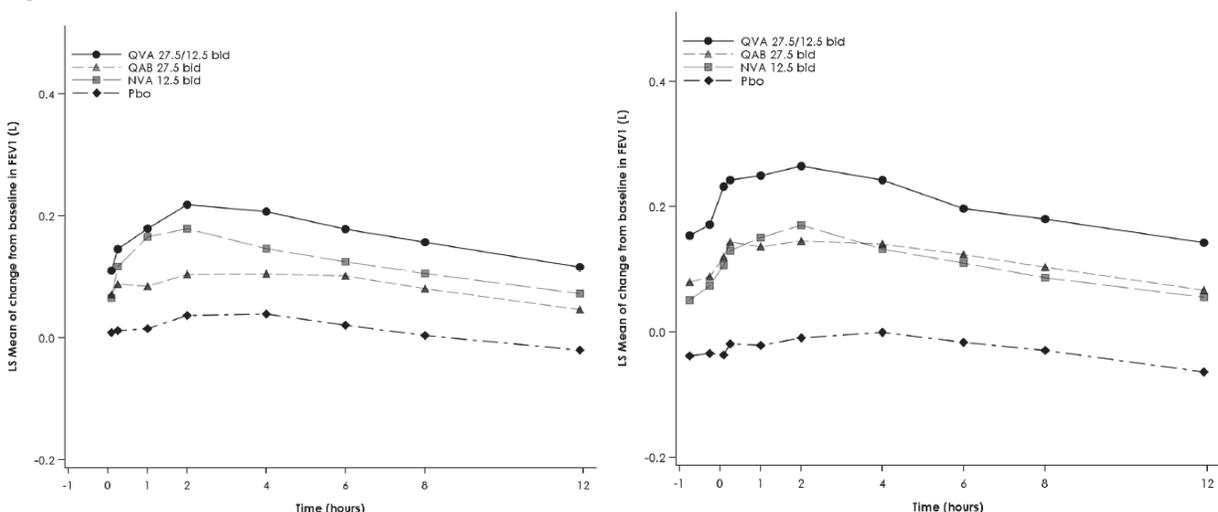
Demographic and baseline disease characteristics were balanced across treatment groups and typical of a COPD population. Patients ranged from 41 to 89 years old, with a mean age of 63 years, with 63% being male and 91% Caucasian. Mean baseline pre-bronchodilator FEV₁ (L) was 1.2 to 1.3L across all treatment groups. A majority of the patients (69%) had no exacerbations in the previous year and were classified as having moderate (GOLD 2) COPD (61%). The majority of patients (94 to 99%) completed the planned treatment phase. The number of patients who discontinued was fairly balanced across treatment groups, but slightly numerically higher in the placebo (5-6%) and single-ingredient indacaterol groups (4%) versus the combination and single-ingredient GP groups (1-2%) in both trials.

GPI 12.5/27.5 mcg BID demonstrated a statistically significant improvement in the FEV₁ AUC (0-12h) at Week 12 compared to each monotherapy, GP and indacaterol. In both trials, each monotherapy (GP and indacaterol) demonstrated a statistically significant improvement in FEV₁ AUC(0-12h) at Week 12 compared to placebo. The results of the primary efficacy analysis are displayed in Table 5 and a representative figure from trial A2336 is shown in Figure 3 below.

Table 5. Primary efficacy results: change from baseline in FEV₁(L) AUC (0-12h) at Week 12 – Trials A2336 and A2337 (Full Analysis Set)

Treatment *	N†	Change (L)	Diff from Placebo (95% CI)	Diff from GP (95% CI)	Diff from Ind (95% CI)
Trial A2336					
GPI 12.5/27.5 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 BID	261	0.11	0.13 (0.09, 0.17)‡	---	---
Ind 27.5 BID	260	0.12	0.14 (0.10, 0.18)‡	---	---
Placebo	260	-0.02	---	---	---
Trial A2337					
GPI 12.5/27.5 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 BID	250	0.16	0.18 (0.15, 0.22)‡	---	---
Ind 27.5 BID	251	0.12	0.15 (0.11, 0.19)‡	---	---
Placebo	246	-0.03	---	---	---
* GPI = Utibron Neohaler(indacaterol/glycopyrrolate inhalation powder); GP = glycopyrrolate; Ind = indacaterol † N=number of observations used in the analysis; FAS: 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 (L) over 12 hours on Day 1 (Left Panel) and Day 85 (Right Panel) -- Trial A2336



Source; Module 2.7.3, Summary of Clinical Efficacy, Figures 3-2 and 3-4, pp. 58, 61.

- Estimates obtained from MMRM: Change from baseline in FEV1 = treatment + baseline FEV1 + smoking status at baseline + baseline ICS use + visit + treatment*visit interaction + baseline FEV1*visit interaction.
- Separate MMRM were performed for each timepoint using visit as repeated variable.
- QVA149 = GPI 12.5/27.5 BID; QAB149 = Ind 27.5 BID; NVA 12.5 BID= GP 12.5 BID; Pbo= placebo

Subgroups analysis on the primary endpoints were conducted by gender, age, race, airflow limitation, smoking status, and ICS use. In general, the subgroup analyses were consistent with the primary results from the overall population.

The St. George's Respiratory Questionnaire (SGRQ) is a patient-reported outcome instrument which measures symptoms, activities, and the impact of disease on daily life in patients with COPD. The minimal clinical important difference (MCID) for the SGRQ has been determined to be 4 points for COPD patients. The SGRQ was assessed as a secondary endpoint in both trials A2336 and A2337. In both trials, the active treatment groups achieved an improvement in the mean total score that exceeded the MCID of 4. Numerically, GPI achieved the greatest change from baseline (-6.4 points in trial A2336 and -7.5 in trial A2337). In Trial 1, the SGRQ responder rate (defined as a change in score of 4 or more as threshold) for the GPI treatment arm was 57% compared to 39% for placebo [Odds Ratio: 2.2; 95% CI: 1.5, 3.2]. In Trial 2, the SGRQ responder rate for the GPI treatment arm was 59% compared to 35% for placebo [Odds Ratio: 2.85; 95% CI: 1.93, 4.21]. The SGRQ responder rate comparing GPI to each of the monotherapies demonstrated inconsistent results across the two trials. The results of the analysis of SGRQ are shown in Tables 6 and 7.

Table 6. Mean change from baseline SGRQ total score – Trials A2336 and A2337 (full analysis set)

Treatment *	N†	Mean Score at Week 12	Difference vs. Placebo (95% CI)	Difference vs. GP (95% CI)	Difference vs. Indacaterol (95% CI)
Trial A2336					
GPI	246	-6.4	-3.8 (-5.7, -1.8)‡	-1.7 (-3.6, 0.2)	-1.9 (-3.8, 0.0)
GP	243	-4.8	-2.1 (-4.0, -0.1)‡	---	---
Indacaterol	244	-4.6	-1.9 (-3.8, 0.1)	---	---
Placebo	223	-2.7	---	---	---
Trial A2337					
GPI	238	-7.5	-6.4 (-8.5, -4.2)‡	-1.4 (-3.5, 0.7)	-1.5 (-3.6, 0.6)
GP	237	-6.0	-4.9 (-7.1, -2.8)‡	---	---
Indacaterol	234	-5.9	-4.8 (-7.0, -2.7)‡	---	---
Placebo	226	-1.1	---	---	---

* GPI = Utibron Neohaler(indacaterol/glycopyrrolate inhalation powder); GP = glycopyrrolate; Ind = indacaterol
 OR: odds ratio
 † N=number of patients with a SGRQ total score
 ‡ p-values for comparison = < 0.05
 Source: Statistical Review, NDA 207930

Table 7. Proportion of patients with an improvement of at least 4 units in the SGRQ total score at Week 12 – Trials A2336 and A2337 (full analysis set)

Treatment *	N†	Proportion of Patients with Response	OR compared to placebo (95% CI)	OR compared to GP (95% CI)	OR compared to indacaterol (95% CI)
Trial A2336					
GPI	246	57%	2.2 (1.5, 3.2)‡	1.6 (1.1, 2.3)‡	1.5 (1.1, 2.2)‡
GP	243	46%	1.4 (0.9, 2.0)	---	---
Indacaterol	244	48%	1.4 (0.98, 2.1)	---	---
Placebo	223	39%	---	---	---
Trial A2337					
GPI	238	59%	2.9 (1.9, 4.2)‡	1.4 (0.96, 2.0)	1.1 (0.8, 1.7)
GP	237	52%	2.0 (1.4, 3.0)‡	---	---
Indacaterol	234	57%	2.5 (1.7, 3.7)‡	---	---
Placebo	226	35%	---	---	---

* GPI = Utibron Neohaler(indacaterol/glycopyrrolate inhalation powder); GP = glycopyrrolate; Ind = indacaterol
 OR: odds ratio
 † N=number of patients with a SGRQ total score
 ‡ p-values for comparison = < 0.05
 Source: Statistical Review, NDA 207930

Supportive Trial: A2340

Trial A2340 was a 52-week, randomized, double-blind, parallel group study to compare the safety and tolerability of GPI 12.5/27.5 mcg BID (n=204) and GPI 25/27.5 mcg BID (204) versus indacaterol 75 mcg QD (n=207) in moderate to severe COPD patients. With respect to demographics, the patient population as similar to trials A2336 and A2337. The majority of patients completed the planned treatment period (89%). While primarily designed to evaluate long-term safety, trial A2340 provided an important comparison of the new combination product GPI 12.5/27.5 mcg to the marketed indacaterol 75 mcg QD (Arcapta Neohaler, NDA 22-823), with respect to lung function (trough FEV₁). GPI 12.5/27.5 mcg BID demonstrated a difference in treatment effect with an improvement of 0.08L in pre-dose trough FEV₁ at Week 52 compared to indacaterol 75 mcg QD. This improvement supports the demonstration of benefit of the

combination product over the marketed indacaterol 75 mg QD (Arcapta Neohaler). The results of trial A2340 are shown in Table 8.

Table 8. Change from baseline in pre-dose trough FEV₁- Trial A2340 (Full Analysis Set)

Treatment *	N [†]	Change at Day 29 (L)	Diff from Ind (95% CI) Day 29	Change at Day 365 (L)	Diff from Ind (95% CI) Day 365
GPI 12.5/27.5 BID	192	0.16	0.06 (0.02, 0.09) [‡]	0.12	0.08 (0.03, 0.13) [‡]
Ind 75 QD	199	0.11	---	0.04	---

* GPI = Utibron Neohaler(indacaterol/glycopyrrolate inhalation powder); Ind = indacaterol
[†] N=number of observations used in the analysis; FAS: all randomized patients who received at least one dose of study drug.
[‡] p-values for comparison = < 0.05
 Pre-dose trough FEV₁ is defined as the mean of FEV₁ at -45 min and -15 min before morning dose.
 Analyzed using a mixed model for repeated measures (MMRM) with treatment, baseline FEV₁, smoking status at baseline, baseline ICS use, region, visit, treatment-by-visit interaction, and baseline FEV₁-by-visit interaction
 Note: No multiplicity adjustments were made for any secondary endpoints (including trough FEV₁) evaluated in this study; results are therefore descriptive.

Efficacy Conclusions

The Applicant provides support for the efficacy of GPI 12.5/27.5 mcg BID (Utibron Neohaler) for the maintenance treatment of COPD by demonstrating a statistically significant improvement in lung function in terms of FEV₁ AUC (0-12) hours as compared to both monotherapies (GP and indacaterol) as well as placebo, in two replicate 12-week studies. As the dosing regimen of the combination product includes a different dosing frequency and nominal dose for the indacaterol component as compared with the marketed Arcapta, trial 2340 provides important supportive evidence that the combination confers an improvement in lung function over indacaterol 75 mcg QD. The efficacy of GPI 12.5/27.5 mcg BID was also supported by other measures of lung function (including peak and trough FEV₁) and health-related quality of life, as measured by the SGRQ, although evaluation of the SGRQ with respect to comparison to the monotherapies did not demonstrate consistent results across trials A2336 and A2337.

The clinical and statistical review teams are in agreement that the data provided are adequate to support the efficacy of GPI 12.5/27.5 mcg BID (Utibron Neohaler; QVA149) for the maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease.

8. Safety

To evaluate the safety of GPI 12.5/27.5 mcg twice daily (BID), the Applicant submitted a pooled safety database that includes two 12-week trials (A2336, A2337) and 52-week long-term safety study (A2340) which included GPI 12.5/27.5 mcg BID (n=204), 25/27.5 mcg BID (n=204), and indacaterol 75 mg QD (n=206) treatment arms. Trials A2336 and 2337 were the same trials that provided the pivotal efficacy results as described above. As the long-term safety was consistent with what was observed in the 12-week pooled safety information, this review of safety will focus on the pooled 12-week database.

A total of 2,040 subjects were included in the 12-week pooled safety database: 508 subjects received GPI 12.5/27.5 mcg BID, 511 subjects received indacaterol 27.5 mcg BID, 513 subjects received GP 12.5 mcg BID, and 508 subjects received placebo. An adequate number of patients were exposed to both doses for up to 6 months and 1 year.

In the 12-week pooled safety database, the majority of the subjects were white and male, with a mean age of 63 years. Approximately 4% of subjects were African American. Most patients were current smokers with a moderate (GOLD 2) COPD. The patient population (n=614) in the long-term safety study was similar to the 12-week pooled database.

There were 7 deaths in the clinical development program, with 3 in the indacaterol and GP monoproduct treatment groups, and 1 in the placebo group. There were no deaths in the GPI treatment group. Causes of death in the 3 indacaterol-treated patients included sudden death, COPD, and suicide. In the GP-treated group, causes of death included sudden death, infection, and unknown. In the placebo group, one patient died due to myocardial infarction. Overall, death was a rare occurrence in the 12-week pooled safety database, with causes of death that are typically seen in an older, COPD population, with multiple co-morbid conditions.

Similarly, serious adverse events (SAEs) were also infrequent in the clinical development program. In the 12-week pooled safety database, 75 subjects reported SAEs (3.2% GPI, 3.5% indacaterol, 3.9% GP, and 4.1% placebo). The most frequent SAE was COPD reported by 3 (0.6%) subjects in the GPI group, 6 (1.2%) in the indacaterol group, 9 (1.8%) in the GP group, and 10 (2.0%) in the placebo group. Other SAEs (when examined by preferred term) each occurred in ≤ 2 subjects. In addition, adverse events (AEs) leading to premature discontinuation were uncommon, with more patients discontinuing in the placebo group (4%) than in the active treatment groups (1.6-3.0%). The most common AE leading to discontinuation was also COPD (1-2%) across active treatment and placebo groups. Analysis of SAEs and AEs leading to discontinuation did not raise concern for any new safety signals.

Given the historical concern with the anticholinergic class of drugs, adverse events of interest included adjudicated major adverse cardiovascular events (MACE), and adjudicated atrial fibrillation/flutter. Overall, adjudicated MACE and/or cardiovascular death occurred infrequently in the GP development program (GPI: 0.6%, indacaterol: 0.6%, GP: 0.4%, placebo: 0.2%). Adjudicated atrial fibrillation/atrial flutter events also occurred infrequently (GPI: 1.6%, indacaterol 0.8%, GP: 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.

Adverse events typical of the anticholinergic class (i.e. urinary retention) and LABA class were reported infrequently as well. The most common adverse events in the 12-week pooled safety database that occurred with an incidence of $\geq 1\%$ 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.

Safety Conclusions

In summary, the safety data for the GPI development program in COPD do not reveal any new anticholinergic- or LABA-related safety concerns. Adverse events were few and generally those observed were similar to other approved anticholinergic and LABA products. The safety of GPI 12.5/27.5 mcg is supported.

9. Advisory Committee Meeting

A pulmonary allergy drug advisory committee (PADAC) meeting was neither convened nor required for this submission as the safety and efficacy of an anticholinergic, such as GP, and LABA, such as indacaterol, in the maintenance treatment of COPD is well-described and well-understood.

10. Pediatrics

Novartis is requesting a claim for COPD. Since COPD is a disease that occurs only in adults, specific pediatric studies would not be required. The 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 entity of COPD does not exist in pediatric patients.

11. Other Relevant Regulatory Issues

- Financial Disclosure: Appropriate financial disclosure information was provided by the Applicant. None of the investigators reported any proprietary interests. One investigator reported significant payments over the threshold of honoraria; however, given the international scope of this clinical development program, and the relatively low percentage of overall recruitment from this single investigator, any potential conflict of interest is not likely to impact study results.
- DSI audits information: 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 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 trials were conducted in accordance with accepted ethical standards.
- Office of Compliance: The overall EES conclusion is pending at the time of the finalization of this review.

12. Labeling

- Proprietary Name: The name Utibron Neohaler was determined to be acceptable.
- Physician Labeling: The label was reviewed by various disciplines within DPARP, the Office of Medical Policy Programs (OMPP), DRISK, DMEPA, and by OPDP. Various changes to different sections of the label were made to reflect the data accurately and better communicate the findings to healthcare providers. Labeling discussions are ongoing at the time of finalization of this review.
- Carton and Immediate Container Label: These were reviewed by various disciplines of the Division and DMEPA, and found to be acceptable.

The FDA-edited labeling has been conveyed to the Applicant. Final labeling language between the Applicant and the Division is still under discussion at the time of this review.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

The recommended regulatory action is Approval for GPI 12.5/27.5 mcg twice-daily for the long-term maintenance treatment of airflow obstruction, in patients with COPD.

- **Risk Benefit Assessment**

The overall risk benefit assessment supports the approval of GPI inhalation powder at a dose of 12.5/27.5 mcg twice-daily for the long-term, maintenance treatment of airflow obstruction in patients with COPD. GP is an addition to the class of anticholinergic drugs, which has a well-characterized and well-understood safety profile; additionally, a large safety study conducted for another anticholinergic drug, further supports the safety profile of this class. Indacaterol, a LABA, is already approved as a single-entity for the maintenance treatment of COPD. From an efficacy standpoint, the clinical program was able to demonstrate that indacaterol 27.5 mcg/glycopyrrolate 12.5 mcg twice-daily provided a statistically significant bronchodilator effect, as measured by FEV₁ AUC (0-12hours).

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**

No additional post-marketing risk management activities are recommended beyond standard pharmacovigilance methods.

- **Recommendation for other Postmarketing Requirements and Commitments**

None.

- **Recommended Comments to Applicant**

No additional comments are necessary at this time.

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/s/

BANU A KARIMI SHAH
10/08/2015