CENTER FOR DRUG EVALUATION AND RESEARCH

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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 # Supplement#	NDA 207923
Applicant	Novartis
Date of Submission	December 29, 2014
PDUFA Goal Date	October 29, 2015
Proprietary Name / Established (USAN) names	Seebri Neohaler/glycopyrrolate inhalation powder
Dosage forms / Strength	15.6 mcg glycopyrrolate/capsule = 12.5 mcg glycopyrronium
Proposed Indication(s)	Long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD)
Recommended:	*Approval*

1. Introduction

Novartis submitted a 505(b)(1) New Drug Application (NDA) 207923 on December 29, 2014, for glycopyrrolate inhalation powder (NVA237;Seebri Neohaler) indicated for the long-term maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD). 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 will be available as 15.6 mcg glycopyrrolate/capsule, which corresponds to 12.5 mcg of the active moiety, glycopyrronium (GP). Throughout this review, the dose strength of the drug product will be referred to as the dose of the active moiety, GP 12.5 mcg.

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, and 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.

To support the GP 12.5 mcg twice daily (BID) dose for COPD, Novartis has conducted a clinical program that includes one dose-ranging trial, two confirmatory phase 3 clinical trials, and three supportive phase 3 clinical trials (including two efficacy/safety trials from a combination development program with indacaterol that included GP-only treatment arms, and a long-term safety trial). This memo provides an overview of the application, reviewing the data which demonstrate the efficacy and safety of GP 12.5 mcg BID in patients with COPD. Focus is placed on the FEV_1 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.

GP is an anticholinergic drug with specificity for muscarinic receptors; Seebri Neohaler (NVA237) inhalation powder is a new formulation of glycopyrrolate. 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 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.

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[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://ww fda.gov/cder/drug/early_comm/tiotropium.htm
[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.

Relevant Regulatory History for GP

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

- End-of-Phase 2 Meeting: July 15, 2008
- Type A Meeting: May 4, 2009
- Type A Meeting: July 13, 2009
- End-of-Phase 2A Meeting: January 29, 2010
- Pre-NDA Meeting: September 28, 2011

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 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)

3. CMC/Device

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

The drug substance glycopyrronium bromide, or glycopyrrolate, is an anticholinergic drug that has been previously used in oral and injectable forms for indications other than COPD. The drug substance is a white powder which is freely soluble in water. Per the CMC review, the starting materials and their specifications are adequate to control drug substance quality. In general, there are very small amounts of impurities in the drug substance, and these were well characterized and controlled in the drug substance. No degradants were observed except under very stressful conditions. The drug substance is very stable and no significant change in any measured parameter was observed during long-term or accelerated stability studies.

The drug product consists of glycopyrrolate (15.6 mcg), lactose monohydrate (24.9 mg), and magnesium stearate (37.5 mcg). The drug product is filled into an orange hypromellose capsule. While the active moiety is glycopyrronium 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, and device robustness was also evaluated as part of the GP development program. The Applicant evaluated inhalers returned from clinical trials and those which were associated with

patient complaints. Overall, 5 out of 17670 devices were associated with complaints (0.03%), further supporting the robustness of the device.

The Seebri Neohaler is supplied as glycopyrrolate 15.6 mcg 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 orange capsules each. The proposed shelf-life of 18 months is appropriate.

The drug substance and drug product are manufactured by Novartis Ringaskiddy Ltd. (Co. Cork, Ireland) and Novartis Pharma Stein AG (Stein, Switzerland) with (b) (4) stability testing conducted at Novartis Pharma AG (Basel, Switzerland), (b) (4), and Novartis Ringaskiddy Ltd. (Co. Cork Ireland).

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 nonclinical program included general chronic toxicology studies, genetic toxicology studies, carcinogenicity assessment, reproductive and developmental toxicity studies, and pre- and post-natal development (PPND) studies.

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 that GP impaired fertility in the rat fertility study, and the recommended labeling language reflects this result.

GP carries a Pregnancy Category C designation because there are no adequate and well-controlled studies with Seebri Neohaler in pregnant women.

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 16 clinical pharmacology studies, of which 5 studies have also been submitted to support NDA 207930. Highlights of the clinical pharmacology review are summarized here.

- Following oral inhalation via the Neohaler device, the absolute bioavailability of GP is estimated to be ~40%, of which 90% systemic exposure is due to lung absorption and 10% is due to 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 account for the non-renal elimination. The apparent elimination half-life of glycopyrronium following oral inhalation was ~33 to 53 hours. Glycopyrronium is a substrate for the cationic SLC transporter OCT2 and MATE1. Glycopyrronium does not significantly inhibit or induce CYP450 enzymes, ABC transporters or solute carriers at therapeutic concentrations, suggesting the potential of relevant drug-drug interactions to be low.
- The dosing regimen and dosing frequency of GP 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 GP 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.
- No dosing adjustment is recommended for any intrinsic or extrinsic factors. However, the systemic exposure (AUC last) of GP was over 2-fold higher in patients with severe renal impairment (RI) and end stage renal disease (ESRD).

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 1. All listed studies were conducted in patients with moderate to severe COPD.

Table 1: Glycopyrrolate clinical development program

Trial *Trial period*	Design	Treatment (mcg)	N*	Endpoint	Sites *% US sites[1]*
Dose Selection Trials					
A2208 *Apr 2010-* *Dec 2010*	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					
A2317 *Nov 2012 –* *Oct 2013*	12-wk, R, DB, PC, PG	GP 12.5 BID Placebo BID	222 219	FEV_1 AUC(0-12h)	55 sites in the US *100%*
A2318 *Nov 2012 –* *Dec 2013*	12-wk, R, DB, PC, PG	GP 12.5 mcg BID Placebo BID	216 216	FEV_1 AUC(0-12h)	64 sites in the US *100%*
Supportive Trials					
A2336 *Nov 2012-* *Feb 2014*	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 *Dec 2012 –* *Feb 2014*	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%*
A2319 *Oct 2012 –* *Nov 2014*	52-wk, R, DB, DD, AC, PG	GP 12.5 BID Ind 75 QD	251 256	Long-Term Safety	65 sites in the US *100%*

mcg: micrograms; R=randomized, DB=double-blind, PG=parallel group, PC=placebo controlled, AC=active controlled, XO=crossover, DD: double dummy, 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 one dose selection trial (A2208), two confirmatory efficacy/safety trials (A2317 and A2318), and three supportive trials (A2336, A2337, and A2319). Trials A2336 and A2337 were conducted as part of the combination indacaterol/glycopyrrolate development program (reviewed concurrently under NDA 207930);

these trials included single-ingredient GP-treatment and placebo treatment arms as part of the typical factorial design, and therefore contribute to the GP safety database, as well as provide supportive efficacy information for GP. With respect to efficacy, this summary review focuses on trials A2317 and A2318; these were randomized, double-blind, placebo-controlled, lung function trials of 12 weeks duration, in adult patients with moderate to severe COPD. A brief overview of the efficacy information relevant to GP from trials A2336 and A2337 is included here as supportive information. The dose selection trial (A2208) is also summarized here. The long-term safety trial (A2319) is briefly summarized in the safety discussion.

Dose selection

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 then conducted trial A2208, which forms the basis 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.

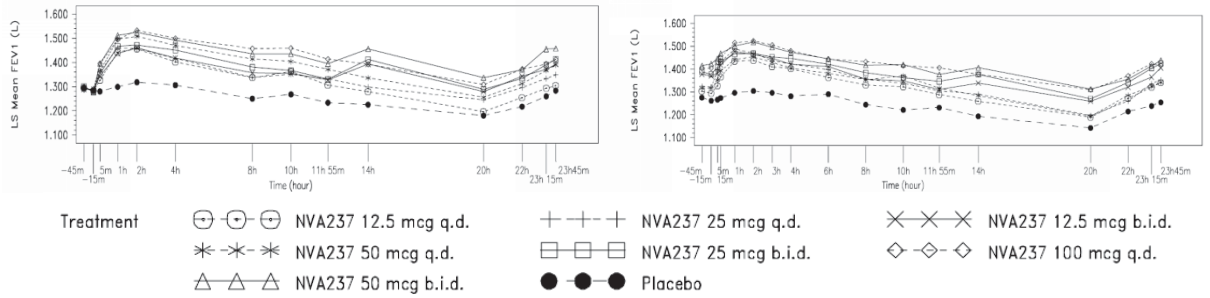
Trial A2208 was a 28-day, double-blind, randomized, dose finding trial in 385 COPD patients. The GP doses studied were 12.5 mcg QD, 25 mcg QD, 50 mcg QD, 100 mcg QD, 12.5 mcg BID, 25 mcg BID, 50 mcg BID, and placebo. Both nominal dose and dose frequency were investigated in this trial. The primary endpoint was the change from baseline in trough FEV1 at Day 28. The results of trial A2208 are presented below in Table 2 and Figure 1.

Table 2: Mean change from baseline in trough FEV_1(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 FEV_1 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 FEV1when 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.

Confirmatory Trials: A2317 and A2318

The confirmatory trials were designed to evaluate the safety and efficacy of GP 12.5 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 the change from baseline in FEV_1 AUC(0-12 h). The baseline FEV_1 was defined as the mean of the pre-dose FEV_1 measured 45 and 15 minutes prior to dosing on Day 1.

Trials A2317 and A2318 were 12-week, randomized, placebo-controlled trials which evaluated a total of 866 subjects with moderate to severe COPD. Of these, 447 patients received GP 12.5 mcg BID and 429 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 the COPD population. Patients ranged from 41 to 87 years old, with a mean age of 63 years, with 58% being male, and 89% Caucasian. Mean baseline pre-bronchodilator FEV_1 was 1.3L across all treatment groups. A majority of the patients (78%) had no exacerbations in the previous year and were classified as having moderate (GOLD 2) COPD (63%).

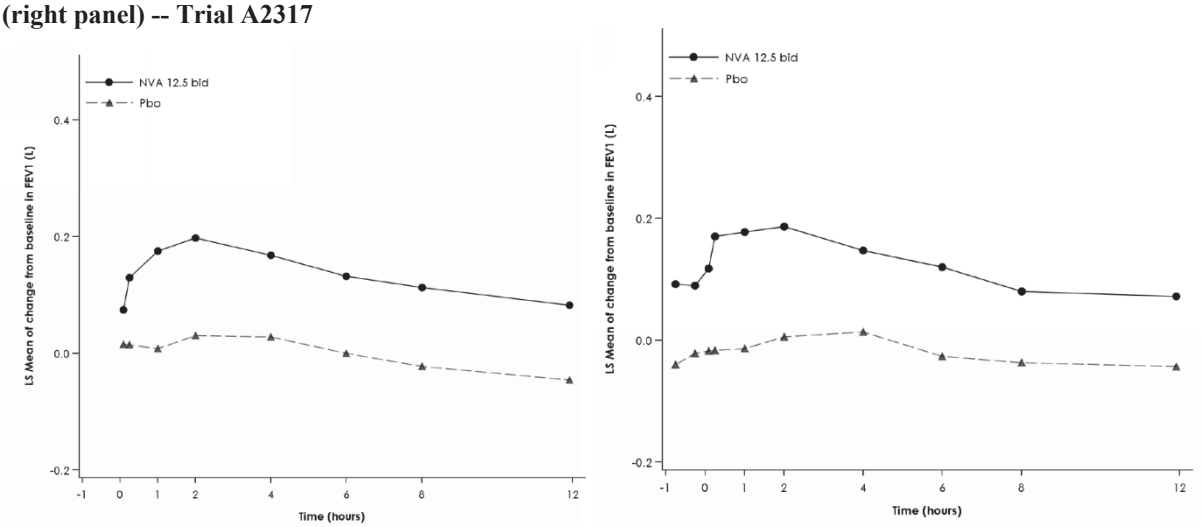
The majority of patients (95 to 97%) completed the planned treatment phase. The number of patients who discontinued was balanced across treatment groups and numerically higher in the placebo groups of both trials (5% placebo vs. 3% GP). In both trials, GP 12.5 mcg BID demonstrated a statistically significant improvement in the FEV_1 AUC(0-12h) at Week 12 compared to placebo, with treatment differences of 0.14L and 0.12L in trials A2317 and A2318, respectively. The results of the primary efficacy analysis are displayed in Table 3 and a representative figure from trial A2317 is shown in Figure 2 below.

Table 3. Primary efficacy results: change from baseline in FEV_1(L) AUC (0-12h) at Week 12 – Trials A2317 and A2318

	Trial A2317		Trial 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 (SE)	0.125 (0.016)	-0.014 (0.017)	0.115 (0.015)	-0.008 (0.015)
Treatment Difference vs. Placebo	0.139		0.123	
95% CI	0.095, 0.184		0.081, 0.165	
p-value	< 0.001		< 0.001	

Efficacy analysis conducted on full analysis set which was defined as all randomized patients who received at least one dose of study drug
Analyzed using a mixed model for repeated measures (MMRM) with treatment, baseline FEV1, smoking status at baseline, baseline ICS use, visit, treatment-by-visit interaction, baseline FEV_1-by-visit interaction. Treatment, smoking status at baseline, ICS use at baseline and visit were treated as categorical variables
GP = glycopyrronium = NVA237 = glycopyrrolate 15.6 mcg BID
N= Intent to Treat Population (ITT)

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



Source; Module 2.7.3, Summary of Clinical Efficacy, Figures 3-1 and 3-2, pp. 56-57.

- 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.
- NVA 12.5 BID= GP 12.5 mcg 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 A2317 and A2318. In both trials, the GP treatment group achieved an improvement in the total score that exceeded the MCID of 4. The responder rate (% of subjects with an improvement of 4 or more) in trial A2317 was 49% and 41% for the GP and placebo treatment arms, respectively [Odds Ratio: 1.43; 95% CI: 0.95, 2.15]. For trial A2318, the responder rate for the GP treatment arm was 55% compared to 42% for the placebo [Odds Ratio: 1.78; 95% CI: 1.17, 2.71]. The results of the analysis of SGRQ are shown in Table 4.

Table 4: SGRQ results - Trials A2317 and A2318 (full analysis set)

Trial	Treatment	Mean Change from Baseline		Proportion of Patients with Improvement of at least 4 Units	
		Mean Score at Week12	Difference from Placebo (95% CI)	% with improvement of ≥ 4	Odds Ratio (95% CI)
A2317	GP 12.5 mcg BID N‡=210	-4.4	-2.8 (-5.0, -0.50)	49%	1.43 (0.95, 2.15)
	Placebo N‡=192	-1.7		41%	
A2318	GP 12.5 mcg BID N‡=195	-6.4	-5.2 (-7.7, -2.7)	55%	1.78 (1.17, 2.71)
	Placebo N‡=196	-1.2		42%	

Source: Agency's Statistical Review, NDA 207923; Analysis conducted on the Full Analysis Set (FAS)
GP=Seebri Neohaler (glycopyrrolate inhalation powder; ‡N = number of patients with a SGRQ total score

Supportive Trials: A2336 and A2337

Trials A2336 and A2337 were conducted as part of the indacaterol/glycopyrrolate combination product development program. Each of these trials is reviewed in detail in NDA 207930 (Utibron Neohaler), which was submitted concurrently with this application for single ingredient glycopyrrolate. Trials A2336 and A2337 included four treatment arms, two of which were glycopyrrolate and placebo. GP 12.5 mcg BID demonstrated a statistically significant improvement in FEV_1 AUC(0-12h) compared to placebo, with treatment differences of 0.13L (95% CI: 0.09, 0.17) and 0.18L (95% CI: 0.15, 0.22), in both trials A2336 and A2337, respectively.

Efficacy Conclusions

The Applicant provides support for the efficacy of GP 12.5 mcg BID for the maintenance treatment of COPD by demonstrating a statistically significant improvement in lung function in terms of FEV_1 AUC(0-12h) compared to placebo in two replicate 12-week studies. Trials A2336 and A2337 also provide support of efficacy. The efficacy of GP 12.5 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.

The clinical and statistical review teams are in agreement that the data provided are adequate to support the efficacy of GP 12.5 mcg BID (Seebri Neohaler; NVA237) for the maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease.

8. Safety

To evaluate the safety of GP 12.5 mcg twice daily (BID), the Applicant submitted a pooled safety database that included four 12-week trials (A2317, A2318, A2336, A2337) and a 52-week

long-term safety study (A2319) which included GP 12.5 mcg BID and indacaterol 75 mg QD treatment arms. Trials A2317 and 2318 were the same trials that provided the pivotal efficacy results as described above in Section 7. Trials A2336 and A2337 were conducted as part of the indacaterol/glycopyrrolate combination development program (submitted concurrently under NDA 207930); these two trials included both GP 12.5 mcg BID and placebo arms, and therefore were also included in the safety database. 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.

In the pooled safety database, 951 subjects received GP 12.5 mcg BID and 938 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. Six percent (6%) of subjects were African American. Most patients were current smokers with a moderate (GOLD 2) COPD. The patient population in the long-term safety study was similar to the 12-week pooled database.

There were 5 deaths in the clinical development program, with 3 in the GP treatment group, and 2 in the placebo group. Causes of death in the 3 GP-treated patients included sudden death, infection, and unknown. In the placebo group, one patient died to due to myocardial infarction, and one secondary to pump failure. 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 comorbid conditions.

Similarly, serious adverse events (SAEs) were also infrequent in the clinical development program. In the pooled safety database, 78 subjects reported SAEs (4.2% GP, 4.1% placebo). The most frequent SAE was COPD reported by 14 (1.5%) subjects in the GP group and 16 (1.7%) subjects in the placebo group; pneumonia was the second most frequent SAE, reported by 4 (0.42%) subjects in the GP group and 1 (0.11%) in the placebo group. Other SAEs (when examined by preferred term) each occurred in fewer than 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 GP group (2.5%). The most common AE leading to discontinuation was also COPD (1 to 1.6% across GP and placebo groups, respectively). 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 and were balanced between groups (GP: 0.5%, placebo: 0.6%). There was a small numerical imbalance of "increase in atrial fibrillation/flutter" events in the GP 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 GP 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.

Adverse events typical of the 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.

Safety Conclusions
In summary, the safety data for the GP development program in COPD do not reveal any new anticholinergic-related safety concerns. Adverse events were few and generally those observed with similar approved anticholinergic products. The safety of GP 12.5 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 in the maintenance treatment of COPD is well-described and well-understood.

10. Pediatrics

Novartis is requesting a claim for GP 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 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 trials were conducted in accordance with accepted ethical standards.

- Office of Compliance: The overall EES conclusion is pending at the time of finalization of this memorandum.

12. Labeling

- Propietary Name: The name Seebri 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 at this time. 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 GP 12.5 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 GP inhalation powder at a dose of 12.5 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. From an efficacy standpoint, the clinical program showed that GP 12.5 mcg twice-daily provided a statistically significant bronchodilator effect, as measured by FEV_1 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