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APPLICATION NUMBER:

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CLINICAL REVIEW(S)

Cross-Discipline Team Leader Review

Date	May 15, 2017
From	Banu A. Karimi-Shah, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 208437
Applicant	Sunovion Pharmaceuticals
Date of Submission	July 29, 2016
PDUFA Goal Date	May 26, 2017
Proprietary Name / Established (USAN) names	Lonhala Magnair/glycopyrrolate inhalation solution
Dosage forms / Strength	25 mcg inhalation solution
Proposed Indication(s)	Long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD)
Recommended:	*Complete Response*

1. Introduction

Sunovion submitted a 505(b)(2) New Drug Application (NDA) 208437 on July 29, 2017, for glycopyrrolate inhalation solution (GP, SUN-101, Lonhala Inhalation Solution) indicated for the long-term maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD). Lonhala is formulated as a solution for inhalation contained within a unit-dose vial, which is to be inserted into the PARI eFlow CS nebulizer (Magnair). The unit-dose, single use vial will contain 25 mcg of glycopyrrolate (GP) in 1 mL. The proposed dose is one vial (25 mcg) by inhalation twice daily.

To support the GP 25 mcg twice daily (BID) dose for COPD, Sunovion has conducted a clinical program that includes two dose-ranging trials, two confirmatory phase 3 clinical trials, and one supportive long-term safety trial. This memo provides an overview of the application, with a focus on the clinical data which demonstrate the efficacy and safety of GP 25 mcg BID in patients with COPD. Focus is placed on the trough FEV_1 (lung function), which was the primary endpoint in the lung function studies designed to demonstrate efficacy. This memo also addresses the recommendations from each of the individual review disciplines and consultants. Specifically, this memo summarizes the device biocompatibility deficiencies identified by CDRH which are the reason from the Complete Response action.

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, 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-4 inhibitors. With the exception of methylxanthines and PDE-4 inhibitors, all others are inhalation products.

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 three approved GP-containing products for COPD. GP was approved as a dry powder for inhalation both as a single ingredient (Seebri Neohaler, NDA 207923) and in combination with indacaterol (Utibron Neohaler, NDA 207930), as well as in fixed-combination with formoterol fumarate as a inhalation aerosol (Bevespi Aerosphere, NDA 208924)

Prior to the approvals of the other glycopyrrolate-containing products, inhaled anticholinergics were widely available in the U.S., including 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) . All of these products have anticholinergic adverse effects, such as dry mouth, constipation, and urinary retention.

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

Relevant Regulatory History for GP

Sunovion met with the Agency for the usual milestone meetings. Specifically, key regulatory interactions included:

- Pre-IND Meeting: March 16, 2011
- Type C Meeting: June 20, 2012
- End-of-Phase 2 Meeting: October 17, 2013
- Type C Meeting: October 8, 2014
- Pre-NDA Meeting: May 11, 2016

[1] FDA Early Communication about Ongoing Safety Review of Tiotropium. http: //ww fda.gov/cder/drug/early_comm/tiotropium.htm
[2] Tashkin DP, Celli B, Senn S. et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Eng J Med 2008; 359: 1543-54.
[3] Wise RA, Anzueto A, Cotton D, et al. Tiotropium Respimat inhaler and the risk of death in COPD. N Eng J Med 2013; 369:1491-501.

The main topic for discussion at earlier meeting was dose selection. Specifically, at the End-of-Phase 2 Meeting, the Division recommended that further dose exploration was necessary. The Division also recommended the evaluation of MACE and stroke-related events as part of the safety analysis in phase 3.

3. CMC/Device

The recommended action from a CMC/Quality perspective is Approval.

This application consists of a drug product that is part of a drug/device combination. The drug product (GP, Lonhala) is proposed to be co-packaged with the device (PARI eFlow CS nebulizer, Magnair).

Drug Product and Drug Substance

Glycopyrrolate USP, the active component of Lonhala Inhalation Solution, is a synthetic quaternary ammonium compound that acts as a competitive antagonist at muscarinic acetylcholine receptors. Glycopyrrolate, C19H28BrNO3, is a white, odorless, crystalline powder that is soluble in water and in alcohol.

The drug product, Lonhala Inhalation Solution, is supplied in low-density polyethylene (LDPE) unit-dose vials, each containing 1.0 mL of the solution. Each vial contains 25 mcg of glycopyrrolate in sterile, isotonic saline, pH-adjusted to 4.0 with citric acid and sodium hydroxide. The active ingredient, glycopyrrolate (GP), is very soluble in the buffer. All the excipients are commonly used for inhalation/injection products and at levels within that of already approved products. The drug product is sterilized (b) (4) Extractables and leachables have been studied and have been found to be adequately low. The drug product manufacturer, (b) (4) is a contract manufacturer and the associated facility was found to be acceptable. Stability studies support the expiry of 24 months.

The information for the drug substance is mainly provided by reference to two drug master files (DMF (b) (4)), both of which has been reviewed and have been found to be acceptable. The drug substance is manufactured at two facilities by two separate firms and both were deemed acceptable based on their inspectional history and manufacturing capability.

Device

The recommended regulatory action from the CDRH perspective is Complete Response. The outstanding issues are related to device biocompatibility.

The drug product is intended to be delivered using a specific nebulizer device co-packaged and co-marketed with the inhalation solution drug product. The device is an eFlow® Closed System nebulizer, referred to as eFlow CS. The eFlow CS is a portable, hand-held, electronic nebulizer intended for single patient use that uses a vibrating perforated membrane to generate an inhalation aerosol. The eFlow CS device including the nebulizer handset (hand-held unit, with

installed aerosol head and drug vial), the connection cord, the controller, and the AC adapter, and 2 additional drug vials are shown below.

Figure 1. The eFlow Closed System Nebulizer

The eFlow CS is intended for single patient use to deliver GP Inhalation Solution drug product by patients who self-administer treatments at home, by caregivers, and in nursing homes and hospitals by healthcare professionals. The eFlow CS is a modified version of three PARI Respiratory Equipment (PRE) FDA-cleared electronic nebulizers: the TRIO®, the Altera®, and the eRapid®.

The eFlow CS technology uses a wafer-thin plate of stainless steel (the membrane), which is perforated with numerous laser-drilled holes. This micro-perforated membrane vibrates at high frequencies against a reservoir of liquid (i.e., drug product). The vibration source is the piezoelectric actuator that is activated by an electronic drive circuit. The actuator and the perforated membrane are the main components of the aerosol head that is in contact with the liquid medication to be aerosolized. Liquid jets are created as an inertial response to the vibration of the membrane. Surface tension and hydrodynamic effects then cause these jets to disperse to produce a stream of precisely controlled droplets.

The eFlow Closed System Nebulizer (eFlow CS) is manufactured by PARI Respiratory Equipment (PRE). Sunovion offers two commercial configurations that include a starter kit and a refill kit. The Office of Compliance at CDRH also finds the application to be approvable from a Quality Systems Requirements perspective.

The manufacturer of the eFlow CS has similar versions of the device which have been previously 510(k) cleared, as an open system nebulizer not intended to be used with a specific drug formulation. While the eFlow CS proposed under the current NDA submission has similar operating principles and components, it has undergone modifications to the controller, nebulizer handset, reservoir cap, and aerosol head. These changes can impact the performance, electrical safety, and biocompatibility of the device and required a new device review. To aid in the device review, additional sub-consults were sent to the following review areas within CDRH: human factors, electrical safety, device biocompatibility, cleaning/disinfection, and software.

- The human factors validation study identified one situation which may lead to potential high severity harm. This use error occurred when the drug vials were pierced prior to inserting the aerosol head and may cause medication to leak from the handset and patients to receive an incomplete dose of their prescribed medication. If this occurs, the patient may be unaware that they did not receive the full dose, and may continue to use the device incorrectly. The clinical team in CDER felt that this deficiency was addressed by the scope of the clinical program.
- A biocompatibility issue was identified and communicated to the Applicant in December 2016. The Applicant provided their response in January 2017; upon review, CDRH identified outstanding issues for biocompatibility and cleaning. The Applicant provided information through interactive review which adequately addressed the outstanding concerns for cleaning by removing their optional disinfection procedure. They also submitted new extractables and leachables (E&L) testing to address the outstanding biocompatibility concerns. However, the new E&L testing resulted in significant degradation of the test article for their non-polar solvent used. This degradation invalidates these test results. E&L testing with toxicological risk assessment was conducted in lieu of genotoxicity, implantation, and systemic toxicity tests per ISO 10993. Therefore, CDRH has determined that in order to support the device biocompatibility based on the results of their E&L testing, the Applicant will need to repeat the testing using an appropriate non-polar solvent which does not degrade the device material. It is this deficiency that is the basis of the Complete Response action.

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 Applicant is pursuing a 505(b)(2) NDA pathway, relying on nonclinical safety information from previous glycopyrrolate NDAs to support their application and labeling. The nonclinical information relies on previously demonstrated safety from approved products Robinul Injection (NDA 17-558), Robinul Tablets (NDA 12-827), and Cuvposa oral solution (NDA 22-571). The Applicant conducted additional inhalation toxicology studies to support the new inhalation route of administration. However, during development of SUN-101 Inhalation Solution, other inhalation glycopyrrolate products were approved, lessening the essential need for the Applicant's nonclinical inhalation studies. These products were formulated as a dry powder (Seebri Neohaler; NDA 207923), dry powder in combination with indacaterol (Utibron Neohaler; NDA 207930), and an aerosol in combination with formoterol fumarate (Bevespi Aerohaler NDA 208294). Furthermore, during the NDA review cycle, the Applicant notified the FDA on March 16, 2017 (SD-15) that they acquired ownership of Seebri Neohaler on January 27, 2017. Utibron Neohaler was also acquired, effective January 27, 2017. The Applicant now owns data that supported the approval of these two 505(b)(1) applications.

Due to the reliance on previously approved glycopyrrolate products for safety through the 505(b)(2) pathway, few nonclinical studies were submitted. The nonclinical program consisted of 1-month repeated-dosing inhalation studies in rats and dogs, followed by a 6-month repeated-dosing inhalation study in rats. The applicant acquired ownership of Seebri Neohaler on January 27, 2017 (during the application review period), and could rely solely on that data to support the safety of glycopyrrolate for the inhalation route of administration. The Applicant's nonclinical inhalation toxicity studies, conducted prior to approval of any inhalation product for glycopyrrolate, produced results that were generally similar to those approved products.

The toxicities in the rat associated with inhaled glycopyrrolate in 1- and 6-month studies included reduced body weight and food intake; dilated pupils; increased red blood cell counts, hemoglobin, and hematocrit; increased lung weight associated with alveolar macrophages; laryngeal inflammation; and increased porphyrin secretion of the Harderian gland. The following findings were observed in the 1- month inhalation study in dogs: dilated pupils, dry mouth, reduced body weight and food consumption, emesis, and thymus atrophy with a reduction in thymus weights. All these effects were partly or completely reversible during a recovery phase.

Two impurities of the drug substance, α-cyclopentylmandalic acid (CPMA) and benzoic acid, were also assessed for safety. Neither of these compounds were detected in the drug substance used in the 6-month inhalation study and these were not tested for their presence in the earlier drug substance used in the 1-month inhalation studies in rats and dogs. CPMA is also a major human metabolite of glycopyrrolate formed upon hydrolysis of glycopyrrolate. CPMA lacks the pharmacological profile of GP, but its potential pharmacology and toxicity is unknown. The safety of CPMA is confounded with the safety of glycopyrrolate due to CPMA's unavoidable presence as a metabolite in humans. Benzoic acid is a potential oxidative degradant that was formed in forced degradation studies. These two compounds lack mutagenic structural alerts and are negative in genotoxic tests. While the systemic safety of CPMA is established, the local safety from inhalation of CPMA has not been established and the specifications were reduced from those proposed by the Applicant to those requested by the CMC reviewer to NMT (b) (4) % for both compounds.

Pregnancy risk summary in the product labeling for GP-containing drugs states that "there are no adequate and well-controlled studies in pregnant women." This was formerly known 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.

The Applicant supports this NDA submission with 3 three key clinical pharmacology studies, including two dose-ranging studies (EP-101-104 and SUN101-201) and one PK study (SUN101-105) with the CS eFlow® nebulizer. These studies used the same nebulizer system as proposed in the to-be-marketed product. The Applicant conducted three additional exploratory dose-ranging studies (EP-101-01, EP-101-02 and EP-101-103) with an open-system (OS) eFlow®

nebulizer prior to proceeding with the two pivotal dose-ranging studies (i.e., EP-101-104 and SUN101-201). The dose-ranging studies will be discussed in more detail in the clinical efficacy section.

The following are the major findings from the current review:

1) Following administration of glycopyrrolate inhalation solution via CS eFlow® nebulizer, the median Tmax for glycopyrrolate occurs around approximately 20 minutes and the elimination half-life is approximately 5 hours.
2) The systemic exposure following single-dose administration of glycopyrrolate inhalation solution (50 mcg) in subjects with moderate to severe COPD was approximately 5- to 6-fold lower as compared to that attained following single-dose administration of Cuvposa® Oral solution in healthy adults under fasted conditions (cross-study comparison, Cuvposa® oral solution data is from its prescribing label).
3) Neither age, body weight, race, nor ethnicity had relevant effects on drug exposure.

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 microbiology reviewer reports that the Applicant provided an adequate description of the drug product composition and the container closure system and how product sterility would be maintained. Container-closure integrity testing is performed on 100% of manufactured vials during commercial production and any leaking vials are rejected. This is consistent with regulatory expectations for a sterile pharmaceutical product. The microbial attributes of the drug product and drug product manufacturing were assessed and found to be acceptable.

7. Clinical/Statistical-Efficacy

Overview of the clinical program

The studies relevant to regulatory decision-making for this application are listed in Table 1.

Table 1. Relevant clinical studies with glycopyrrolate inhalation solution in COPD patients

Study ID *Dates*	Design/ Duration	Treatment Arms†	N (ITT)	Efficacy Variables	Sites *% US Sites*
Dose-ranging studies – COPD patients					
EP-101-04 *Oct 2012-* *April 2013*	- R, DB, PG, PC - mod/svr COPD - FEV_1 30-70% - 42 to 75 yrs. old - 28 days	GP 12.5 mcg BID GP 25 mcg BID GP 50 mcg BID GP 100 mcg BID Placebo BID *Serial Spirometry Substudy* GP 12.5 mcg BID GP 25 mcg BID GP 50 mcg BID GP 100 mcg BID Placebo BID	55 54 57 59 57 26 24 25 26 24	FEV_1 Trough	US (*100%)*
SUN101-201 *Jan 2014-* *May 2014*	-R, DB, PC -XO, OL, AC - mod/svr COPD - FEV_1 40-70% - 40 to 65 yrs. Old - 7 days	GP 3 mcg BID GP 6.25 mcg BID GP 12.5 mcg BID GP 50 mcg BID Aclidinium 400 mcg BID‡ Placebo BID	91 92 89 92 92 92	FEV_1 Trough	US (*100%)*
Pivotal bronchodilator (lung function) efficacy and safety studies – COPD patients					
SUN101-301 *Feb 2015-* *Nov 2015*	- R, DB, PG, PC - mod/svr COPD - 42 to 87 yrs. old - FEV_1 20-79% - 12 weeks	GP 25 mcg BID GP 50 mcg BID Pbo BID *Serial Spirometry Substudy* GP 25 mcg BID GP 50 mcg BID Placebo BID	217 218 218 49 62 42	FEV_1 Trough	US (*100%)*
SUN101-302 *Feb 2015-* *Dec 2015*	- R, DB, PG, PC - mod/svr COPD - 40 to 84 yrs. old - FEV_1 20-79% - 12 weeks	GP 25 mcg BID GP 50 mcg BID Pbo BID	214 214 212	FEV_1 Trough	US (*100%)*
Supportive long-term safety studies – COPD patients					
SUN101-303 *Oct 2014-* *Feb 2016*	-R, OL, PG, AC - mod/svr COPD - 41-89 yrs. old - FEV_1 15-80% - 48 weeks	GP 50 mcg BID Tiotropium 18 mcg QD♦	620 466	Adverse Events/Safety	Czech Republic, Hungary, Russia, US *(90%)*

† All GP treatments administered via the eFlow CS nebulizer; ‡Aclidinium administered via Tudorza Pressair; ♦Tiotropium administered via Spiriva HandiHaler; R=randomized, DB=double-blind, PC=placebo-controlled, PG=parallel-group, OL=open label, AC=active control, CO=cross over, WO=wash out, BID=twice daily, GP = glycopyrrolate (Lonhala inhalation solution), Pbo= placebo; FEV1 trough was the average of the 23.5 and 24 hour measurements collected after the in-clinic morning dose of study medication

Dose Ranging Studies: EP-101-04 (Study 04) and SUN101-201 (Study 201)

The dose ranging studies were designed to characterize the dose-response for glycopyrrolate (GP). The study designs, treatment arms, and primary efficacy variable measured are shown in Table 1.

Study 04 assessed the efficacy of GP 12.5, 25, 50, and 100 mcg administered BID via the eFlow CS nebulizer, in a placebo-controlled, 28-day, parallel group study in patients with moderate-to-severe COPD. The primary efficacy endpoint was the change from baseline in morning trough FEV_1. The results of Study 04 are shown in Figure 1 and Table 2 below.

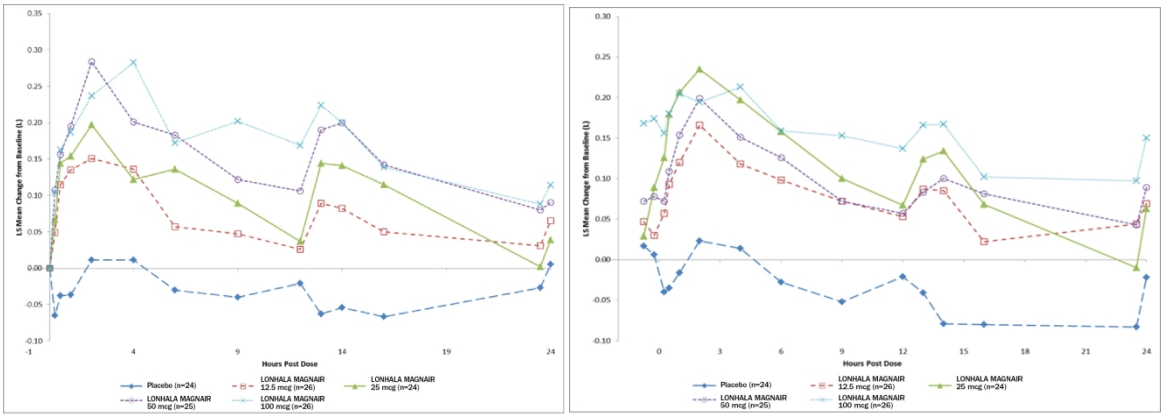

Figure 1. Mean change from baseline in trough FEV_1 on Day 1 (left) & Day 28 (right) -Study 04

Table 2. Mean change from baseline in trough FEV_1(L) – Dose-ranging Study 04 (ITT)

Treatment	N	LS Mean (SE)	Treatment Difference vs. Placebo	
			LS Mean (95% CI)	p-value
GP 12.5 mcg BID	55	0.106 (0.03)	0.117 (0.037, 0.197)	<0.01
GP 25 mcg QD	54	0.117 (0.03)	0.128 (0.048, 0.209)	< 0.01
GP 50 mcg BID	57	0.135 (0.03)	0.146 (0.067, 0.226)	< 0.01
GP 100 mcg BID	59	0.166 (0.03)	0.177 (0.099, 0.255)	< 0.01
Placebo	57	-0.011 (0.03)	--	--

Statistics are from a mixed model for repeated measures with fixed factors for treatment, visit, inhaled corticosteroid use, substudy participation, an interaction for visit by treatment; a covariate for baseline FEV1; and a random factor for subject.
Morning trough is the average of the 23.5 and 24 hour values.
N = ITT population
The results of this study are reported as Study A in Section 14 of the package insert.

The results of Study 04 demonstrated efficacy for all tested doses of GP, including the lowest dose of 12.5 mcg BID. Therefore, Study 201, a 7-day crossover study, was conducted to better characterize and explore the lower end of the dose-response. Study 201 explored the efficacy of GP 3 mcg, 6.25 mcg, 12.5 mcg, and 50 mcg, administered BID via the eFlow CS nebulizer. The study was double-blind for GP and placebo, and included an open-label aclidinium bromide treatment arm as an active control. Upon review of the results of Study 201, the Division concluded that the lower end of the dose-response relationship had been adequately explored; based on the results of the dose-ranging studies, the Division agreed with carrying both the 25 mcg and 50 mcg BID doses of glycopyrrolate into the phase 3 program.

Confirmatory Studies: Studies SUN101-301 (Study 301) and SUN101-302 (Study 302)

Studies 301 and 302 were 12-week, randomized, double-blind, placebo-controlled studies designed to evaluate the safety and efficacy of GP 25 mcg and GP 50 mcg administered twice daily via the eFlow CS nebulizer in patients with moderate to severe COPD.

Studies 301 and 302 enrolled adult male and female subjects ≥ 40 years of age with a clinical diagnosis of moderate-to-very severe COPD according to the GOLD 2014 guidelines. Subjects were current or ex-smokers with ≥ 10 pack-year smoking history, with a post-bronchodilator FEV1 of < 80% of predicted normal and greater than 0.7 L, an FEV1/FVC ratio less than 0.70, and had the ability to perform reproducible spirometry according to the ATS/ERS guidelines.

The primary endpoint in both studies was the change from baseline in trough FEV_1 at Week 12. 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. Trough FEV1 was defined as the mean of the two FEV1 values obtained at 23 hours 30 minutes and 24 hours after the in-clinic morning dose (i.e., approximately 12 hours after the previous evening dose).

Baseline demographics were fairly balanced across treatment groups and were generally representative of the population in whom COPD is known to occur. The median age for the two studies ranged from 63-64 years, with the majority being white (86-92%) males (51-59%), <65 years of age (50-62%). These studies were conducted fully in the United States. Of the study population, 7% to 13% were black patients.

Most patients completed the study (88-94%) on treatment (81-89%). The number of patients who discontinued from treatment and the study was also fairly balanced, with higher premature discontinuations in the placebo group. The most common reason for premature discontinuation from the study was withdrawal by subject.

Studies 301 and 302 were the primary studies that support the bronchodilator claim for Lonhala Magnair. Results from the primary efficacy analysis from these studies showed statistically significant differences between Lonhala Magnair and placebo for both GP 25 mcg and 50 mcg doses. FEV_1 time profile curves for Studies 301 and 302 also showed consistent efficacy over time. The curves for Study 301 are shown below in Figure 3; the curves for Study 302 showed similar results. There was no meaningful difference between the 25 mcg and 50 mcg doses, and therefore, the Applicant proposed the lower dose for registration.

Table 3. Primary Efficacy Results: LS Mean Difference in Change From Baseline in Trough FEV_1 (L) at Week 12 (ITT) – Studies 301 and 302

		Treatment Difference		
Study Treatment	**CFB in Trough FEV_1 LS Mean (SE)**	**LS Mean (SE) Vs. Placebo**	**95% CI**	**p-value**
Study 301				
GP 25 mcg BID N=217	0.089 (0.014)	0.096 (0.019)	(0.059, 0.133)	<0.0001
GP 50 mcg BID N=218	0.096 (0.014)	0.103 (0.019)	(0.066, 0.141)	<0.0001
Placebo N=218	-0.008 (0.014)	-	-	-
Study 302				
GP 25 mcg BID N=214	0.092 (0.014)	0.081 (0.020)	(0.042, 0.120)	<0.0001
GP 50 mcg BID N=214	0.085 (0.014)	0.074 (0.020)	(0.035, 0.113)	0.0002
Placebo N=212	0.011 (0.015)	-	-	-

BID = twice daily; CFB = change from baseline; CI = confidence interval; FEV1 = forced expiratory volume in 1 second; ITT = intent to treat; L = liter(s); LS = least squares;; SE = standard error, N= ITT population ; CFB = Change from Baseline. Source: Module 5.3.5.1, SUN101-301 CSR, Table 19, Page 100, Table 14.2.1.2, Page 216, SUN101-302 CSR, Table 14.2.1.2, Page 173

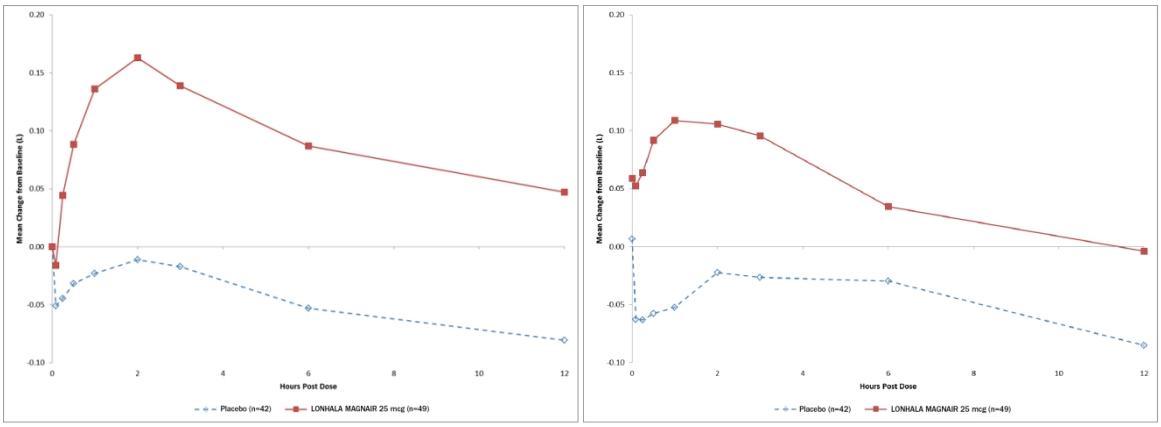

Figure 3. Mean change from baseline in FEV_1(L) over time on Day 1 (left) & Day 84 (right) - Study 301

Subgroup analyses 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 studies 301 and 302. In Study 301, the SGRQ responder rate for the LONHALA MAGNAIR 25 mcg treatment arm was 50% compared to 40% for placebo [Odds Ratio: 1.49; 95% CI: 0.97, 2.27]. In Study 302, the SGRQ responder rate for the LONHALA MAGNAIR 25 mcg treatment

arm was 44% compared to 30% for placebo [Odds Ratio: 1.91; 95% CI: 1.22, 2.98]. The responder rates and odds ratios for the 50 mcg treatment are shown in Table 4 as well.

Table 4. SGRQ Responder Analysis at Week 12- Studies 301 and 302

Study 301			
	Placebo BID N = 218	**GP 25 mcg BID N = 217**	**GP 50 mcg BID N= 217**
# of subjects with evaluable data	179	189	179
Responders, n (%)	71 (39.7)	94 (49.7)	79 (44.1)
Non-responders, n(%)	108 (60.3)	95 (50.3)	100 (55.9)
Odds Ratio (95% CI)		1.49 (0.94, 2.27)	1.22 (0.79, 1.87)
Study 302			
	Placebo BID N = 212	**GP 25 mcg BID N = 217**	**GP 50 mcg BID N = 217**
# of subjects with evaluable data	186	183	188
Responders, n(%)	55 (29.6)	80 (43.7)	74 (39.4)
Non-responders, n(%)	131 (70.4)	103 (56.3)	114 (60.6)
Odds Ratio (95% CI)		1.91 (1.22, 2.98)	1.54 (0.99, 2.40)

Source: Statistical Review Mingyu Xi, PhD.

Efficacy Conclusions

The Applicant provides support for the efficacy of GP 25 mcg BID for the maintenance treatment of COPD by demonstrating a statistically significant improvement in lung function in terms of change from baseline in trough FEV_1 compared to placebo in two replicate 12-week studies. The efficacy of GP 25 mcg BID was also supported by other measures of lung function 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 25 mcg BID (Lonhala Magnair; SUN101) for the maintenance treatment of airflow obstruction in patients with COPD.

8. Safety

The safety evaluation of GP relies primarily on 3-month data from Studies 301 and 302. Pooling of data across the two trials to examine the emergence of safety signals was deemed acceptable as these trials were similar in design/duration and the patient population was comparable in terms of demographics, baseline characteristics, and doses of GP received (25 and 50 mcg BID). Safety assessments included adverse events (AEs), physical examinations, vital signs, ECGs, and clinical laboratory testing. In addition, a long-term safety study (Study 303) was conducted, and did not reveal any additional safety signals.

The 3-month safety database included 1,293 COPD patients; 431 treated with GP 25 mcg BID, 432 patients treated with GP 50 mcg BID, and 430 patients treated with placebo.

Few patients discontinued treatment prematurely in the GP development program. Study drug withdrawal occurred more frequently in the placebo group compared to GP 25 mcg and 50 mcg groups, respectively [n=40 (9.3%), n=22 (5.1%), n=17 (3.9%)]. The most common AE leading to discontinuation were events occurring in the respiratory, mediastinal and thoracic system organ class (SOC). Overall, adverse events were not a significant cause for patient discontinuation. Death was a rare occurrence, with one event (diastolic dysfunction, COPD exacerbation, pulmonary hypertension) occurring in the high dose (50 mcg) dose group in the 3-month studies. The overall occurrence of SAEs was low and fairly balanced across GP 25 mcg and GP 50 mcg treatment groups, respectively [n=13 (3.0%), n=18 (4.2%)] with more events occurring in the placebo group [n=24 (5.6%)]. In general, the numbers of patients experiencing individual SAEs were small, and without meaningful imbalances.

Adverse events of special interest (AESI) were identified by the Applicant based upon known class effects for anti-muscarinic drugs which included pneumonia, anticholinergic syndrome, cardiovascular, cerebrovascular, gastrointestinal obstruction, glaucoma-related, and adjudicated major adverse cardiovascular events (MACE). As expected, anticholinergic events (e.g. dry mouth, dizziness, blurred vison) were reported more frequently in the GP treatment arms compared to the placebo arms and appeared to be dose-related. The most frequently reported anticholinergic AE was dry mouth [n=1 (0.2%) subject in the placebo group, n=4 [0.9%] subjects in the GP 25 mcg BID group, and 7 [1.6%] subjects in the GP 50 mcg BID group). Cardiovascular events of special interest occurred more frequently in the placebo group compared to the GP 25 mcg and 50 mcg treatment arms, respectively [n=11 (2.6%), n=7 (1.6%), n=9 (2.1%)]. MACE was reported in 5 subjects, which included 3 subjects (0.7%) who received GP 50 mcg, 2 subjects (0.5%) who received placebo, and 0 subjects who received GP 25 mcg. Cerebrovascular events were rare and fairly balanced across the treatment groups [GP 25mcg n=3 (0.7%), GP 50 mcg n=1 (0.2%), placebo n=2 (0.5%)]. Gastrointestinal obstruction AEs were reported for only 1 (0.2%) subject in the GP 25 mcg group (small intestinal obstruction), while no subjects in the placebo or GP 50 mcg BID groups reported an AE related to gastrointestinal obstruction. Glaucoma-related AEs were reported in 3 subjects with vision blurred in 2 (90.5%) subjects who received GP 25 mcg and eye pain in 1 (0.2%) subject who received 50 mcg. Overall, these differences were small and not clinically meaningful.

Adverse events were generally balanced between the GP and placebo groups. Common adverse events occurring in ≥ 2% of patients and at a higher incidence than placebo included dyspnea 4.9% vs. 3.0%) and urinary tract infection (2.1% vs. 1.4%). Adverse events occurring in 1-2% of patients and more commonly in GP 25 mcg vs. placebo included wheezing, upper respiratory tract infection, nasopharyngitis, and fatigue. The findings from the long-term safety study were consistent with the results seen for the primary 3 month safety database. No new safety signal was identified.

Safety Conclusions

In summary, the safety data for the Lonhala Magnair development program in COPD do not reveal any new safety concerns. Adverse events were few and generally those observed in patients with COPD and with similar approved anticholinergic products. The safety of GP 25 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

Sunovion 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. Two investigators reported significant payments ; however, given the international scope of this clinical development program, and the relatively low percentage of overall recruitment from these two investigators, any potential conflict of interest is not likely to impact study results.
- DSI audits information: 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. An evaluation of effect size by site did not reveal any sites which enrolled a disproportionally large number of patients and/or had a treatment effect that was much different than the overall treatment effect. This was a large clinical development program that enrolled relatively small numbers of patients at each clinical site. Therefore, it is unlikely that one clinical site would drive the treatment effect. In addition, glycopyrrolate is known clinical entity (as stated above). For all these reasons, an OSI inspection was not conducted for this application.
- Office of Compliance: The overall EES conclusion is acceptable.

12. Labeling

- Propietary Name: The name Lonhala Magnair was determined to be acceptable.
- Physician Labeling: The label was reviewed by various disciplines within DPARP and the patient labeling team (OPDP and DMPP). 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 were halted given the device biocompatibility issues precluding approval in this cycle.

- Carton and Immediate Container Label: These were reviewed by various disciplines of the Division and DMEPA, and found to be acceptable.

The package insert and instructions for use are substantially complete with all consultants having provided input on the label. Further labeling discussions will be postponed awaiting the resolution to the device biocompatibility deficiencies.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

The recommended regulatory action is Complete Response for Lonhala Magnair 25 mcg twice-daily for the long-term maintenance treatment of airflow obstruction, in patients with COPD. Deficiencies identified by CDRH in the biocompatibility evaluation of the Magnair device are the primary reason behind the Complete Response Action.

- **Risk Benefit Assessment**

From a clinical standpoint, the overall risk benefit assessment supports the approval of Lonhala Magnair (GP inhalation solution) 25 mcg BID for the long-term, maintenance treatment of airflow obstruction in patients with COPD. However, the Applicant has not adequately evaluated the biocompatibility of the Magnair device.

- **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**

The extractables and leachables testing provided during the review cycle revealed that there was significant degradation of the device with the non-polar solvent that was used; this degradation invalidates the tests results. The extractables and leachables testing was conducted in lieu of genotoxicity, implantation, and systemic toxicity tests per ISO 10993. Therefore, the device biocompatibility has not been adequately evaluated.

In order to resolve the deficiency, the Applicant will need to repeat the testing using an appropriate non-polar solvent which does not degrade the device material.

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/s/

BANU A KARIMI SHAH
05/22/2017

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	208437
Priority or Standard	Standard
Submit Date(s)	July 29, 2016
Received Date(s)	July 29, 2016
PDUFA Goal Date	May 29, 2017
Division / Office	DPARP/ODEII/OND/CDER/FDA
Reviewer Name(s)	Erika Torjusen, MD, MHS
Review Completion Date	April 27, 2017
Established Name	Glycopyrrolate Inhalation Solution
(Proposed) Trade Name	Lonhala Magnair
Therapeutic Class	Anticholinergic
Applicant	Sunovion Pharmaceuticals, Inc.
Formulation(s)	Inhalation Solution
Dosing Regimen	25 mcg BID
Indication(s)	long-term, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema
Intended Population(s)	Adults with COPD

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Based on my review of the risk-benefit assessment, my recommendation, from a clinical perspective, supports approval of glycopyrrolate (GP) 25 mcg inhaled twice daily for the treatment of chronic obstructive pulmonary disease (COPD). However, due to significant and outstanding deficiencies identified by the Center for Devices and Radiological Health (CDRH) that pertain to the device component that cannot be resolved by the action date (5/26/17), the Division plans to take a **Complete Response** action on this pending NDA.

1.2 Risk Benefit Assessment

The proposed indication for GP is for the long-term, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema.

Glycopyrrolate has been on the market in other formulations for indications different from COPD for over 40 years, with a well-known safety profile.

To support the proposed indication, the Applicant submitted data from two dose ranging studies (EP-101-04 and SUN101-201) and two replicate 12-week confirmatory trials (SUN101-301 and SUN101-302). Study EP-101-04 was a 28-day randomized, double blind, placebo-controlled, parallel group, dose-ranging study of glycopyrrolate (GP) in patients with moderate to severe chronic obstructive pulmonary disease (COPD). Study SUN101-201 was a second dose-ranging study to further evaluate the lower end of the dose response curve. SUN101-201 was a randomized, double-blind, placebo-controlled, open-label, active control, 6-way cross-over study of GP in patients with moderate to severe COPD. Studies SUN101-301 and SUN101-302 were replicate, phase 3, 12-week, randomized, double-blind, placebo-controlled, parallel group, multicenter studies to assess the efficacy and safety of GP 25 mcg and 50 mcg BID versus placebo in patients with moderate to severe COPD. Studies (SUN101-301 and SUN101-302) enrolled a total of 1,293 COPD patients (n=431 GP 25 mcg BID, n=432 GP 50 mcg BID, and n=430 placebo).

The primary endpoint in the replicate phase 3 studies (SUN101-301 and SUN101-302) was the change from baseline (CFB) in trough FEV1 at Week 12. The LS mean treatment difference for change from baseline in trough FEV1 was statistically significant for GP 25 mcg and GP 50 mcg versus placebo at 12 weeks (GP 25 mcg: 0.0961 L, 95% CI [0.0589, 0.1334], $p<0.0001$, GP 50 mcg: 0.1036 L, 95% CI [0.0663, 0.1409], $p<0.0001$ and GP 25 mcg: 0.0810 L, 95% CI [0.0416, 0.1204], $p<0.0001$, GP 50 mcg: 0.0736 L, 95% CI [0.0346, 0.1127], $p=0.0002$), respectively for both studies (SUN101-301 and SUN101-302).

The secondary endpoint SGRQ, when analyzed via a responder analysis, where a response was defined an improvement in score of 4 or more, demonstrated that all the results are in the direction to favor the GP treated groups in both studies and both dose levels. However, the logistic regression model analyses only demonstrated a statistically significant effect vs. placebo for the 25 mcg group in study SUN101-302 (SUN101-301 GP 25 mcg: 49.7% (OR: 1.486 [0.974, 2.267]), GP50: 44.1% (OR: 1.215 [0.791, 1.866]), Placebo: 39.7%. SUN101-302 GP 25 mcg: 43.7% (OR: 1.906 [1.220, 2.976]), GP 50 mcg: 39.4% (OR: 1.538 [0.985, 2.401]), Placebo 29.6%.)

The assessment of safety is based on 3-month data from 2 studies (SUN101-301 and in SUN101-302). Pooling of data across trials to examine the emergence of safety signals was deemed acceptable as these trials were similar in design/duration and the patient population was comparable in terms of demographics, baseline characteristics, and doses of GP received (25 mcg and 50 mcg). Safety assessments in these 2 studies included adverse events (AEs), physical examinations, vital signs, ECGs, and clinical laboratory testing. In addition, a long-term safety study, SUN101-303, was conducted in patients receiving GP 50 mcg BID or tiotropium 18mcg QD and did not reveal any additional safety signals.

The 3-month safety database included 1,293 COPD patients; 863 treated with GP 25 mcg and 50 mcg BID and 430 patients treated with placebo. Most patients completed the study (88-94%) on treatment (81-89%). The number of patients who discontinued from treatment and the study was also fairly balanced, with higher premature discontinuations in the placebo group. Death was a rare occurrence, with one event (diastolic dysfunction, COPD exacerbation, pulmonary hypertension) occurring in the high dose (50 mcg) dose group in the 3-month studies.

The overall occurrence of SAEs was fairly balanced across GP 25 mcg and GP 50 mcg treatment groups, respectively [n=13 (3.0%), n=18 (4.2%)] with more events occurring in the placebo group [n=24 (5.6%)]. In general, the numbers of patients experiencing individual SAEs were small, without striking imbalances noted. Cardiac disorders were more common in the placebo arm compared to both GP 25 mcg and 50 mcg, respectively [n=5 (1.2%), n=2 (0.5%), n= 2 (0.5%)]. Similar findings were noted for the frequency of infections and infestations [n=5 (1.2%), n=1 (0.2%), n=3 (0.7%)]. No new safety signal was noted as a result of the SAE analysis by system organ class (SOC) or preferred terms. Overall, SAEs occurred infrequently in the clinical development program, with slight, but clinically insignificant numerical imbalances.

AEs leading to discontinuation were more frequent in the placebo patients [n=40 (9.3%)] compared to [n=22 (5.1%), n=17 (3.9%)] in the GP 25 and 50 mcg treated patients, respectively. The most common AE leading to discontinuation were events occurring in the respiratory, mediastinal, and thoracic SOC. Overall, adverse events were not a significant cause for patient discontinuation.

Adverse events of special interest (AESI) included pneumonia, anticholinergic syndrome, cardiovascular, cerebrovascular, gastrointestinal obstruction, glaucoma special interest events, and adjudicated major adverse cardiovascular events (MACE). Pneumonia-related events

occurred slightly more frequently in the GP 50 mcg compared to the placebo arms, respectively [n=31 (7.2%), n=18 (4.2%)]. As expected, anticholinergic events (e.g. dry mouth, dizziness, blurred vison) were reported more frequently in the GP treatment arms compared to the placebo arms and appeared to be dose-related. The most frequently reported anticholinergic AE was dry mouth [n=1 (0.2%) subject in the placebo group, n=4 [0.9%] subjects in the SUN-101 25 mcg BID group, and 7 [1.6%] subjects in the SUN-101 50 mcg BID group). Cardiovascular events of special interest occurred more frequently in the placebo group compared to the GP 25 mcg and 50 mcg treatment arms, respectively [n=11 (2.6%), n=7 (1.6%), n=9 (2.1%)]. MACE was reported in 5 subjects, which included 3 subjects (0.7%) who received GP 50 mcg, 2 subjects (0.5%) who received placebo, and 0 subjects who received GP 25 mcg. Cerebrovascular events were rare and fairly balanced across the treatment groups [GP 25 mcg: n=3 (0.7%); GP 50 mcg: n=1 (0.2%); placebo: n=2 (0.5%)]. Gastrointestinal obstruction AEs were reported for only 1 (0.2%) subject in the GP 25 mcg group (small intestinal obstruction), while no subjects in the placebo or GP 50 mcg BID groups reported an AE related to gastrointestinal obstruction. Glaucoma-related AEs were reported in 3 subjects with vision blurred in 2 (90.5%) subjects who received GP 25 mcg and eye pain in 1 (0.2%) subject who received 50 mcg. Overall, these differences were small and not clinically meaningful.

Adverse events were generally balanced between the GP and placebo groups. The most frequent AE was in the respiratory, thoracic, and mediastinal disorders SOC with the most frequently reported preferred terms being cough and COPD, both of which had the lowest incidence in the GP 25 mcg group. No new safety signal was identified.

From a clinical perspective, based on the efficacy and safety findings, the risk-benefit assessment supports the approval of glycopyrrolate for COPD. However, due to significant and outstanding deficiencies identified by the Center for Devices and Radiological Health (CDRH) that pertain to the device component that cannot be resolved by the action date (5/26/17), the Division plans to take a **Complete Response** action on this pending NDA.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No postmarket risk evaluation and mitigation strategies are recommended at the time of this review.

1.4 Recommendations for Postmarket Requirements and Commitments

No postmarket requirements or commitments are recommended at the time of this review.

2 Introduction and Regulatory Background

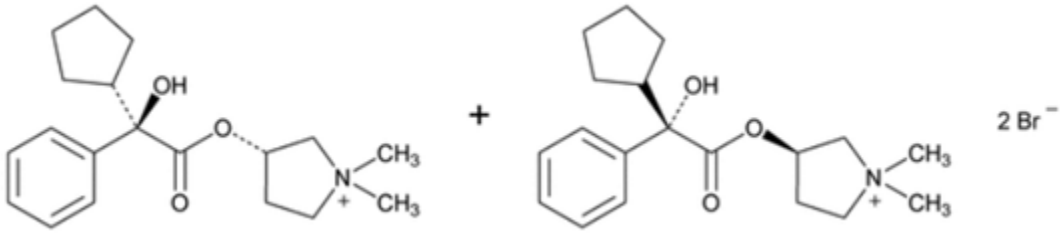
2.1 Product Information

Glycopyrrolate (GP) Inhalation Solution is a sterile, non-preserved solution for oral inhalation, supplied in low-density polyethylene (LDPE) unit dose vials, each containing 1.0 mL of the solution. The drug solution is formulated in a (b) (4) buffer with pH adjusted to 4.0. Sodium chloride is used (b) (4) .

One mL of solution is filled into LDPE vials (b) (4) . Two unit dose vials are overwrapped with (b) (4) foil as a sealed pouch. The strengths are expressed as the amount of glycopyrrolate, USP (glycopyrronium bromide) in the one mL vial: 25 mcg/mL and 50 mcg/mL. Only the 25 mcg/mL strength, however, is being sought for approval and commercialization.

Glycopyrrolate, USP is a quaternary ammonium salt with the appearance of a white, odorless crystalline powder. It is a chiral compound with a tapped density approximately 0.5-0.7 g/mL, and exhibits a melting point in the range between 193-198°C. Glycopyrrolate, USP is soluble in water and alcohol and practically insoluble in chloroform or ether. The structural formula is:

Figure 1. Drug Structure



Source: GP Proposed Product Label

The eFlow Closed System Nebulizer (eFlow CS) is manufactured by PARI Respiratory Equipment (PRE) and is specifically designed to deliver GP Inhalation Solution drug product. The eFlow CS is a portable, hand-held, electronic nebulizer intended for single patient use that uses a vibrating perforated membrane to generate an inhalable aerosol. The eFlow CS device configuration with the nebulizer handset (hand-held unit, with installed drug vial), the connection cord, the controller, the AC adapter, and 2 additional drug vials is shown Figure 2. eFlow CS Commercial Device.

Figure 2. eFlow CS Commercial Device

Source: Module 3.2.R.1.2, Device Description, Figure 1, Page 4

The eFlow CS is intended for single patient use to deliver GP Inhalation Solution drug product by patients who self-administer treatments at home, by caregivers, and in nursing homes and hospitals by Healthcare Professionals (HCPs). The eFlow CS is a modified version of three PARI Respiratory Equipment (PRE) FDA-cleared electronic nebulizers: the TRIO®, the Altera®, and the eRapid®.

The eFlow CS, as well as the Trio, eRapid and Altera nebulizer systems are identical in overall purpose, function, aerosol technology, and method of operation. They are single-patient use, reusable electronic nebulizers that can be used for inhalation therapy for the home, nursing home, or hospital environments. All devices are hand-held and portable. Their main components are a nebulizer handset, a controller, and a connection cord. The devices are powered by either AA batteries or an AC adapter.

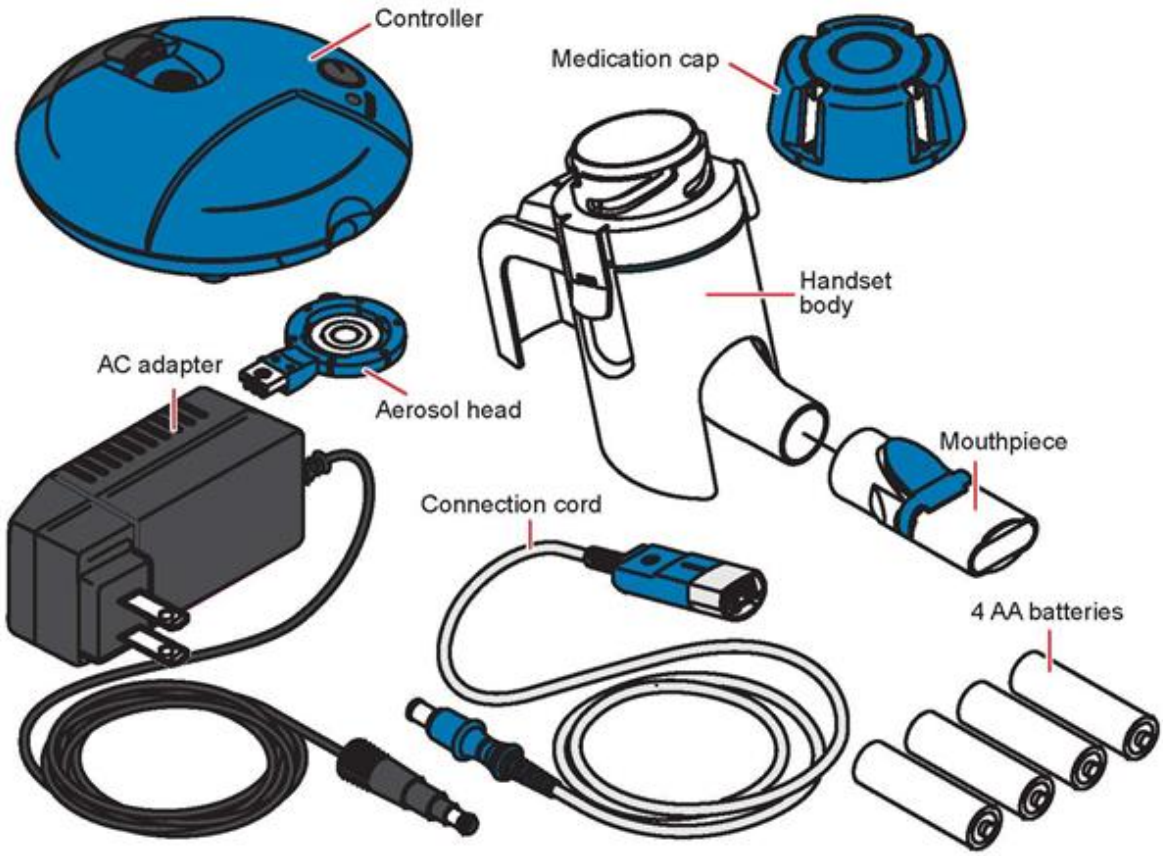
The eFlow CS uses a proprietary, prefilled unit-dose vial of SUN-101 (glycopyrrolate) Inhalation Solution drug product. This unit-dose vial is required to operate the nebulizer and it replaces the medication reservoir on the other eFlow Electronic Nebulizers.

The eFlow CS technology uses a wafer-thin plate of stainless steel (the membrane), which is perforated with numerous laser-drilled holes. This micro-perforated membrane vibrates at high frequencies against a reservoir of liquid (i.e., drug product). The vibration source is the piezo-electric actuator that is activated by an electronic drive circuit. The actuator and the perforated membrane are the main components of the aerosol head that is in contact with the liquid medication to be aerosolized. Liquid jets are created as an inertial response to the vibration of the membrane. Surface tension and hydrodynamic effects then cause these jets to disperse to produce a stream of precisely controlled droplets.

The eFlow CS nebulizer system will be supplied in 2 forms:

- Starter Kit: See figure below
- Refill Kit: Contains replacement handset parts only: Medication cap, Handset body, Mouthpiece, Aerosol head. IMPORTANT: Please discard the old handset and use this replacement with your next 60 vials.

Figure 3. Device Components



Source: GP Proposed Product Label

The delivered dose is reproducible across different GP batches of the same strength. The mean delivered dose increased proportionally with product strength.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1. Treatments available for COPD

Class		Generic Name	Brand Name
$Beta_2$-adrenergic agonists	Short-acting (SABA)*	Albuterol sulfate	Accuneb ProAir HFA Proventil HFA Ventolin HFA
		Levalbuterol tartrate	Xopenex HFA
		Terbutaline sulfate	Multiple
	Long-acting (LABA)	Salmeterol xinafoate	Serevent Diskus
		Formoterol fumarate	Foradil Aerolizer
		Arformoterol tartrate	Brovana
		Formoterol Solution	Perforomist
		Indacaterol maleate	Arcapta Neohaler
		Olodaterol hydrochloride	Striverdi Respimat
Anticholinergics		Ipratropium bromide	Atrovent HFA
		Tiotropium bromide	Spiriva Handihaler Spiriva Respimat
		Aclidinium bromide	Tudorza Pressair
		Umeclidinium bromide	Incruse Ellipta
		Glycopyrrolate	Seebri Neohaler
Combination	SABA/anticholinergic	Albuterol/Ipratropium	DuoNeb Combivent Combivent Respimat
	Corticosteroid/LABA	Fluticasone/Salmeterol	Advair Diskus
		Budesonide/Formoterol	Symbicort
		Fluticasone/Vilanterol	Breo Ellipta
	Anticholinergic/LABA	Umeclidinium/Vilanterol	Anoro Ellipta
		Tiotropium/Olodaterol	Stiolto Respimat
		Glycopyrrolate/Indacaterol	Utibron Neohaler
		Glycopyrrolate/Formoterol	Bevespi Aerosphere
Xanthines		Theophylline	Multiple
Phosphodiesterase inhibitors	PDE4 Inhibitors	Roflumilast	Daliresp
*General bronchodilator claim, not specifically indicated for COPD			

2.3 Availability of Proposed Active Ingredient in the United States

Glycopyrrolate is available in tablet form as Robinul (1mg) and Robinul Forte (2mg) injection solution, and dry powder for inhalation (Seebri Neohlaer, 15.6 mcg of glycopyrrolate). Glycopyrrolate is also available in two combination products: a dry powder for inhalation (Utibron Neohaler, 27.5 mcg/15.6 mcg of indacaterol/glycopyrrolate) and an inhalation aerosol via MDI (Bevespi Aerosphere, glycopyrrolate/formoterol fumarate 9 mcg/4.8 mcg).

2.4 Important Safety Issues With Consideration to Related Drugs

Class effects of anticholinergics include worsening of narrow angle glaucoma and worsening of urinary retention.

The Agency has also historically been concerned with the cardiovascular safety of these agents. The concerns have been discussed extensively both in the medical literature and in open public forums (November 2009 FDA Allergy Drugs Advisory Committee Meeting). As a result of these concerns, the Agency released Early Communications on March 18, 2008 and October 7, 2008 about the ongoing safety review of Spiriva HandiHaler (SHH) that described these observations. Following the Early Communication, Boehringer Ingelheim submitted data from a 6,000 patient, 4-year study with the SHH [Understanding Potential Long-term Impacts on Function with Tiotropium trial (UPLIFT[1], trial 205.235)] which was analyzed by the Agency and discussed at a Pulmonary Allergy Drug Advisory Committee (PADAC) in November of 2009. As a result, in January 2010 the Agency provided a Follow-Up to the previous Early Communications regarding the safety of tiotropium marketed as the SHH. In this update, the Agency communicated its conclusion that the available data, including results from UPLIFT do not support an association between the use of SHH (tiotropium) and an increased risk for stroke, heart attack, or death from a cardiovascular cause. Additional evaluation of tiotropium was conducted by Boehringer Ingelheim in the TIOSPIR[2] (Tiotropium Safety and Performance in Respimat) trial after clinical trials data showed that tiotropium 5 mcg delivered via the Respimat inhaler showed more deaths reported compared to placebo. The trial involved over 17,000 COPD patients with a mean follow up period of 2.3 years and concluded that Spiriva Respimat 5 mcg or 2.5 mcg had a safety profile and exacerbation efficacy similar to that of Spiriva HandiHaler 18 mcg in patients with COPD.

Cardiovascular concerns have also been identified during the development of other anticholinergics, such as glycopyrrolate (Seebri Neohaler, 15.6 mcg of glycopyrrolate). Evaluation of a higher 50 mcg dose revealed the presence of atrial fibrillation/flutter and resulted in both the selection and ultimate approval of the lower 15.6 mcg dose.

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

Key Regulatory Interactions with the Agency

March 16, 2011- Pre-IND Meeting

- The Division informed the Applicant that the NDA would rely upon absorption, distribution, metabolism, and elimination (ADME) data available in the public domain from previously approved products. These data included the following listed drugs for which the Division has made a finding of safety and effectiveness: Robinul® Injectable (NDA 17-558), Robinul® Oral (NDA 12-827), Cuvposa® oral solution (NDA 22-571) as well as associated published literature. (Subsequently, the Division also approved

glycopyrrolate as an inhalation powder (Seebri™ Neohaler®) for the treatment of patients with COPD and Sunovion has appropriately incorporated available information throughout the NDA to provide a current presentation of available safety information.) Since the product had a new administration route from the proposed reference products, characterizing the pharmacokinetics of the drug-device combination product following inhalation administration was required.

June 20 2012-Type C Meeting

- Following review of data from early phase 2 single and once daily dose studies (EP-101-01, EP-101-02, and EP-101-03), the Division concluded that the data only supported twice-daily dosing and provided guidance on doses and study design for the phase 2 study, EP-101-04.

October 17, 2013- End of Phase 2 Meeting

- The Division concluded that the data from EP-101-04 was not sufficient to adequately characterize the dose response for the phase 3 studies and recommended another study (SUN101-201) to characterize the lower end of the dosing curve, including identification of a dose which could be viewed as likely ineffective.
- The Division recommended that the proposed phase 3 patient population should be more representative of a "real world" population including patients at least 40 years of age with concomitant LABA or LABA/ICS therapies, with moderate to very severe COPD, and/or stable cardiovascular conditions. Evaluation of MACE and stroke-related events by an independent adjudication committee should be conducted
- The Division agreed that the completed clinical pharmacology studies were adequate and no additional clinical pharmacology studies were required for the proposed market application.
- The Division agreed that the systemic levels of the glycopyrrolate inhalation solution were lower than that of the approved reference listed drugs (Rubinol and Cuvposa), and assessment of QTc intervals in routinely collected ECG recordings from SUN-101 studies did not show any increase in QTc intervals. Therefore, the Division agreed a formal QTc study would not be required.

October 8, 2014 - Type C Meeting

- Following review of the data from SUN101-201, the Division agreed with Sunovion's proposal to investigate two doses (25 mcg and 50 mcg) in the phase 3 pivotal studies, and the higher dose in the long term safety study.
- Regarding the proposed phase 3 study design, the Division advised that allowing antimuscarinic use was appropriate, with capping at 30% of enrollment. The Division agreed that the proposed number of subjects for the serial spirometry group in SUN101-301 were acceptable (50 subjects/treatment).

May 11, 2016 - Pre-NDA Meeting

- The Division agreed that the phase 3 studies, pending review of the data, would provide substantial evidence of safety and efficacy in support of an NDA submission. In addition, the Division recommended that SGRQ be evaluated as a responder analysis and included in the NDA and package insert.

2.6 Other Relevant Background Information

Clinical studies of the SUN-101 (GP) Inhalation Solution administered via the investigational PARI eFlow closed system (CS) nebulizer for the treatment of COPD have been performed under IND 110,663, which was originally submitted by Elevation Pharmaceuticals, Inc. (Elevation) on April 13, 2011. Clinical development was initiated by Elevation. On Sept 5, 2012, Elevation was acquired by merger with Sunovion Pharmaceuticals, Inc. and Elevation's name has been changed to Sunovion Respiratory Development, Inc., a direct wholly-owned subsidiary of Sunovion Pharmaceuticals, Inc. This NDA is being submitted by Sunovion Respiratory Development, Inc. (Sunovion).

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was appropriately indexed and complete to permit review. An evaluation of effect size by site did not reveal any sites which enrolled a disproportionally large number of patients and/or had a treatment effect that was much different than the overall treatment effect. This was a large clinical development program that enrolled relatively small numbers of patients at each clinical site. Therefore, it is unlikely that one clinical site would drive the treatment effect. In addition, glycopyrrolate is known clinical entity (as stated above). For all these reasons, an OSI inspection was not conducted for this application.

3.2 Compliance with Good Clinical Practices

The Applicant certified that all clinical investigations in this NDA were performed in compliance with the principles of the Declaration of Helsinki, and studies in the US conducted under IND 48655 were conducted in compliance with 21 CFR Subchapter D, part 312, part 50, and part 56. All study site personnel received training on all aspects of the conduct of the studies and in good clinical practices (GCP).

3.3 Financial Disclosures

The Applicant's compliance with the Final Rule on Financial Disclosure by Clinical Investigators is attested to in Module 1.3.4 of this NDA application. Details of the financial disclosure are outlined below:

Covered Clinical Studies (Name and/or Number): EP-101-01 (formerly known as RD 311/24784), EP-101-02, EP-101-03 and EP-101-04, SUN101-105, SUN101-201, SUN101-301, SUN101-302 and SUN101-303

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified:		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

Based on the signed financial disclosure forms collected for all principal investigators and sub-investigators who participated in clinical trials that support efficacy and/or safety claims for glycopyrrolate inhalation solution (SUN-101/EP-101), as referenced in this NDA, Sunovion certifies that to the best of the company's knowledge, no investigators or sub-investigators received compensation for Categories 1 and 2, or compensation beyond the acceptable limits for Category 3 ($50,000) and 4 ($25,000) with the following exceptions noted:

(b) (6) M.D., Principal Investigator at (b) (6)

- Study (b) (6), Category 4: Significant payments >$25,000.00. Dr. (b) (6) research site randomized (b) (6) of (b) (6) subjects into Study (b) (6)
- Study (b) (6), Category 4: Significant payments >$25,000.00. Dr. (b) (6) research site randomized (b) (6) of (b) (6) subjects into Study (b) (6)

(b) (6) MD, Principal Investigator a (b) (6)

- Study (b) (6), Category 4: Significant payments >$25,000.00. Dr. (b) (6) s research site randomized (b) of (b) (6) subjects into Study (b) (6)

To ensure full compliance with EP-101-01 (formerly known as RD 311/24784), EP-101-02, EP-101-03 and EP-101-04, SUN101-105, SUN101-201, SUN101-301, SUN101-302 and SUN101-303 study protocols and minimize bias of the clinical study results, the following steps were taken with all sites, including Dr. (b) (6) and Dr. (b) (6), and their respective study staffs:

- The investigators and the study coordinators attended an investigators' meeting and/or a site initiation meeting where protocol specifications and regulatory responsibilities were reviewed in detail.
- The study sites were monitored by trained and qualified Clinical Research personnel. Sites were monitored as outlined in the study specific monitoring plan and a 100% review of the source documentation to the case report form data was conducted.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Glycopyrrolate USP, the active component of Lonhala Inhalation Solution, is chemically described as (3RS)-3-[(2SR)-(2-cyclopentyl-2-hydroxy-2-penylacetyl)oxy]-1,1-dimethlypyrrolidinium bromide. Glycopyrrolate is a synthetic quarternary ammonium compound that acts as a competitive antagonist at muscarinic acetylcholine receptors, also referred to as an anticholinergic. Glycopyrrolate, C19H28BrNO3, is a white, odorless, crystalline powder that is soluble in water and in alcohol. It has a molecular mass of 398.33.

The inactive ingredients in GP are: citric acid monohydrate, sodium chloride, sodium hydroxide and water for injection. GP Inhalation Solution is supplied in low-density polyethylene (LDPE) unit dose vials, each containing 1.0 mL of the solution. Each unit-dose vial contains 25 mcg of glycopyrrolate in a sterile, isotonic saline solution, pH-adjusted to 4.0 with citric acid and sodium hydroxide. GP requires no dilution before administration by nebulization.

The amount delivered to the lungs will depend upon patient factors. Under standardized in-vitro testing per USP<1601> adult breathing pattern (500 mL tidal volume, 15 breaths per minute, and inhalation: exhalation ratio of 1:1), eFlow CS delivered 14.2 mcg glycopyrrolate (56.8% nominal) from the mouthpiece for the 25 mcg/mL dose strength (equivalent to 20 mcg of glycopyrronium). The mean nebulization time was approximately 2-3 minutes. GP vials should only be administered with eFlow CS. Patients should be instructed on the correct use of this drug product and device.

The Chemistry, Manufacturing, and Controls review was pending at the time of this review.

4.2 Clinical Microbiology

The clinical microbiology review was pending at the time of this review.

4.3 Preclinical Pharmacology/Toxicology

The pharmacology/toxicology review was pending at the time of this review.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

GP is a long-acting muscarinic antagonist, which is often referred to as an anticholinergic. It has similar affinity to the subtypes of muscarinic receptors M1 to M5. In the airways, it exhibits pharmacological effects through inhibition of M3 receptor at the smooth muscle leading to bronchodilation.

4.4.2 Pharmacodynamics

The effect of glycopyrrolate on the QTc interval was evaluated in a multicenter, randomized, double-blind trial that enrolled 73 healthy volunteers. At plasma concentrations >20 times those observed following administration of GP 50 mcg BID (mean Cmax of 1495 pg/mL versus 69 pg/mL) GP did not prolong QTc to any clinically relevant extent.

In the dose ranging and confirmatory clinical studies, the administration of GP did not demonstrate any clinically relevant changes in cardiac function including: vital signs (heart rate, blood pressure), electrocardiograms (including QTc) and Holter monitoring. In addition, no major adverse cardiovascular events (MACE) were reported following the administration of GP 25 mcg in any clinical study.

The clinical pharmacology review was pending at the time of this review.

4.4.3 Pharmacokinetics

Based on a population analysis of the observed concentration-time data, the pharmacokinetics of GP were linear at doses up to at least 400 mcg.

Absorption
Following oral inhalation using eFlow CS, GP was rapidly absorbed and reached peak plasma levels <20 minutes post dose. In an absorption study, the absolute systemic bioavailability of glycopyrrolate is approximately 15% with use of GP.

In patients with COPD, pharmacokinetic steady-state plasma levels of GP were reached within one week of the start of treatment. A twice daily dose regimen leads to approximately 2-3 fold accumulation of systemic glycopyrrolate exposure at steady-state.

Distribution
After intravenous dosing, the steady-state volume of distribution of GP was 51 L and the volume of distribution in the terminal phase was 156 L. The in vitro human plasma protein binding of GP was 38% to 41% at concentrations of 1 to 10 ng/mL.

Metabolism
In vitro metabolism studies showed consistent metabolic pathways for GP between animals and humans. Hydroxylation resulting in a variety of mono-and bis-hydroxylated metabolites and direct hydrolysis resulting in the formation of a carboxylic acid derivative (M9) were seen. In vivo, M9 is formed from the swallowed dose fraction of inhaled GP. Glucuronide and/or sulfate conjugates of glycopyrrolate were found in urine of humans after repeated inhalation, accounting for about 3% of the dose.

Multiple CYP isoenzymes contribute to the oxidative biotransformation of GP. Inhibition or induction of the metabolism of GP is unlikely to result in a relevant change of systemic exposure to the active substance.

Elimination
After intravenous administration of [3H]-labelled glycopyrrolate to humans, the mean urinary excretion of radioactivity in 48 hours amounted to 85% of the dose. A further 5% of the dose was found in the bile. Renal elimination of parent drug accounts for about 60 to 70% of total clearance of systemically available GP here as non-renal clearance processes account for about 30 to 40%. Biliary clearance contributes to the non-renal clearance, but the majority of non-renal clearance is thought to be due to metabolism. Mean renal clearance of glycopyrrolate following inhalation was in the range of 17.4 and 24.4 L/h. Active tubular secretion contributes to the renal elimination of GP. Up to 23% of the delivered dose was found in urine as parent drug.
GP plasma concentrations declined in a multi-phasic manner. The mean terminal elimination half-life was much longer after inhalation (33 to 53 hours) than after intravenous (6.2 hours) administration. The elimination pattern suggests sustained lung absorption and/or transfer of GP into the systemic circulation at and beyond 24 hours after inhalation.

Drug Interactions
In vitro inhibition studies demonstrated that GP has no relevant capacity to inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4/5, the efflux transporters MDR1, MRP2 or MXR, and the uptake transporters OATP1B1, OATP1B3, OAT1, OAT3, OCT1 or OCT2. In vitro enzyme induction studies did not indicate a clinically relevant induction by GP for cytochrome P450 isoenzymes, or for UGT1A1 and the transporters MDR1 and MRP2. These results taken together with the observed plasma concentrations of GP at the recommended dose indicate the potential for GP to be a perpetrator or victim of drug-drug interactions with CYP450 or transporter substrates/inhibitors is remote.

The concurrent use of GP with other anticholinergics or medications with anticholinergic activity, such as phenothiazines, anti-Parkinson's drugs, or tricyclic antidepressants, may intensify the antimuscarinic effects and may result in an increase in anticholinergic side effects

Specific Populations
A population pharmacokinetic analysis of data in COPD patients indicated no clinically relevant effect of age (41 to 80 years) or body weight (40.1 to 154.8 kg) on systemic exposure to glycopyrrolate. In addition, there was no evidence of clinically significant ethnic/race effect

Renal Impairment
Renal impairment has an impact on the systemic exposure to GP. A moderate mean increase in total systemic exposure (AUClast) of up to 1.4-fold was seen in subjects with mild and moderate renal impairment [estimated GFR greater than or equal to 30 mL/min/1.73m2] and up to 2.2-fold in subjects with severe renal impairment and end stage renal disease [estimated GFR less than 30 mL/min/1.73m2].

Hepatic Impairment
The effects of hepatic impairment on the pharmacokinetics of GP have not been studied. GP is cleared predominantly from systemic circulation by renal excretion.

The clinical pharmacology review was pending at the time of this review.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 2. Sources of Clinical Data

Study ID *Dates*	Design	Study Duration	Treatment Arms	N	Population	Endpoint	Sites *% US Sites*
Dose-Ranging Studies							
EP-101-04 *Oct 2012-April 2013*	R, DB, PG, PC Dose finding	28 days	GP 12.5 mcg BID GP 25 mcg BID GP 50 mcg BID GP 100 mcg BID Pbo BID Serial Spirometry Sub Study GP 12.5 mcg BID GP 25 mcg BID GP 50 mcg BID GP 100 mcg BID Pbo BID All via eFlow CS nebulizer	55 54 57 59 57 26 24 25 26 24	moderate to severe COPD	Trough FEV_1	US *100%*
SUN101-201 *Jan 2014-May 2014*	R, DB,PC, 6-way CO, OL, AC Dose finding	7 days each separated by 5-7 day WO	GP 3 mcg BID GP 6.25 mcg BID GP 12.5 mcg BID GP 50 mcg BID Aclidinium 400 mcg BID Pbo BID GP and Pbo via eFlow CS nebulizer Aclidinium via Tudorza Pressair DPI	91 92 89 92 92 92	moderate to severe COPD	Trough FEV_1	US *100%*
Pivotal Efficacy and Safety Studies							
SUN101-301 *Feb 2015-Nov 2015*	R, DB, PG, PC Safety/ Efficacy	12 wks	GP 25 mcg BID GP 50 mcg BID Pbo BID Serial Spirometry Sub Study GP 25 mcg BID GP 50 mcg BID Pbo BID All via eFlow CS nebulizer	217 218 218 49 62 42	moderate to severe COPD	Trough FEV1	US *100%*
SUN101-302 *Feb 2015-Dec 2015*	R, DB, PG, PC Safety/ Efficacy	12 wks	GP 25 mcg BID GP 50 mcg BID Pbo BID All via eFlow CS nebulizer	214 214 212	moderate to severe COPD	Trough FEV1	US *100%*

Table 2. Sources of Clinical Data							
Long Term Safety Study							
SUN101-303 *Oct 2014-Feb 2016*	R, OL, PG, AC Safety	48 wks	GP 50 mcg BID Spiriva (tiotropium) 18 mcg QD Serial Spirometry Sub Study GP 50 mcg BID Tiotropium 18 mcg QD Via eFlow CS nebulizer or Handihaler	620 466 61 41	moderate to severe COPD	AEs (evaluated lung function)	Czech Republic, Hungary, Russia, US *90%*
R=randomized, DB=double-blind, PC=placebo-controlled, PG=parallel-group, OL=open label, AC=active control, CO cross over, WO wash out, BID=twice daily, GP = glycopyrrolate, Pbo= placebo, COPD=chronic obstructive pulmonary disease, AEs=adverse events Source: Module 5.3.5.1, CSR EP-101-04, SUN101-201, SUN101-301, SUN101-302, SUN101-303							

5.2 Review Strategy

The focus of this review is the efficacy and safety of GP 25 mcg BID via inhalation through the closed system nebulizer (eFlow, PARI device).

This clinical review focuses on four randomized, double-blind, placebo-controlled studies: two dose-ranging studies (EP-101-04 and SUN101-201) and two confirmatory phase 3 studies (SUN101-301 and SUN101-302). The active-controlled long-term safety study SUN101-303 did not reveal any new safety findings and is consistent with the safety findings from the two confirmatory phase 3 trials. Any differences noted in the long-term safety trial as compared to the placebo-controlled safety database will be noted in Section7 Review of Safety.

Section 5.3 Discussion of Individual Studies/Clinical Trials, describes the protocols in detail for each individual study. Section 6 Review of Efficacy, reviews the individual efficacy results for SUN101-301 and SUN101-302. Section 7 Review of Safety, describes pooled safety for the two pivotal efficacy and safety trials (SUN101-301 and SUN101-302). The results of the long-term safety study (SUN101- 303) are consistent with the results in the pivotal 3-month trials and are discussed in the relevant sections when additional data provides clarification.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Studies SUN101-301 and SUN101-302

Studies SUN101-301 and SUN101-302 were identically designed trials. The following section outlines the protocol for these studies.

Administrative Information

Study SUN101-301

- **Study title**: A randomized, double blind, placebo-controlled, parallel group, multicenter, efficacy and safety trial of 12 weeks of treatment with nebulized SUN-101 (GP) in patients with COPD: GOLDEN-3 (glycopyrrolate for obstructive lung disease via electronic nebulizer)
- **Study dates:** Feb 2015- Nov 2015
- **Study sites:** 45 sites in the USA
- **Study report date:** June 16, 2016

Study SUN101-302

- **Study title**: A randomized, double blind, placebo controlled, parallel group, multicenter, efficacy and safety trial of 12 weeks of treatment with nebulized SUN-101 (GP) in patients with COPD: GOLDEN-4 (glycopyrrolate for obstructive lung disease via electronic nebulizer)
- **Study dates:** Feb 2015- Dec 2015
- **Study sites:** 49 sites in the USA
- **Study report date:** June 16, 2016

Objectives/Rationale

Primary Objectives

- To compare the efficacy of nebulized GP given as 25 mcg BID and 50 mcg BID with placebo following 12 weeks of treatment in subjects with COPD
- To assess the safety and tolerability of nebulized GP given as 25 mcg BID and 50 mcg BID following 12 weeks of treatment in subjects with COPD

Study Design and Conduct

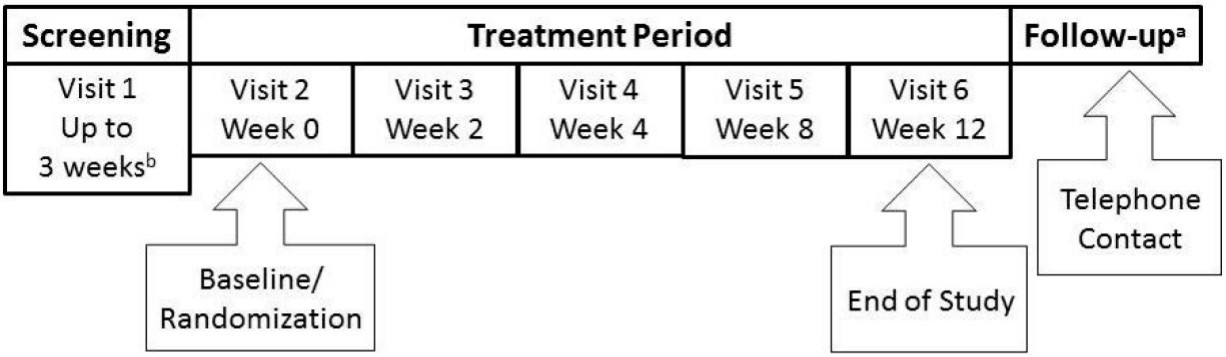
Overview
Studies SUN101-301 and SUN101-302 were replicate, phase 3, 12-week, randomized, double-blind, placebo-controlled, multicenter studies of GP 25 mcg BID and 50 mcg BID versus placebo in patients with moderate to severe COPD.

The studies consisted of a screening period, a 12-week treatment period (GP 25 mcg BID, GP 50 mcg BID, or Pbo BID) and a safety follow-up phone call.

The study design for both studies is depicted in

Figure 4.

Figure 4. Study Design: SUN101-301 and SUN101-302



Abbreviation: EOT = End of Treatment.
[a] All subjects were contacted by telephone 5 to 7 days after the last study visit (ie, Visit 6 or End of Study visit) for a safety assessment unless seen in the clinic in the same time frame.
[b] Visit 1 may have occurred over more than 1 clinic visit and may have been up to 3 weeks, but must have been a minimum of 1 week prior to randomization (Visit 2) to ensure that at least 1 week of rescue medication use and chronic obstructive pulmonary disease symptoms were recorded prior to randomization.
Note: Visit 6 (Week 12) was the EOT. All subjects were to be followed for the full 12 weeks of the treatment period, regardless of discontinuation of study treatment. Subjects who discontinued study drug but remained on the study underwent an EOT visit at the time of study drug discontinuation and then continued with all regularly scheduled study visits and protocol assessments, even though the subject was no longer taking study drug. Subjects who discontinued the study prior to Visit 6 (Week 12) underwent End of Study procedures and assessments at the time of study discontinuation.

Source: Module 5.3.5.1, CSR SUN101-301, Figure 1, Page 24, CSR SUN101-302, Figure 1, Page 24

The schedule of assessments is shown in

Table 3.

APPEARS THIS WAY ON ORIGINAL

Table 3. Schedule of Assessments: SUN101-301 and SUN101-302

	Screen[a]	Treatment					End of Treat-ment	End of Study[b]	Follow-up[c]
Visit No.	**1**	**2**	**3**	**4**	**5**	**6**			
Weeks on Therapy	**-3 to -1**	**0**	**2**	**4**	**8**	**12**			
Study Day	**NA**	**1 to 2**	**14 (± 3 days)**	**28 (± 3 days)**	**56 (± 3 days)**	**84 to 85 (± 3 days)**	**NA**	**NA**	**NA**
Informed Consent	X								
Review Inclusion/Exclusion Criteria	X	X							
Administer Intent to Complete Questionnaire	X								
Medical History	X								
Physical Examination	X					X	X	X	
Height and Weight	X								
Begin Washout of Prohibited Medication (if Applicable)	X								
Chest Auscultation	X	X	X	X	X	X	X	X	
Pregnancy Test[d]	X	X				X	X	X	
Randomization		X							
24-hour Holter Monitoring[e]	X					X[f]			
Vital Signs[g]	X	X				X[f]	X	X	
12-lead ECG[g]	X	X				X[f]	X	X	
Clinical Laboratory Tests[h]	X					X	X	X	
PIFR (All Subjects)[i]		X							
Trough Spirometry (All Subjects)[j]	X	X	X	X	X	X	X	X	
Serial Spirometry (Substudy Subjects)[k]		X				X			

	Screen[a]	Treatment					End of Treatment	End of Study[b]	Follow-up[c]
Visit No.	**1**	**2**	**3**	**4**	**5**	**6**			
Weeks on Therapy	**-3 to -1**	**0**	**2**	**4**	**8**	**12**			
Study Day	**NA**	**1 to 2**	**14 (± 3 days)**	**28 (± 3 days)**	**56 (± 3 days)**	**84 to 85 (± 3 days)**	**NA**	**NA**	**NA**
Dispense Drugs/Study Supplies	X	X	X	X	X				
Collect Used/Unused Drug/Supplies			X	X	X	X	X	X	
Clean eFlow Device; Return to Subject			X	X	X				
Instruct Subjects on Use of and Cleaning of eFlow Device; and Administration of Study Drug		X	X	X	X				
Administer Morning Dose in Clinic[l]		X	X	X	X	X			
Daily eDiary Completion[m]	X	X	X	X	X	X	X	X	
Administer Intent to Attend Questionnaire		X	X	X	X				
SGRQ Completion[n]		X				X	X	X	
Concomitant Medications	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X
Schedule Next Visit	X	X	X	X	X	X	X	X	

Abbreviations: COPD = chronic obstructive pulmonary disease; ECG = electrocardiogram; eDiary = electronic diary; EOS = End of Study; EOT = End of Treatment; EXACT = EXAcerbations of Chronic Pulmonary Disease Tool; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; NA = not applicable; PIFR = peak inspiratory flow rate; SGRQ = St George's Respiratory Questionnaire.

[a] Screening (Visit 1) may have occurred over more than one clinic visit and may have been up to 3 weeks, but must have been a minimum of 1 week prior to Visit 2 (Week 0) to ensure that at least 1 week of rescue medication use and COPD symptoms were recorded prior to randomization.

[b] All subjects were to be followed for the full 12 weeks of the treatment period, regardless of discontinuation of treatment. However, subjects who discontinued the study for any reason prior to Visit 6 (Week 12) had EOS procedures and assessments performed at the time of study discontinuation.

[c] All subjects were contacted by telephone 5 to 7 days after Visit 6 or EOS visit for a safety assessment unless seen in the clinic in the same time frame.

[d] Serum pregnancy testing was performed for females of childbearing potential (in the opinion of the Investigator) at Visit 1. Urine pregnancy tests were performed for females of childbearing potential (in the opinion of the Investigator) at Visit 2 (Week 0) and Visit 6 (Week 12), as well as at the EOT or EOS visits.

[e] Holter monitoring was performed for all subjects at Screening (Visit 1) to determine study eligibility and at Visit 6 (Week 12) for the substudy population.

[f] Serial measurements of vital signs, performance of 12-lead ECGs, and 24-hour Holter monitoring were only to be performed for subjects in the sub study population who completed 12 weeks of study treatment. Subjects who discontinued study drug prior to Visit 6 did not complete serial assessments.

[g] At Visit 2 (Week 0), predose vital signs and 12-lead ECGs were performed for all subjects prior to the morning dose. For those subjects not included in the substudy population, predose vital signs and 12-lead ECGs were performed at Visit 6 (Week 12) at approximately the same time as the Visit 2 (Week 0) predose assessments (± 1 hour). In the substudy population, vital signs and 12-lead ECGs were performed at Visit 2 (Week 0) and Visit 6 (Week 12) prior to the morning dose and postdose at 1, 3, 12, and 24 hours after the morning dose. All vital signs and ECGs obtained postdose had a window of ± 15 minutes. Note: For subjects who discontinued study drug or the study prior to Visit 6, vital signs and 12-lead ECGs were recorded only once, at either the EOT or EOS visit.

[h] Clinical safety laboratory tests consisted of chemistry, hematology, and urinalysis.

[i] Peak inspiratory flow rate was collected for all subjects at Baseline (Visit 2, Week 0) using the In-Check™ Dial (Alliance Tech Medical, Inc.; Granbury, Texas, United States) handheld device.

[j] Trough (predose) spirometry including FEV1 and FVC) was performed for all subjects at Baseline (Visit 2, Week 0), and at each on treatment visit at 45 minutes and 15 minutes prior to the morning dose, except at Visit 6 [Week 12]. For subjects who were not included in the substudy population, trough spirometry at Visit 6 (Week 12) was performed at two time points 30 minutes apart (± 5 minutes) at approximately 24 hours (± 1 hour) after the previous morning dose. For subjects who were included in the substudy population, trough spirometry at Visit 6 (Week 12) was performed at 45 minutes and 15 minutes prior to the morning dose. Trough spirometry was performed at each on treatment visit at approximately the same time as the Baseline (Visit 2 [Week 0]) predose spirometry assessment. Predose assessments were based on study drug start time, while postdose assessments were based on study drug stop time. Spirometry assessments performed at 5 minutes postdose had a window of ± 2 minutes, while all other spirometry assessments prior to and up to 1 hour postdose had a window of ± 5 minutes; all spirometry assessments beginning with the 2-hour postdose time point had a window of ± 15 minutes. Spirometry assessments must have been performed following vital signs and ECG assessments for each shared time point. Subjects who discontinued study drug prior to Visit 6 (Week 12) and who completed the EOT and EOS visits had two spirometry assessments performed approximately 30 minutes apart at each of these visits; every attempt was made for these spirometry assessments to be performed at the same time of day as the trough measurements.

[k] In the substudy population, serial spirometry assessments were taken at Visit 2 (Week 0) and Visit 6 (Week 12; only in subjects who completed the 12 weeks of study treatment). Predose spirometry assessments were relative to the start time of the morning dose and were taken at 45 and 15 minutes predose. Postdose spirometry assessments were relative to the stop time of the morning dose and were taken at 5, 15, 30, and 60 minutes after the morning dose; at 2, 3, 6, and 12 hours after the morning dose; and then at 23 hours and 15 minutes and at 23 hours and 45 minutes after the previous morning dose.

[l] Only subjects who were included in the substudy population were to receive the morning dose in clinic at Visit 6 (Week 12). Subjects who were included in the substudy population were to also take their evening dose in clinic at Visit 2 (Week 0) and Visit 6 (Week 12).

[m] At each visit, the subjects were instructed on the proper completion of the eDiary. For at least 1 week prior to randomization, subjects were to utilize the eDiary to record rescue medication use, COPD symptoms, and complete the EXACT. Each day during the 12 week treatment period, the eDiary was used to record dosing information, rescue medication use, COPD symptoms, and to complete the EXACT. The eDiary was reviewed at each study visit to confirm study drug was administered as instructed and the minimum washout for allowed medications prior to spirometry was met.

[n] Each subject completed the SGRQ at the clinical site at Visit 2 (Baseline; Week 0) and Visit 6 (Week 12). Subjects who discontinued treatment early completed the questionnaire at the EOT visit. Subjects who were unable to complete the 12 weeks of the study completed the questionnaire at the EOS visit.

Note: Serial spirometry, serial measurements of vital signs, performance of 12-lead ECGs, and 24-hour Holter monitoring were only performed for subjects in the sub study population in study SUN 101-301 who completed 12 weeks of study treatment. Subjects who discontinued study drug prior to Visit 6 did not complete serial assessments.

Source: Module 5.3.5.1, CSR SUN101-301, Table 2, Page 26, CSR SUN101-302, Table 2, Page 24

Subjects who discontinued study drug but remained on the study underwent an end of treatment visit at the time of study drug discontinuation, and then continued with all regularly scheduled study visits and protocol assessments even though the subject was no longer taking study drug.

Key Inclusion Criteria

- Male or female at least 40 years of age, inclusive
- Current smoker or ex-smoker with at least 10 pack-year smoking history
- If female and of childbearing potential, negative serum pregnancy test at Visit 1 and required to use an acceptable method of birth control throughout the study
- Clinical diagnosis of COPD according to the GOLD 2014 guidelines for COPD severity
- Ability to perform reproducible spirometry according to the American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines (2005)
- At Screening (Visit 1), post-bronchodilator (following inhalation of ipratropium bromide) FEV1
- < 80% of predicted normal and > 0.7 L, with an FEV1/FVC ratio < 0.70
- Able and willing to provide written informed consent, attend all study visits, and adhere to all study assessments and procedures

Key Exclusion Criteria

- Severe comorbidities (unstable cardiac, pulmonary disease, or any other medical condition) that would have, in the opinion of the Investigator, precluded the subject from safely completing the required tests or the study, or would have likely resulted in disease progression that would have required withdrawal of the subject
- Current or history of the following: unstable cardiac or current pulmonary disease, long QT syndrome, bladder outflow obstruction, catheterization for relief of bladder outflow obstruction within the previous 6 months, narrow angle glaucoma, documented history of substance abuse within the previous 3 months, significant psychiatric disease, or malignancy of any organ system, treated or untreated within the past 5 years
- Concomitant clinically significant respiratory disease other than COPD (asthma, tuberculosis, bronchiectasis, or other nonspecific pulmonary disease) or respiratory tract infection within 6 weeks prior to Screening (Visit 1); daily oxygen therapy for 12 hours or more per day; the use of oral, IV, or IM steroids within 3 months prior to Screening (Visit 1); or recent history of COPD exacerbation requiring hospitalization or need for increased treatments for COPD within 6 weeks prior to Screening (Visit 1)
- Participation in another investigational drug study where drug was received within 30 days prior to Screening (Visit 1) or during the current study treatment period

    - This also included any prior GP SUN-101 (active treatment; formerly known as EP-101) studies
- Contraindications for treatment with, or having a history of reactions/hypersensitivity to anticholinergic agents, β2 agonists, sympathomimetic amines, or aerosol medications.

Reviewer comment: The trial design and inclusion/exclusion criteria are appropriate. The exclusion criteria address potential risks due to mechanism of action and known adverse events such as worsening narrow angle glaucoma and urinary retention.

Prohibited Medications Studies SUN101-301 and SUN101-302

Subjects were not be permitted to use any of the following medications during Screening (Visit 1), and had to meet the minimum specified washout period prior to performing the study qualifying spirometry assessments during Screening (Visit 1):

- Long-acting anti-muscarinic agents (LAMA, e.g., tiotropium and aclidinium) require a minimum washout of 7 full days
- Short-acting bronchodilators (e.g., albuterol, ipratropium) require a minimum 6-hour washout
- Theophylline requires a minimum 24-hour washout

With the exceptions of albuterol MDI (provided by the site as rescue medication) and ipratropium bromide MDI (provided at the discretion of the investigator for supplemental use [2 inhalations 4 times a day, and not to exceed 12 inhalations in 24 hours]), none of the above medications were permitted throughout the 12-week treatment period.

Any subjects taking a LAMA (e.g, tiotropium or aclidinium) had to undergo the specified washout period prior to performing study qualifying spirometry assessments during Screening (Visit 1). For these subjects, sites were permitted to replace LAMA use with ipratropium bromide MDI during Screening (Visit 1). However, subjects had to strictly adhere to the minimum 6-hour withholding requirement for ipratropium MDI prior to study qualifying spirometry assessments, and had to discontinue use of ipratropium during the 12-week treatment period, unless provided by the investigator for supplemental use (in accordance with the approved product labeling) following randomization. Supplemental ipratropium had to be withheld prior to each study visit for at least 6 hours, and for the duration of each on-treatment visit.

Permitted Medications Studies SUN101-301 and SUN101-302

Albuterol MDI was dispensed after study consent and was permitted as rescue medication for as-needed use throughout study participation. Subjects were instructed to withhold albuterol for 6 hours prior to study visits. In order to confirm study eligibility during Screening (Visit 1), each subject was administered ipratropium MDI (Atrovent®) and pre- and post-bronchodilator spirometry assessments were performed. Ipratropium was not permitted after randomization,

unless provided by the Investigator for supplemental use in accordance with the approved product labeling. Subjects requiring supplemental ipratropium were instructed to withhold the medication for 6 hours prior to study visits, and for the duration of each on-treatment visit.

Albuterol MDI and ipratropium MDI were considered Non-Investigational Medicinal Product (NIMP) for use in this study. Both medications will be provided by Sunovion Pharmaceuticals, or by the clinical site.

Any subject taking a LABA, inhaled corticosteroid (ICS), fixed dose combination of LABA and ICS (e.g., salmeterol/fluticasone, formoterol/budesonide), or PDE 4 inhibitor (e.g., Roflumilast) was permitted during the study, provided that the subject was on a stable dosing regimen (i.e., same dose and frequency) for at least 4 weeks prior to beginning Screening (Visit 1) and continued this dosing regimen through the end of study participation. Subjects using LABA or LABA/ICS (capped at 30% of randomized subjects) were required to withhold their LABA or LABA/ICS treatment for 48 hours prior to spirometry assessments, and for the duration of each on-treatment visit. If LABA or LABA/ICS treatment was used within 48 hours prior to spirometry testing at any study visit, then the visit had to be rescheduled to allow the appropriate washout.

Other permitted medications included H1 receptor antagonists, leukotriene modifiers, selective beta1 blockers, provided that the subject had been on a stable dosing regimen for at least 4 weeks prior to beginning Screening (Visit 1). There were no disallowed medications or washout periods for subjects who discontinued treatment early and remained in the study.

Treatment Groups

Treatment groups are outlined in Table 4.

Table 4. Treatment groups: Studies SUN101-301, SUN101-302

Substance	GP	GP	Placebo
Unit strength	25 mcg	50 mcg	-
Pharmaceutical form	Inhalation solution		
Frequency	Twice Daily		
Route of administration	Inhalation via eflow nebulizer device		

Source: CSR SUN101-301, CSR SUN101-302

To maintain blinding, the placebo was designed to match GP; administered twice daily as an oral inhalation using the investigational eFlow closed system nebulizer. Each morning (AM) dose was administered between 6:00 AM and 10:00 AM, and each evening (PM) dose was administered approximately 12 hours later (between 6:00 PM and 10:00 PM).

Efficacy Endpoints

Primary Endpoint

- Change from baseline in trough FEV1 at Week 12

Key Secondary Endpoints

- Standardized change from baseline at Week 12 in FEV1 AUC(0-12) in the spirometry sub-study population (SUN101-301)
- Change from baseline in trough forced vital capacity (FVC) at Week 12
- Change from baseline in health status measured by St. George's Respiratory Questionnaire (SGRQ) at Week 12/End of Study
- Change in number of rescue medication puffs per day over the 12-week double-blind treatment period

Other Efficacy Endpoints

- Change from baseline in Respiratory Symptoms Total Score measured by the Exacerbations of Chronic Pulmonary Disease Tool (EXACT)
- Percent change from baseline in trough FEV1
- Change from baseline in peak FEV1 at Week 0 and Week 12 in the spirometry sub-study population (SUN101-301)
- Standardized change from baseline at Week 0 and Week 12 in FEV1 AUC(0-3h) in the sub-study population (SUN101-301)
- Number and percent of subjects with bronchodilation (where bronchodilation is defined as an increase of at least 100 mL from baseline in FEV1) on Day 1 in the sub-study population (SUN101-301)
- Time to onset of bronchodilation on Day 1 in the sub-study population (SUN101-301)
- Number of rescue medication-free days per week
- Number and percent of subjects with supplemental ipratropium use
- Change from baseline in COPD symptoms
- Incidence of COPD exacerbations, defined as an increase in COPD symptoms (e.g., dyspnea, cough, sputum volume, or sputum purulence) during at least 2 consecutive days, and will be classified as mild (self-managed with increased short acting bronchodilator and/or ICS use), moderate (treated with antibiotics and/or systemic corticosteroids, but not requiring hospitalization), or severe (requiring overnight stay at hospital or emergency room). Any event occurring within 30 days of a prior event will be considered a continuation of the index event.
- Time to onset of first COPD exacerbation

Secondary Safety Endpoints

- Number and percentage of subjects with treatment emergent adverse events (TEAE)
- Number and percentage of subjects with treatment emergent serious adverse events (SAE)
- Number and percentage of subjects who discontinue treatment due to TEAE

- Number and percentage of subjects with major adverse cardiac events (MACE), including cardiovascular death, ischemia/infarction, and stroke

Other Safety Endpoints

- Changes from baseline in vital signs
- Changes from visit pre-dose in vital signs for the sub-study population (SUN 101-301)
- Changes from baseline in 12-lead electrocardiogram (ECG), including QTc interval
- Changes from visit pre-dose in 12-lead ECG, including QTc interval, for the sub-study population (SUN101-301)
- Changes from baseline in clinical laboratory tests

Efficacy Endpoint Parameters

Primary Efficacy Parameter

Change from baseline in trough FEV1 at Week 12

Spirometry assessments were performed using a standardized pneumotach spirometry system. Spirometry involved the determination of FEV1, FVC, and FEV1/FVC ratio. Predicted FEV1 was obtained using the normal prediction equations obtained from The Third National Health and Nutrition Examination Survey (NHANES III). Spirometry measurements were conducted in accordance with the current ATS/ERS 2005 guidelines (Miller 2005).

At least 3 "acceptable" spirometry maneuvers (up to 8 blows total per time point) were obtained during each assessment. The highest and second highest FEV1 values and the highest and second highest FVC values should have been within 150 mL to be acceptable. The single highest FEV1 and the single highest FVC values from acceptable and repeatable maneuvers were reported even if they do not come from the same maneuver. The FEV1/FVC ratio was determined from the reported highest FEV1 and highest FVC values.

All "acceptable quality" spirometry efforts that meet ATS/ERS guidelines for quality, acceptability, and repeatability requirements were transmitted to a central spirometry laboratory. A dedicated team of blinded, registered respiratory therapists reviewed all spirometry data for acceptability and repeatability, and could re-rank efforts to ensure the highest data quality is used.

Reviewer comment: The use of ATS/ERS Spirometry criteria (2005) is appropriate.

Secondary Efficacy Parameters

EXACT ePRO

Respiratory symptoms were recorded using the EXACT; an electronic patient reported outcome (PRO) instrument designed to standardize the method for evaluating the frequency, severity, and duration of COPD exacerbations in clinical trials. The EXACT assesses patients' breathlessness,

cough and sputum, chest symptoms, difficulty bringing up sputum, feeling tired or weak, sleep disturbance, and feeling scared or worried about their condition with a 14-item questionnaire (Leidy 2010 The EXACT PRO Initiative). The EXACT was completed by the study subject via the eDiary.

SGRQ
Each subject completed the SGRQ at the clinical site prior to dosing or any study-related procedures. The SGRQ is a standardized disease-specific, 50-item questionnaire designed to measure impact on overall health, daily life, and perceived well-being in patients with obstructive airway disease (Jones 1991).

COPD Symptoms
COPD symptoms were assessed each day in the eDiary.

Safety Assessments
The investigator or appropriate designee reviewed results of safety assessments on a regular basis and the Sponsor was fully informed of any clinically significant findings throughout the study.

Adverse Events
Adverse events were collected for each subject. Subjects were queried in a non-leading manner, without specific prompting (e.g., "Has there been any change in your health status since your last visit?"). AEs and SAEs were monitored throughout the study at all visits including the follow-up telephone contact.

Clinical Laboratory Tests
Blood and urine samples were collected for clinical laboratory tests for each subject and processed and analyzed centrally to ensure consistency. All clinical laboratories were College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendments (CLIA) (or equivalent) certified.

Vital Signs
Vital signs consisted of supine systolic and diastolic blood pressure and heart rate. Vital signs were obtained after the subject rested in the supine position for at least 5 minutes, and prior to the performance of an ECG, clinical laboratory collection, and spirometry measurements for each shared time point.

Centrally-read ECG and Holter Monitoring
Centrally read ECG: ECGs were obtained while the subject was in the supine position, after the subject rested supine for at least 5 minutes. ECGs were 12-lead with a 10-second rhythm strip. ECGs were obtained after recording vital signs and prior to drawing blood samples or performing spirometry assessments for each shared time point. All attempts were made to use the same ECG recorder for all visits within individual subjects. ECGs were centrally read at a core lab according to established quality assurance procedures for inter/intra reader variability.

Holter Monitor
Data collected from the monitor could be held at the core laboratory for future extraction or could undergo ongoing over read for Holter parameters. Holter analysis could be initiated based on interim and/or retrospective reviews of the study data. Immediate over reads could be performed at the Investigator's discretion.

Physical Examinations and Chest Auscultation
Physical examinations evaluated the major body systems in order to identify any clinically significant disease or abnormality that, in the opinion of the Principal Investigator, could exclude a subject from the study or preclude further study participation. Physical examinations were performed by the Principal Investigator, or a designee with appropriate medical qualifications who was experienced and routinely conducted physical examinations.

COPD Exacerbations
COPD exacerbations were defined as an increase in COPD symptoms (e.g., dyspnea, cough, sputum volume, or sputum purulence) during at least 2 consecutive days, and were classified as mild (self-managed with increased short-acting bronchodilator and/or ICS use), moderate (treated with antibiotics and/or systemic corticosteroids, but not requiring hospitalization), or severe (requiring overnight stay at hospital or emergency room). Any event occurring within 30 days of a prior event will be considered a continuation of the index event. The incidence and severity of COPD exacerbations was summarized by treatment group and visit interval for the ITT population, as well as over the 12-week double-blind treatment period.

The time in days to the first COPD exacerbation was summarized for subjects who had an exacerbation. Subjects without a COPD exacerbation were censored at the date of treatment discontinuation or, if unknown, the date of last contact. Kaplan-Meier plots of the cumulative probability of exacerbations for each treatment group were presented.

COPD Exacerbations
A COPD exacerbation was defined as an increase in clinician-assessed COPD symptoms (e.g., dyspnea, cough, sputum volume, or sputum purulence) during at least 2 consecutive days, and was classified as follows:

- Mild: self-managed with increased short-acting bronchodilator and/or ICS use
- Moderate: treated with antibiotics and/or systemic corticosteroids, but did not require hospitalization
- Severe: required an overnight stay at hospital or emergency room

Any event that occurred within 30 days of a prior event was considered a continuation of the index event. For example, if a subject had COPD exacerbations on Days 10, 25, and 50, they were all considered one event, as the event on Day 25 was within 30 days of the event on Day 10, and the event on Day 50 was within 30 days of the event on Day 25 (which was previously

associated with the event on Day 10). The occurrence and severity of COPD exacerbations was captured on the AE page of the eCRF.

Compliance Parameters

Subjects recorded dosing information utilizing the eDiary.

Proper administration of study medication was assessed by the site during each on-treatment visit. Subjects were instructed to bring all used (e.g., empty drug vials) and unused IMP and nebulizer devices to each study visit. Designated site staff thoroughly documented and re-instructed the subject any time after significant noncompliance with study drug or completion of the eDiary was noted.

Safety Parameters

The investigator or appropriate designee reviewed the results of safety assessments on a regular basis and the sponsor was kept fully informed of any clinically significant findings throughout the study.

Ethics

The study was to be conducted according to the protocol, ICH GCP, ICH guidelines and the ethical principles that have their origin in the Declaration of Helsinki. The investigator was to conduct all aspects of the study in accordance with applicable local law(s) and regulation(s).

Documented approval for conducting the study from appropriate Institutional Review Board (IRB) was obtained for all participating centers prior to initiation of the study, according to ICH GCP, applicable local law(s) and regulation(s).

Statistical Plan

Primary Endpoint

The primary objective of the study was to demonstrate the superiority of GP 25 mcg and 50 mcg BID compared to placebo in terms of change from baseline in trough FEV1 at Week 12.

The change from baseline to each week's trough was calculated as trough FEV1 minus baseline FEV1. Baseline was defined as the mean of the two pre-dose FEV1 values at 45 minutes and 15 minutes prior to the morning dose at Visit 2 (Week 0).

Spirometry values may have been missing intermittently, between two non-missing values, or from a given study visit onwards, in a monotonic pattern. In order to explore how these mechanisms may have affected the efficacy data, sensitivity analyses were undertaken for the primary and key secondary efficacy analyses.

The primary efficacy endpoint was analyzed for the ITT population by means of a mixed model repeated measures analysis (MMRM), with change from baseline in trough FEV1 as the response

variable and with factors for treatment group, cardiovascular risk (high/low), background LABA use (yes/no), visit week, and visit week by treatment group interaction, and baseline FEV1 as a covariate. Subjects were included as a random effect. For tests of fixed effects, an unstructured covariance matrix and the Kenward and Roger correction to the degrees of freedom was used. Should the unstructured covariance matrix not converge, a first-order autoregressive covariance matrix was utilized.

From this model, the least squares means for change in trough FEV1 was estimated for each treatment group at each visit week. The primary comparisons of interest were the comparisons of the change from baseline in trough FEV1 at Week 12 between each GP dose (25 and 50 mcg) and placebo. Graphical displays of the LS Mean difference vs placebo were also be presented.

Key Secondary Endpoints

FEV1 AUC (0-12) hours
The key secondary efficacy endpoint of standardized change from baseline in FEV1 AUC (0-12) hours at Week 12 for the Sub-study Population was calculated using the trapezoidal method from the changes in FEV1 from the baseline value (the mean of the two pre-dose FEV1 values at 45 minutes and 15 minutes pre-dose at Visit 2 [Week 0]) and dividing by the actual length of the time interval. This endpoint was analyzed using the same MMRM model as the primary efficacy endpoint.

FVC
The key secondary efficacy endpoint of change from baseline in trough FVC at Week 12 was analyzed for the ITT population using the same MMRM model as the primary efficacy endpoint, except that baseline FVC will be used as the covariate.

SGRQ total score
The key secondary efficacy endpoint of change from baseline in health status measured by SGRQ total score at Week 12/End of Treatment was analyzed for the ITT population using an analysis of covariance (ANCOVA) model with treatment group, cardiovascular risk, and background LABA use as factors and baseline SGRQ total score as a covariate.

Reviewer's Comment: While SGRQ was pre-specified to be analyzed in this manner, the more appropriate evaluation is a responder analysis, which the Applicant was also asked to perform and will ultimately be included in Section 14 of the package insert.

Number of Rescue Medication Puffs Per Day
The key secondary efficacy endpoint of the change from baseline in the number of rescue medication puffs per day averaged over the double-blind treatment period was analyzed for the ITT population using an ANCOVA model with the average number of rescue medication puffs per day during baseline as a covariate and treatment, cardiovascular risk, and background LABA use as factors.

To control the overall type I error rate of the study, a multiplicity adjustment was applied to the primary and the key secondary efficacy endpoint analyses.

5.3.2 Study SUN101-303

Administrative Information

Study SUN101-303

- **Study title:** A randomized, open-label, active-controlled, parallel-group, multicenter, long-term safety study trial of treatment with nebulized SUN-101 (GP) in patients with COPD: GOLDEN-5 (Glycopyrrolate for obstructive lung disease via electronic nebulizer)
- **Study dates:** Oct2014 – Feb2016
- **Study sites:** 111 sites in 4 countries: Czech Republic, Hungary, Russia, US
- **Study report date:** July 7, 2016

Objectives/Rationale

Primary Objective
To assess the long-term safety and tolerability of GP 50 mcg BID over 48 weeks of treatment.

Secondary Objective
To assess the long-term efficacy of GP 50 mcg BID over 48 weeks of treatment.

Study Design and Conduct

Overview

Study SUN101-303 was a, 48-week, randomized, open-label, active-controlled, parallel group, multicenter, long-term safety study that evaluated treatment with either GP 50 mcg BID or tiotropium QD, as an active comparator, in subjects diagnosed with moderate to very severe COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (GOLD 2014).

The total duration of the study was up to 52 weeks, consisting of a screening period of up to 3 weeks prior to randomization, a 48-week treatment period, and a safety follow-up phone call 5 to 7 days after the last study treatment.

The schedule of assessments is shown in

Table 5.

Table 5. Schedule of Assessments: Study SUN101-303

	Screen	Treatment						
Visit No.	**1**[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Weeks on Therapy	**-3 to -1**	**0**	**2**	**4**	**8**	**12**	**18**	**24**
Study Day	**NA**	**1-2**	**14 (± 3 days)**	**28 (± 3 days)**	**56 (± 3 days)**	**84-85 (± 3 days)**	**126 (± 3 days)**	**168-169 (± 3 days)**
Informed Consent	X							
Eligibility Assessment	X	X						
Administer Intent to Complete Questionnaire	X							
Medical History	X							
Physical Examination	X					X		X
Height and Weight	X							
Begin Washout of Prohibited Medication (if Applicable)	X							
Chest Auscultation	X	X	X	X	X	X	X	X
Pregnancy Test[b]	X	X						
Randomization		X						
24-hour Holter Monitoring[c]	X							
Vital Signs[d]	X	X				X		X
12-Lead ECG[d]	X	X						X
Clinical Laboratory Tests[e]	X					X		X
PIFR (All Subjects)[f]		X						
Trough Spirometry (All Subjects)[g]	X	X	X	X	X	X	X	X
Serial Spirometry (Substudy Subjects)[h]		X				X		X
Dispense Drugs/Study Supplies[i]	X	X	X	X	X	X	X	X

	Screen	Treatment						
Visit No.	**1[a]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Weeks on Therapy	**-3 to -1**	**0**	**2**	**4**	**8**	**12**	**18**	**24**
Study Day	**NA**	**1-2**	**14 (±3 days)**	**28 (± 3 days)**	**56 (± 3 days)**	**84-85 (± 3 days)**	**126 (± 3 days)**	**168-169 (± 3 days)**
Collect Used/Unused Drug/Supplies			X	X	X	X	X	X
Clean eFlow Device; Return to Subject			X	X	X	X	X	X
Administer Dose In-clinic[j]		X	X	X	X	X	X	X
Daily eDiary Completion[k]	X	X	X	X	X	X	X	X
Administer Intent to Attend Questionnaire		X	X	X	X	X	X	X
SGRQ Completion		X				X		X
Concomitant Medications	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X
Schedule Next Visit	X	X	X	X	X	X	X	X

Abbreviations: COPD = chronic obstructive pulmonary disease; ECG = electrocardiogram; eDiary = electronic diary; EXACT = EXAcerbations of Chronic Pulmonary Disease Tool; MDI = metered dose inhaler; PIFR = peak inspiratory flow rate; SGRQ = St George's Respiratory Questionnaire

[a] Screening may have occurred over more than 1 clinic visit. Screening may have been up to 3 weeks, but must have been completed a minimum of 1 week prior to Visit 2 to ensure that at least 1 week of rescue medication use and COPD symptoms were recorded prior to randomization.

[b] Serum pregnancy testing was performed for females of childbearing potential (in the opinion of the Investigator) at Visit 1. Urine pregnancy testing was performed for females of childbearing potential (in the opinion of the Investigator) only at Visit 2.

[c] At Visit 1, 24-hour Holter monitoring was performed for all subjects to determine study eligibility.

[d] Vital signs consisted of supine systolic and diastolic blood pressures and heart rate. Vital sign measurements were obtained after the subject had rested in the supine position for at least 5 minutes, prior to obtaining an ECG, clinical laboratory collection, and spirometry measurements for each shared time point. Electrocardiograms were to have been obtained after recording vital signs and prior to drawing blood samples or performing spirometry assessments for each shared time point. At Visit 1 (Screening), vital signs and 12-lead ECGs were performed on all subjects. At Visit 2 (Week 0), Visit 6 (Week 12) **(vital signs only; no ECG)**, and Visit 8 (Week 24), vital sign measurements and 12-lead ECG evaluations were performed for all subjects prior to the morning dose. At Visit 2 (Week 0), Visit 6 (Week 12) **(vital signs only; no ECG)**, and Visit 8 (Week 24), vital sign measurements and 12-lead ECG evaluations were performed in the substudy population 1, 3, 12, and 24 hours after the morning dose.

[e] Clinical safety laboratory tests were comprised of chemistry, hematology, and urinalysis.

[f] Peak inspiratory flow rate was collected for all subjects at Baseline (Visit 2, Week 0) using the In-Check handheld device.

[g] At each on-treatment visit, trough spirometry was performed for all subjects 45 and 15 minutes prior to the morning dose for Visit 3 through Visit 8. Trough spirometry was to have been performed at each on-treatment visit at approximately the same time as the baseline (Visit 2 [Week 0]) predose spirometry assessment. Predose assessment timing was based on study drug start time, while postdose assessment timing was based on study drug stop time. Note: Trough spirometry was to have been performed only once at the time of discontinuation for subjects who discontinued the study prior to Visit 11 (Week 48).

[h] At Visit 2 (Week 0), Visit 6 (Week 12), and Visit 8 (Week 24), serial spirometry was performed in the substudy population 5, 15, 30, and 60 minutes, and 2, 3, 6, and 12 hours after the morning dose and 23.25 and 23.75 hours after the previous morning dose. Predose spirometry assessment timing was relative to the start time of the morning dose; postdose spirometry assessment timing was relative to the stop time of the morning dose.

[i] Only albuterol/salbutamol was dispensed at Visit 1 for use as rescue medication. Albuterol MDI was permitted as rescue medication for as-needed use throughout study participation. Albuterol MDI must have been withheld prior to each study visit for at least 6 hours, and for the duration of the visit, unless medically necessary. In addition, ipratropium MDI may have been provided by the Investigator for supplemental use (in accordance with approved product labeling) after randomization. Supplemental ipratropium MDI must have been withheld prior to each study visit for at least 6 hours, and for the duration of each on-treatment visit.

[j] Subjects randomized to SUN-101 who were included in the substudy population took their evening dose in-clinic at Visit 2 (Week 0), Visit 6 (Week 12), and Visit 8 (Week 24).

[k] At each visit, each subject was instructed on the proper completion of the eDiary. For at least 1 week prior to randomization, subjects used the eDiary to record rescue medication use, COPD symptoms, and to complete the EXACT. Each day during the open-label treatment period, subjects used the eDiary to record dosing information, rescue medication use, COPD symptoms, and to complete the EXACT. The eDiary was reviewed at each study visit to confirm that study drug was administered as instructed and that the minimum washout period for allowed medications prior to spirometry was observed.

	Treatment			Early Termination[a]	Follow-up[b]
Visit No.	**9**	**10**	**11**		
Weeks on Therapy	**32**	**40**	**48**		
Study Day	**224 (± 3 days)**	**280 (± 3 days)**	**336-337 (± 3 days)**	-	-
Physical Examination			X	X	
Chest Auscultation	X	X	X	X	
Pregnancy Test[c]			X	X	
Vital Signs[d]			X	X	
12-Lead ECG[d]			X	X	
Clinical Laboratory Tests[e]			X	X	
Trough Spirometry (All Subjects)[f]	X	X	X	X	
Serial Spirometry (Substudy Subjects)[g]			X		
Dispense Drugs/Study Supplies[h]	X	X			
Collect Used/Unused Drug/Supplies	X	X	X	X	
Clean eFlow Device; Return to Subject	X	X			
Administer Dose In-clinic	X	X	X[i]		
Daily eDiary Completion[j]	X	X	X	X	
Administer Intent to Attend Questionnaire	X	X			
SGRQ Completion			X	X	
Device Use Questionnaire[k]			X	X	
Subject Satisfaction Questionnaire			X	X	
Concomitant Medications	X	X	X	X	X
Adverse Events	X	X	X	X	X

	Treatment			Early Termination[a]	Follow-up[b]
Visit no	**9**	**10**	**11**		
Weeks on Therapy	**32**	**40**	**48**		
Study Day	**224 (± 3 days)**	**280 (± 3 days)**	**336-337 (± 3 days)**	**NA**	**NA**
Schedule Next Visit	X	X	X	X	-

Abbreviations: COPD = chronic obstructive pulmonary disease; ECG = electrocardiogram; eDiary = electronic diary; EXACT = EXAcerbations of Chronic Pulmonary Disease Tool; MDI = metered dose inhaler; SGRQ = St George's Respiratory Questionnaire

[a] Subjects who discontinued the study for any reason prior to Visit 11 (Week 48) will have early termination procedures and assessments performed at the time of discontinuation.

[b] All subjects were contacted by telephone 5 to 7 days after their last study treatment for final safety assessments.

[c] Urine pregnancy testing was performed for females of childbearing potential (in the opinion of the Investigator) at Visit 11 (Week 48).

[d] Vital signs consisted of supine systolic and diastolic blood pressures and heart rate. Vital sign measurements were obtained after the subjects had rested in the supine position for at least 5 minutes, prior to obtaining an ECG clinical laboratory collection, and spirometry measurements for each shared time point. Electrocardiograms were obtained after recording vital signs and prior to drawing blood samples or performing spirometry assessments for each shared time point. At Visit 11 (Week 48), vital sign measurements and 12-lead ECG evaluations were performed for all subjects. In the substudy population, vital sign measurements and 12-lead ECG evaluations were performed at Visit 11 (Week 48) prior to the morning dose and 1, 3, 12, and 24 hours after the morning dose. Note: Vital signs and 12-lead ECG were to have been recorded only once at the time of discontinuation for subjects who discontinued the study prior to Visit 11 (Week 48).

[e] Clinical safety laboratory tests were comprised of chemistry, hematology, and urinalysis.

[f] At each on-treatment visit, trough spirometry was performed for all subjects at 45 minutes and 15 minutes prior to the morning dose. Trough spirometry was to have been performed at each on-treatment visit at approximately the same time as the baseline (Visit 2 [Week 0]) predose spirometry. For subjects not included in the substudy population, trough spirometry at Visit 11 (Week 48) was performed at 2 time points 30 minutes apart at approximately 24 hours (± 1 hour) after the previous morning dose. Note: Trough spirometry was to have been performed only once at the time of discontinuation for subjects who discontinued the study prior to Visit 11 (Week 48).

[g] At Visit 11 (Week 48), serial spirometry was performed in the substudy population at 5, 15, 30, and 60 minutes, and at 2, 3, 6, and 12 hours after the morning dose and 23.25 and 23.75 hours after the previous morning dose.

[h] Albuterol MDI was permitted as rescue medication for as-needed use throughout study participation. Albuterol MDI must have been withheld prior to each study visit for at least 6 hours, and for the duration of the visit, unless medically necessary. In addition, ipratropium MDI may have been provided by the Investigator for supplemental use (in accordance with approved product labeling) after randomization. Supplemental ipratropium MDI must have been withheld prior to each study visit for at least 6 hours, and for the duration of each on-treatment visit.

[i] Only subjects included in the substudy population received the morning dose in-clinic at Visit 11 (Week 48). Subjects randomly assigned to SUN-101 who were included in the substudy population took their evening dose in-clinic at Visit 11 (Week 48). Subjects not included in the substudy population did not receive study drug at Visit 11 (Week 48), and took their last dose of study drug the day prior to Visit 11 (Week 48).

[j] At each visit, each subject was instructed on the proper completion of the eDiary. Each day during the open-label treatment period, subjects used the eDiary to record dosing information, rescue medication use, COPD symptoms, and to complete the EXACT. The eDiary was reviewed at each study visit to confirm that study drug was administered as instructed and that the minimum washout period for allowed medications prior to spirometry was observed.

[k] SUN-101 subjects only.

Source: Module 5.3.5.1, CSR SUN101-303, Table 2, Page 26, Table 3, Page 29

Subjects who discontinued the study prior to Visit 11 (Week 48) were to undergo the procedures and assessments scheduled for the ET visit. These subjects were to have a follow-up phone contact 5 to 7 days after their last study treatment for a final safety assessment.

Key Inclusion Criteria

- Male or female at least 40 years of age
- Current or ex-smoker with at least a 10 pack-year smoking history
- If female and of childbearing potential, the subject was required to have a negative serum pregnancy test at Visit 1 and was required to use an acceptable method of birth control throughout the study.
- Subjects were required to have a clinical diagnosis of COPD according to the GOLD 2014 guidelines for COPD severity
- Ability to perform reproducible spirometry according to the American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines (2005).
- During screening (Visit 1), post-bronchodilator (following inhalation of ipratropium bromide) FEV1 was to be less than 80% of predicted normal and greater than 0.7 L, and the FEV1/FVC ratio was to be less than 0.70.
- Willing and able to provide written informed consent, to attend all study visits, and to adhere to all study assessments and procedures.

Key Exclusion Criteria

- Severe comorbidities (i.e., unstable cardiac, pulmonary disease or any other medical condition) that would have, in the opinion of the Investigator, precluded the subject from safely completing the required tests or the study, or would likely result in disease progression that would have required withdrawal of the subject.
- Current or history of the following: unstable cardiac or current pulmonary disease, long QT syndrome, bladder outflow obstruction, catheterization for relief of bladder outflow obstruction within the previous 6 months, narrow angle glaucoma, documented history of substance abuse within the previous 3 months, significant psychiatric disease, or malignancy of any organ system, treated or untreated within the past 5 years.
- Concomitant clinically significant respiratory disease other than COPD (e.g., asthma, tuberculosis, bronchiectasis, or other nonspecific pulmonary disease) or respiratory tract infection within 6 weeks prior to screening (Visit 1); required daily oxygen therapy for 12 hours or more per day; used oral, intravenous, or intramuscular steroids within 3 months prior to screening (Visit 1); or had a recent history of COPD exacerbation requiring hospitalization or need for increased treatments for COPD within 6 weeks prior to screening (Visit 1).
- Subjects were not allowed to participate in another investigational drug study where drug was received within 30 days prior to screening (Visit 1) or during the current study treatment period. This also included any prior SUN-101 (active treatment, formerly known as EP-101) studies.
- Subjects were also not allowed to participate in the current study if they were contraindicated for treatment with, or having a history of reactions/hypersensitivity to anticholinergic agents, β2 agonists, sympathomimetic amines, or aerosol medications.

Reviewer comment: The trial design and inclusion/exclusion criteria are appropriate. The exclusion criteria address potential risks due to mechanism of action and known adverse events such as worsening narrow angle glaucoma and urinary retention.

Prohibited Medications

Subjects were not permitted to use any of the following medications during Screening (Visit 1) and must have met the minimum specified washout period prior to performing the study-qualifying spirometry assessments during Screening (Visit 1):

- LAMA (e.g., tiotropium and aclidinium), required a minimum washout period of 7 full days
- Short-acting bronchodilators (e.g., albuterol, ipratropium), required a minimum washout period of 6 hours
- Theophylline, required a minimum washout period of 24 hours

These medications were also not permitted any time during the 48-week treatment period, with the exceptions of albuterol MDI (provided by the site as rescue medication), ipratropium MDI

(provided at the discretion of the investigator for supplemental use in accordance with approved product labeling), and tiotropium (for subjects randomly assigned to tiotropium). Albuterol MDI and ipratropium MDI were considered non-investigational medicinal products for use in this study and both medications were provided by Sunovion, or by the clinical site.

During Screening (Visit 1), supplemental ipratropium MDI use was allowed to help stabilize subjects who experienced difficulty during "wash-out" of their prohibited medications (e.g., tiotropium, aclidinium bromide). However, these subjects had to strictly adhere to the minimum 6-hour withholding requirement prior to performing their qualifying spirometry assessments and discontinue use of ipratropium before randomization. During the treatment period, supplemental ipratropium use was allowed, per investigator discretion, as a retention strategy for subjects to continue in the study. The supplemental ipratropium had to be withheld prior to each study visit for at least 6 hours, and for the duration of each clinic visit.

Permitted Medications

Albuterol MDI was dispensed after study consent and was permitted as a rescue medication for as-needed use throughout study participation. Subjects were instructed to withhold albuterol for 6 hours prior to study visits.

In order to confirm study eligibility during the screening period, each subject was administered ipratropium MDI (Atrovent HFA) for the qualifying post-bronchodilator spirometry assessments.

Subjects taking a LABA, or any fixed-dose combination of LABA and ICS (e.g., salmeterol/fluticasone, formoterol/budesonide), or PDE4 inhibitor (e.g., roflumilast) were eligible for the study, provided that they were on a stable dosing regimen (i.e., same dose and frequency) for at least 4 weeks prior to beginning Screening (Visit 1) and that they continued this dosing regimen through the end of study participation. Subjects taking a LABA or LABA/ICS were required to withhold their LABA or LABA/ICS treatment for 48 hours prior to spirometry assessments. If a LABA or LABA/ICS was used within 48 hours prior to any study visit with scheduled spirometry testing, then the visit had to be rescheduled to accommodate the 48-hour washout period.

Other permitted medications included H1 receptor antagonists, leukotriene modifiers, and selective β1 blockers, provided that the subject was on a stable dosing regimen for at least 4 weeks prior to beginning screening (Visit 1).

Treatment Groups

Treatment groups are outlined in Table 6.

Table 6. Treatment groups: Study SUN101-303

Substance	GP	Tiotropium
Pharmaceutical form	Inhalation Solution	
Unit strength (mcg)	50 mcg	18 mcg
Frequency	Twice a day	Once a day
Route of administration	Inhalation via eflow CS device	Inhalation via HandiHaler

Source: Module 5.3.5.1: Study SUN101-303 CSR, Page 35

Efficacy Endpoints

Study SUN101-303 was primarily a safety study; therefore, the efficacy analysis was secondary and considered supportive in nature.

Primary Safety Endpoint

- Number and percentage of subjects with treatment-emergent adverse events (TEAE)
- Number and percentage of subjects with treatment-emergent serious adverse events (SAEs)
- Number and percentage of subjects who discontinued the study due to TEAE

Secondary Safety Endpoints

- Number and percentage of subjects with major adverse CV events (MACE), including CV death, ischemia/infarction, and stroke.

Other Safety Endpoints

- Changes from baseline in vital signs
- Changes from baseline in 12-lead electrocardiogram (ECG), including the electrocardiographic interval from the beginning of the QRS complex to the end of the T wave (QT) corrected for heart rate (QTc) interval
- Changes from baseline in clinical laboratory tests

Secondary Efficacy Endpoint

- Mean change from baseline over 48 weeks in trough FEV1 for all subjects

Other Efficacy Endpoints

- Mean change from baseline over 48 weeks in peak FEV1 in the sub-study population
- Mean percent changes from baseline over 48 weeks in trough FEV1 for all subjects
- Mean standardized change from baseline over 48 weeks in FEV1 AUC from 0 to 12 hours (AUC0-12) in the sub-study population

- Mean change from baseline over 48 weeks in trough forced vital capacity (FVC) for all subjects
- Number and percent of trough responders (where response was defined as an increase of at least 0.100 L from baseline in FEV1) at Week 48
- Number and percent of responders (where response was defined as an increase of at least 0.100 L from baseline in FEV1), as well as the time to onset of response, on Day 1 in the sub-study population
- Change from baseline in health status measured by St George's Respiratory Questionnaire (SGRQ)
- Number of rescue medication puffs per day
- Number and percent of subjects with supplemental ipratropium use
- Change from baseline in Respiratory Symptoms Total Score measured by the Exacerbations of Chronic Pulmonary Disease Tool (EXACT)
- Number of rescue medication-free days
- Change in COPD symptoms
- Incidence of COPD exacerbations, defined as an increase in COPD symptoms (e.g., dyspnea, cough, sputum volume, or sputum purulence) during at least 2 consecutive days, and classified as mild (self-managed with increased short-acting bronchodilator and/or ICS use), moderate (treated with antibiotics and/or systemic corticosteroids, but not requiring hospitalization), or severe (requiring overnight stay at hospital or emergency room). Any event occurring within 30 days of a prior event was considered a continuation of the index event.
- Time to onset of first COPD exacerbation

Efficacy Endpoint Parameters

Secondary Efficacy Parameters

Spirometry
Spirometry assessments were to be performed using a standardized, PC-based pneumotach spirometry system. Spirometry will involve the determination of FEV1, FVC, and FEV1/FVC ratio. Predicted FEV1 was to be obtained using the normal prediction equations obtained from The Third National Health and Nutrition Examination Survey (NHANES III). Spirometry measurements will be conducted in accordance with the current ATS/ERS 2005 guidelines (Miller 2005).

Reviewer comment: The use of ATS/ERS Spirometry criteria (2005) is appropriate.

EXACT ePRO
Respiratory symptoms will be recorded using the EXACT, an electronic patient-reported outcome (ePRO) instrument designed to standardize the method for evaluating the frequency, severity, and duration of COPD exacerbations in clinical trials. The EXACT assesses patients' breathlessness, cough and sputum, chest symptoms, difficulty bringing up sputum, feeling tired or weak, sleep disturbance, and feeling scared or worried about their condition with a 14-item questionnaire (Leidy 2010 The EXACT PRO Initiative). The EXACT is to be completed by the study subject via the eDiary.

SGRQ
Each subject will complete the SGRQ at the clinical site prior to dosing or any study-related procedures. The SGRQ is a standardized disease-specific, 50-item questionnaire designed to measure impact on overall health, daily life, and perceived well-being in patients with obstructive airway disease (Jones 1991).

COPD Symptoms
COPD symptoms will be assessed each day in the eDiary.

Device Use Questionnaire
Subjects randomized to SUN-101 will be administered a questionnaire at Visit 11 (Week 48) or at the early termination visit to assess their use of the study drug device.

Safety Assessments
The Investigator or appropriate designee will review results of safety assessments on a regular basis and the Sponsor must be kept fully informed of any clinically significant findings throughout the study.

Adverse Events
Adverse events will be collected for each subject. Subjects should be queried in a non-leading manner, without specific prompting (e.g., "Has there been any change in your health status since your last visit?").

AEs and SAEs will be monitored throughout the study at all visits including the follow-up telephone contact 5 to 7 days after the last study treatment.

Clinical Laboratory Tests
Samples will be processed at a central laboratory to ensure consistency. All clinical laboratories will be College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendments (CLIA) (or equivalent) certified.

Vital Signs
Vital signs will consist of supine systolic and diastolic blood pressures and heart rate. Vital signs will be obtained after the subject has rested in the supine position for at least 5 minutes, prior to the performance of an ECG, clinical laboratory collection, and spirometry measurements for each shared time point.

Centrally-read ECG and Holter Monitoring
Centrally-read ECG: ECGs will be obtained while the subject is in the supine position, after the subject has been resting supine for at least 5 minutes. ECGs will be 12-lead with a 10-second rhythm strip. ECGs should be obtained after recording vital signs and prior to drawing blood samples or performing spirometry assessments for each shared time point. All attempts should be made to use the same ECG recorder for all visits within individual subjects. ECGs will be centrally read at a core lab according to established quality assurance procedures for inter/intra reader variability.

Holter Monitor: Data collected from the monitor may be held at the core laboratory for future extraction or may undergo ongoing over-read for Holter parameters. Holter analysis may be initiated based on interim and/or retrospective reviews of the study data. Immediate over-reads may be performed at the Investigator's discretion.

Physical Examinations and Chest Auscultation
Physical examinations will evaluate the major body systems in order to identify any clinically significant disease or abnormality that, in the opinion of the Principal Investigator, would exclude a subject from the study or preclude further study participation. Physical examinations will be performed by the Principal Investigator, or a designee with appropriate medical qualifications who is experienced and routinely conducts physical examinations.

COPD Exacerbations
A COPD exacerbation was defined as an increase in clinician-assessed COPD symptoms (eg, dyspnea, cough, sputum volume, or sputum purulence) during at least 2 consecutive days, and was classified as follows:

- Mild: self-managed with increased short-acting bronchodilator and/or ICS use
- Moderate: treated with antibiotics and/or systemic corticosteroids, but not requiring hospitalization
- Severe: requiring overnight stay at hospital or emergency room

Any event occurring within 30 days of a prior event was considered a continuation of the index event. For example, if a subject had COPD exacerbations on Days 10, 25, and 50, they were all considered 1 event, as the event on Day 25 was within 30 days of the event on Day 10, and the event on Day 50 was within 30 days of the event on Day 25 (which was previously associated with the event on Day 10). The occurrence and severity of COPD exacerbations was captured on the AE page of the eCRF.

Treatment Compliance

Subjects recorded dosing information in an eDiary.

Proper administration of study drug was assessed by the site staff during each study visit. Subjects were instructed to bring all used (e.g., empty drug vials) and unused study drug and nebulizer devices to each study visit.

Designated site staff documented evidence of noncompliance with either study drug administration or completion of the eDiary and, if warranted, reinstructed the subject(s) to complete the eDiary.

Safety Parameters

The investigator or appropriate designee reviewed results of safety assessments on a regular basis and Sunovion was kept fully informed of any clinically significant findings throughout the study. All events with a potential to be considered as MACE were reviewed by a blinded independent adjudication committee. Where the finding of the adjudication committee differed from investigator opinion, the committee ruling took precedence for the MACE endpoint only, i.e., all adverse events were reported in the adverse event database as reported by the Principal Investigator.

Ethics

The study was conducted according to the protocol, International Council for Harmonization (ICH) Good Clinical Practice (GCP), ICH guidelines, and the ethical principles that have their origin in the Declaration of Helsinki.

5.3.3 Study EP-101-04

Administrative Information

- **Study title**: A randomized, double blind, placebo-controlled, dose-ranging study of the efficacy and safety of EP-101 (GP) in subjects with moderate-to-severe chronic obstructive pulmonary disease: GOLDEN-2 (Glycopyrrolate for obstructive lung disease via electronic nebulizer)
- **Study dates:** Oct 2012- Apr 2013
- **Study sites:** 24 sites in the US
- **Study report date:** November 12, 2015

Objectives/Rationale

Primary Objectives

The primary objective of this study was to compare each dose of GP to placebo administered twice daily (BID) via the eFlow closed-system nebulizer following 4 weeks of treatment in subjects with moderate-to-severe COPD.

Secondary Objectives

The secondary objective of this study was to assess the safety and tolerability of GP.

Study Design and Conduct

Overview

EP-101-04 was a randomized, double-blind, placebo-controlled, parallel group study. The study population consisted of subjects 35 to 75 years of age, with a diagnosis of moderate-to-severe COPD according to the Global Initiative for Chronic Obstructive Lung Disease guidelines (GOLD-2011).

Upon confirmation that all study eligibility criteria were met at Visit 3, each subject was centrally randomized to 1 of 5 treatment arms via an interactive web-based response system (IWRS). Randomization was stratified by inhaled corticosteroid (ICS) use (current ICS users versus non-ICS users) and by subject participation in extended spirometry assessments (yes/no). Randomized subjects entered a 1-week placebo run-in period, which provided training on the use of the eFlow nebulizer. Following successful completion of the placebo run-in period, subjects were entered into the 28-day treatment period.

Figure 5. Study EP101-04 Schematic

Screening		Placebo Run-in	Treatment Period					Follow-up
Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
Up to 3 weeks[a]		Days -7 to -1 Randomization	Day 1	Day 7	Day 14	Day 21 Telephone Contact	Day 28 EOS/ET	Day 35 Telephone Contact

Abbreviations: EOS = End of Study; ET = Early Termination.
[a] Up to 7 weeks for specific subjects

Source: Module 5.3.5.1 CSR EP 101-04, Figure 1, Page 22

The schedule of assessments is summarized in

Table 7.

Table 7. Schedule of Assessments EP101-04

Period	Screening[a]		Placebo Run-in[b]	Treatment Period					Follow-up
Visit	1	2	3	4[c]	5[c]	6	7[l]	8[m]	9[l]
Day	-28 to -7		-7 to -1	1	7 ± 1	14 ± 1	21 ± 1	28 ± 1	35 ± 1
Procedure									
Informed Consent	X								
Inclusion/Exclusion Review	X	X							
Study Eligibility Assessment	X	X	X						
Medical History	X								
Physical Examination	X							X	
Clinical Laboratory Tests[d]	X							X	
Serum Pregnancy Test[d]	X								
Urine Pregnancy Test[d]				X				X	
24-Hour Holter Monitoring[e]		X							
12-Lead ECG[f]	X			X	X			X	
Vital Sign Measurements[f]	X	X		X	X			X	
Spirometry[g]		X		X	X			X	
Daily eDiary Completion[h]			X	X	X	X	X	X	
SGRQ-C Completion[i]				X				X	
Sponsor's Device Survey								X	
Randomization[j]			X						
Study Drug Dispensation			X	X	X	X			
Study Drug Administration (in-clinic)			X	X	X			X	
Adverse Events[k]	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X

Abbreviations: ECG = Electrocardiogram; EXACT = EXAcerbations of Chronic Pulmonary Disease Tool; PRO = patient-reported outcome; SGRQ-C = St. George's Respiratory Questionnaire for COPD Patients.

[a] Procedures at screening Visits 1 and 2 may have been combined into 1 visit if the subject did not require any prohibited medication wash-out regimen(s). Screening visit(s) occurred between Day -28 and Day -7. Treatment period Visit 4 (Day 1) occurred within 28 days after commencement of screening Visit 1 (except for specific subjects per the administrative letter #2 described in Section 9.8.1).

[b] Each randomized subject participated in a 1-week placebo run-in period (Day -7 to Day -1) using the eFlow nebulizer. The subject began this period only after study eligibility was confirmed and the subject was randomized into the study.

[c] On Treatment Visits 4, 5, and 8 (Days 1,7, and 28), applicable subjects were discharged from the clinic following 12 hour post-morning dose procedures and following the evening dose in the clinic, but were to come back the next morning to complete protocol required assessments. Assessments conducted the next morning were considered part of the same visit.

[d] Clinical laboratory tests are defined in Protocol Section 19 in Appendix 16.1.1. Serum pregnancy test for female subjects ≤ 65 years of age of child-bearing potential were performed during Screening (Visit 1). Urine pregnancy test for female subjects ≤ 65 years of age of child-bearing potential were performed at Visit 4 (Day 1) and Visit 8 (Day 28).

[e] 24-hour Holter monitoring during Screening was performed only for subjects who had confirmed study-qualifying spirometry results.

[f] Vital signs/ECG were measured at Screening at Visit 8. Vital sign and 12-lead ECG assessments were measured during each applicable Treatment Period Visit at the following time points: within 30 minutes predose and 1 hour after the morning dose.

[g] Study-qualifying spirometry assessments during the Screening Period were only performed after the subject had completed the appropriate protocol-specified washout regimen of prohibited medications. Serial spirometry was performed during each applicable Treatment Period Visit at the following time points: 45 minutes and 15 minutes predose; and 15 and 30 minutes and 1, 2, 4, 6, 9, 12, 23 hours 30 min, and 24 hours after the morning dose. In a subset of subjects, additional assessments were also performed at the following time points on Treatment Visits 4, 5, and 9 (Days 1, 7, and 28); 13, 14, and 16 hours post-morning dose (ie, 1, 2, and 4 hours post-evening dose).

[h] During the Placebo Run-in Period and Treatment Period, subjects completed an eDiary (dosing information and rescue medication use twice daily, and EXACT-PRO once daily [before bedtime]).

[i] Subjects also completed the SGRQ-C electronically at the clinical site during Treatment Period Visits 4 and 8 (Days 1 and 8).

[j] Randomization only occurred after eligibility for study entry was confirmed at Visit 3 (ie, after spirometry and Holter monitoring results were verified).

[k] AE monitoring began once the subject signed the informed consent and continued until 7 days after the last dose of study medication.

Visit 7 and Visit 9 were telephone contacts. Sites contacted each subject via telephone on Day 21 (Visit 7) and on Day 35 (Visit 9) to monitor AEs and concomitant medication use.

[l] Visit 7 and Visit 9 were telephone contacts. Sites contacted each subject via telephone on Day 2 (Visit 7) and on Day 35 (Visit 9) to monitor AEs and concomitant medication use.

[m] Visit 8 was the End of Study/Early Termination visit. Subjects who discontinued prior to Visit 8 were to undergo procedures scheduled for Visit 8 at the time of discontinuation (except study drug dispensation).

Source Module 5.3.5.1 CSR EP 101-04, Table 2, Page 23

Population

Eligible subjects included males and females 35 through 75 years old with moderate-to-severe COPD (GOLD 2011); current or ex-smokers; post-bronchodilator lung function (FEV1 ≥ 30% and ≤ 70% predicted, FEV1/FVC ratio < 0.70) with reversibility (FEV1 ≥ 12% and ≥ 100 mL); and the ability to perform reproducible spirometry.

Prohibited Medications

Subjects were not permitted to use any of the following medications during the screening period up through completion of the 28-day treatment period, and met the minimum specified wash-out period prior to performing the study-qualifying spirometry assessments during the screening period:

- Tiotropium required minimum 14-day wash-out;
- Aclidinium required minimum 7-day wash-out;
- Long-acting β2-agonists (LABA; e.g., formoterol, salmeterol, indacaterol) required minimum 48-hour wash-out;
- Short-acting bronchodilators (e.g., albuterol, ipratropium) required minimum 8-hour wash-out.
- Theophylline required minimum 24-hour wash-out.

None of the above medications were permitted throughout the 28-day treatment period, except for albuterol MDI as rescue medication.

The following medications were not permitted any time within 7 days prior to beginning the screening period up through completion of the 28-day treatment period:

- Sympathomimetics
- Xanthines and methylxanthines
- Other anticholinergics
- Tricyclic antidepressants
- Phenothiazines
- Anti-Parkinson's drugs
- Beta-blockers
- Other investigational drugs
- Any medication that was thought by the Principal Investigator to have the potential to jeopardize the safety of study subjects.

Permitted Medications

Albuterol MDI was provided and permitted as rescue medication for use any time during the study and was withheld prior to each study visit for at least 8 hours and for the duration of each visit, unless medically necessary. If albuterol MDI was used within 8 hours of spirometry testing the visit was rescheduled within the established window or delayed to allow the appropriate wash-out. If albuterol MDI was required during any visit spirometry assessments were continued as scheduled.

Any subjects taking LAMA (e.g., tiotropium, aclidinium) underwent the specified wash-out prior to performing study-qualifying spirometry during the screening period. For these subjects, sites were permitted to replace LAMA use with ipratropium bromide MDI during the screening period and placebo run-in. However, subjects were to strictly adhere to the minimum 8-hour withholding requirement for ipratropium MDI prior to study-qualifying spirometry assessments and prior to Visit 4 (Day 1).

ICS and PDE-4 inhibitor (e.g., roflumilast) use was permitted during the study provided that the subject had been on a stable dosing regimen for at least 4 weeks prior to the screening period and would continue the same regimen throughout the 28-day treatment period. Subjects using fixed combinations of ICS/LABA (e.g., fluticasone/salmeterol, budesonide/formoterol) prior to the study discontinued use and were prescribed the same or equivalent dose of ICS contained in the combination product to allow for the appropriate withholding period of LABA prior to study visits. LABA use was prohibited during the screening period up through completion of the 28-day treatment period.

The investigator was required to contact Sunovion Pharmaceuticals to discuss any necessary changes to these medications or any other medications not listed here that could impact the outcome of the study.

The following medications or therapies were permitted during the course of the study. Any medications or therapies not listed here were subject to approval by the Principal Investigator. The investigator could contact Sunovion for input as necessary.

- Daily oxygen therapy (not to exceed 10 hours/day)
- Mucolytics (not containing bronchodilators)
- Immunotherapy (allergy shots)
- Influenza or other routinely-required vaccinations
- Intranasal, topical, or ophthalmic corticosteroids
- Intranasal anticholinergics

Treatment Groups

Table 8. Treatment groups: Study EP101-04					
Substance	**GP**	**GP**	**GP**	**GP**	**Placebo**
Unit strength (mcg)	12.5 mcg	25 mcg	50 mcg	100 mcg	
Pharmaceutical form	Inhalation Solution				
Frequency	Twice a day				
Route of administration	Inhalation via eflow CS device				
Source: Module 5.3.5.1: CSR Study EP101-04, Page 28					

Efficacy Endpoints

Primary Efficacy Endpoint
Change from baseline in morning trough FEV1 on Day 28 (trough FEV1 was defined as the average of the 23.5 and 24 hour measurements collected after the in-clinic morning dose of study medication). While the actual measurement takes place on the day following the in-clinic dose of study medication (i.e., Day 29), the measure hereafter is referred to the morning trough on Day 28.

Secondary Efficacy Endpoint
The standardized change from baseline FEV1 AUC (0-12)h and AUC (12-24)h, and the peak FEV1 change from baseline on Day 28. (Hereafter standardized AUC will be referred to simply as AUC.)

Safety Endpoints
The number and percentage of subjects with treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (SAEs), or treatment-emergent adverse events leading to study medication discontinuation. Other safety assessments included clinical laboratory tests, vital sign measurements, 12-lead ECGs, 24-hour Holter monitoring, physical examinations, and concomitant medications.

Treatment Compliance
Subjects recorded dosing information utilizing the eDiary. Proper administration of study medication was assessed by the site during each treatment period visit. Subjects were instructed to bring all used (e.g., empty drug vials) and unused study medication and nebulizer device components to each study visit. Designated site staff thoroughly documented and re-instructed the subject any time after significant noncompliance was noted.

Safety Parameters
Subjects were queried in a non-leading manner, without specific prompting (e.g., "Has there been any change in your health status since your last visit?").

Ethics
This study was conducted in accordance with the protocol, ICH GCP and the ethical principles that had their origin in the Declaration of Helsinki. The study was conducted in accordance with applicable local law(s) and regulation(s).

The efficacy parameters and subsequent analysis have previously been described for studies SUN101-301 and 302; the statistical plan for study EP101-04 was generally similar in nature. The primary efficacy endpoint analysis is summarized below.

Statistical Plan

Analysis of Efficacy
All efficacy endpoints were summarized for the ITT population using descriptive statistics. Significance tests were 2-sided and conducted at an alpha level of 0.05, unless otherwise specified.

Analyses of the primary and secondary efficacy endpoints were also performed using the per protocol population.

Baseline for all spirometry measures was defined as the mean of the 2 pre-dose FEV1 values at 45 minutes and 15 minutes pre-dose at Treatment Visit 4 (Day 1). If one of these time points had a missing value, then the non-missing measurement was used.

Primary Analysis
The primary efficacy endpoint was the change from baseline in morning trough FEV1 at Day 28. Trough FEV1 was defined as the mean of the 2 FEV1 values obtained at 23 hours 30 minutes and 24 hours after the in-clinic morning dose (i.e., approximately 12 hours after the previous evening dose). The change in trough FEV1 was calculated as trough FEV1 minus baseline FEV1. Analysis tables presented the number of subjects with a trough FEV1 measurement at Day 28, the least squares mean (LS Mean) change from baseline, the standard error of the LS Mean change from baseline, the 95% confidence interval (CI) for the LS Mean change from baseline, and similar statistics for comparisons between each GP treatment arm and placebo. P-values were also displayed for each comparison between GP treatment arms and placebo.

The primary efficacy endpoint was analyzed for the ITT population by means of an MMRM, with change from baseline in trough FEV1 as the response variable and with factors for treatment group, ICS use (yes/no), subject participation in extended spirometry assessments (yes/no), scheduled visit day, and scheduled visit day by treatment group interaction, and baseline FEV1 as a covariate. An unstructured covariance model was used to model intra-subject correlation in conjunction with treating subject as a random effect. From this model, the least squares means for change in trough FEV1 were estimated for each treatment group at each scheduled visit day. The primary comparisons of interest were the comparisons of the change from baseline in trough FEV1 following the Day 28 morning dose between each of the 4 doses

of GP and placebo. To control for multiple comparisons, a sequential gate-keeping procedure was used.

5.3.4 Study SUN101-201

Administrative Information

- **Study title**: A dose-range finding study of SUN 101 (GP) in subjects with moderate-to-severe COPD: GOLDEN 6 (Glycopyrrolate for obstructive lung disease via electronic nebulizer)
- **Study dates:** Jan 2014 – May 2014
- **Study sites:** 10 clinical sites in the United States
- **Study report date:** November 23, 2015

Objectives/Rationale

Primary Objective
The primary objective of this study was to determine the efficacy and dose-response profile of GP administered twice daily (BID) via the eFlow nebulizer following 7 days of treatment in subjects with moderate-to-severe COPD.

Secondary Objective
The secondary objective of this study was to assess the safety and tolerability of GP.

Other Objective
The other objective of this study was to assess the pharmacokinetic (PK) profile of GP.

Study Design and Conduct

Overview

This was a randomized, 6-way crossover study. The study population consisted of subjects 40 to 65 years of age (inclusive), with a diagnosis of moderate-to-severe COPD. Aclidinium 400 mcg BID was given as an active comparator. The study was double-blind for GP and placebo, and open-label for aclidinium.

The schedule of assessments is summarized in Table 9.

Table 9. Schedule of Assessments SUN101-201

Study Period	Screening[a]	Treatment Period 1		Washout 5-7 Days After Day 7	Treatment Periods 2-6		Washout	Early Termination[b]	Follow-Up Phone Contact[c]
Study Day	-14 to -1	1	7	24-72 Hours After the Last PM Dose (Day 8-10)[d]	1	7	5-7 Days After Day 7	NA	
Procedure									
Informed Consent	X	-	-	-	-	-	-	-	-
Eligibility Assessment	X	X	-	-	-	-	-	-	-
Medical History and Demographics	X	-	-	-	-	-	-	-	-
Physical Examination (Including Height and Weight)	X	-	-	-	-	-	-	-	-
Randomization	-	X	-	-	-	-	-	-	-
Pregnancy Test[e]	X	-	-	-	-	-	-	-	-
Clinical Laboratory Tests[f]	X	-	-	-	-	-	-	-	-
PK Sampling[g]	-	X	X	X	-	-	-	-	-
24-hour Holter Monitoring[h]	X	-	-	-	-	-	-	-	-
Vital Signs[i]	X	X	X	-	X	X	-	X	-
12-Lead ECG[i]	X	X	X	-	X	X	-	X	-
Spirometry[j]	X	X	-	-	X	-	-	X	-
Serial Spirometry[k]	-	-	X	-	-	X	-	-	-
Dispense Drugs/Study Supplies	X	X	-	-	X	-	-	-	-
Collect Used/Unused Drug/Supplies	-	-	X	-	-	X	-	X	-
Administer Dose In-Clinic[l]	-	X	X	-	X	X	-	-	-
Concomitant Medications	X	X	X	X	X	X	-	X	X
Adverse Events	X	X	X	X	X	X	-	X	X
Schedule Next Visit	X	X	X	X	X	X	-	X	-

Abbreviations: ECG = electrocardiogram; NA = not applicable; PK = pharmacokinetic.

[a] Screening may have occurred over more than 1 clinic visit. Screening may have been up to 2 weeks.
[b] Any subject who discontinued the study prior to completing all treatment periods was required to have early termination procedures and assessments performed at the time of discontinuation.
[c] Follow-up phone contact was required to be conducted 5 to 7 days after completion of Day 7 of the last treatment period for subjects who completed all scheduled treatment periods or 5 to 7 days after the Early Termination Visit for subjects who discontinued the study prior to completing all scheduled treatment periods.
[d] Subjects randomly assigned to blinded SUN-101 or placebo only.
[e] Serum pregnancy test was performed for female subjects of childbearing potential only at Screening.
[f] Samples for clinical safety laboratory tests (chemistry, hematology, and urinalysis) were obtained for all subjects at Screening only.
[g] Blood sampling for pharmacokinetics were obtained within 15 minutes prior to the morning dose on Day 1. (NOTE: PK samples were not collected from subjects who were randomly assigned to receive aclidinium in the first treatment period). On Day 7, blood samples for pharmacokinetics were obtained at the following time points (1 sample per time point/window): within 15 minutes prior to the morning dose, 0.25-0.5 hours, 1.5-2.5 hours, 6-8 hours, 12 hours (± 15 minutes), 13-16 hours, and 24 hours (± 15 minutes) after the morning dose on Day 7 of the first treatment period only. A final blood sample was obtained between 24-72 hours after the final (evening) dose on Day 7 of the first treatment period only. (NOTE: PK samples were not collected from subjects who were randomly assigned to receive aclidinium in the first treatment period).
[h] At Screening, 24-hour Holter monitoring was performed for all subjects to determine study eligibility.
[i] At Screening, 12-lead ECGs and vital signs were performed on all subjects. On Day 1, vital signs and 12-lead ECG were performed on all subjects within 30 minutes prior to morning dose. On Day 7, 12-lead ECGs and vital signs were performed for all subjects within 30 minutes prior to the morning dose and at 1 hour (± 5 minutes) after the morning dose.
[j] Spirometry was performed at Screening to confirm study eligibility. Spirometry was performed on Day 1 at 45 and 15 minutes prior to the morning dose as a baseline measure.
[k] On Day 7, serial spirometry was performed at 45 and 15 minutes prior to the morning dose and at 5, 15, and 30 minutes; 1, 2, 4, 6, 8, 10, 14, 20, and 22 hours; 23 hours 15 minutes; and 23 hours 45 minutes after the morning dose. Spirometry assessments performed prior to and up to 1 hour after dosing had a window of ± 5 minutes; all spirometry assessments beginning with the 2-hour postdose time point had a window of ± 15 minutes.
[l] Subjects took the morning dose in the clinic on Day 1 and took their morning and evening doses in the clinic on Day 7.

Source Module 5.3.5.1 CSR SUN101-201, Table 2, Page 19

Population

Male and female subjects between the ages of 40 to 65 years (inclusive) with a clinical diagnosis of moderate to severe COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (GOLD 2011). In addition, subjects were to be current smokers or ex-smokers; have post-bronchodilator (following inhalation of ipratropium) measurements during screening of forced expiratory volume in 1 second (FEV1) ≥ 40% and ≤ 70% of predicted normal, FEV1/FVC (forced vital capacity) ratio ≤ 0.70, and improvement in FEV1 ≥ 12% and ≥ 100 mL; and the ability to perform reproducible spirometry, and ability to participate in study assessments and/or procedures. All subjects had to be willing and able to remain at the clinical site for at least 24 hours at Day 7 of each treatment period.

Prohibited Medications

Subjects were not permitted to use any of the following medications during Screening and were required to meet the minimum specified washout period prior to performing the study-qualifying spirometry assessments during Screening:

- Long-acting muscarinic antagonist bronchodilators (e.g., tiotropium, aclidinium) required a minimum 5-day washout
- Long-acting β2-agonists bronchodilators (e.g., formoterol, salmeterol, indacaterol) required a minimum 48-hour washout
- Short-acting bronchodilators (e.g., ipratropium) required a minimum 6-hour washout
- Theophylline required a minimum 24-hour washout

None of the above medications were permitted throughout study duration except for albuterol MDI provided by the clinical site as rescue medication and aclidinium for the treatment period during which the subject was to receive aclidinium as an open-label active comparator study medication.

Any subjects taking a LAMA were to undergo the specified washout period prior to performing study-qualifying spirometry assessments during Screening. For these subjects, clinical sites were permitted to replace tiotropium and aclidinium with ipratropium MDI during Screening. However, subjects were to strictly adhere to the minimum 6-hour withholding requirement for ipratropium prior to study-qualifying spirometry assessments and prior to beginning Treatment Period 1. Once the subject was deemed eligible to enter the study, ipratropium use was discontinued and was not allowed for the duration of the study.

Permitted Medications

Albuterol was provided and permitted as rescue medication for as-needed use any time during the study. Albuterol was required to be withheld for at least 6 hours prior to each study visit and for the duration of each treatment visit, unless medically necessary. If rescue albuterol was used within 6 hours of the serial spirometry testing for any study visit, then the visit was rescheduled

or delayed (not more than 1 day later) to allow for the appropriate washout. If rescue albuterol was required post dose on Day 7, serial spirometry assessments were performed as scheduled.

To confirm study eligibility during Screening, each subject was administered ipratropium and pre- and post-bronchodilator spirometry assessments were performed. Ipratropium was also allowed to replace treatment with LAMAs during Screening as described in Section 9.4.7.1.1. Ipratropium was not permitted after randomization.

Albuterol and ipratropium were considered NIMP for use in this study. Both medications were administered according to their approved product labeling and were provided by Sunovion or by the clinical site.

ICS and phosphodiesterase-4 inhibitor (e.g., Roflumilast) use was permitted during the study provided that the subject had been on a stable dosing regimen (i.e., same dose and frequency) for at least 4 weeks prior to Screening and the dosing regimen remained constant through the end of study participation. The ICS was to be withheld for at least 12 hours prior to each study visit.

Subjects using fixed combinations of ICS and LABA (e.g., fluticasone/salmeterol) prior to the study were required to discontinue use and were prescribed the same or equivalent dose of ICS contained in the combination product to allow for the appropriate withholding period of the LABA prior to Screening.

Treatment Groups

Table 10. Treatment groups: Study SUN-101-201

Substance	GP	GP	GP	GP	Placebo	Aclidinium
Unit strength (mcg)	3 mcg	6.25 mcg	12.5 mcg	50 mcg	-	400 mcg
Pharmaceutical form	Inhalation Solution					DPI
Route of administration	Inhalation via eflow CS device					Pressair inhaler device
Frequency	Twice a day					

DPI=dry powder inhaler
Source: Module 5.3.5.1: CSR Study SUN101-201, Page 23

Efficacy Endpoints

Primary Efficacy Endpoint
The change from baseline in trough FEV1 at Treatment Visit Day 7 compared to placebo. Trough FEV1 was defined as the mean of FEV1 values obtained at 23 hours 15 minutes and 23 hours 45 minutes after the morning dose on Treatment Visit Day 7.

Key Secondary Efficacy Endpoint
The standardized change from baseline in FEV1 AUC0-12h.

Secondary Safety Endpoint
The number and percentage of subjects with treatment-emergent AEs (TEAEs; overall and by treatment).

Other Safety Endpoints
- Number and percentage of subjects with treatment-emergent SAEs (overall and by treatment)
- Number and percentage of subjects with TEAEs leading to discontinuation (overall and by treatment)
- Changes from baseline (prior to morning dose on Day 1) to trough (prior to morning dose on Day 7) and changes from prior to morning dose to 1 hour after the morning dose on Day 7 in vital sign and ECG parameters

Other Endpoints
The plasma concentrations of GP (measured as glycopyrrolate) were the other endpoints.

Treatment Compliance
Compliance and proper administration of study medication was assessed by the clinical site during each on-treatment visit.

Subjects were instructed to bring all used (e.g., empty drug vials) and unused IMP (including aclidinium) and nebulizer devices to each study visit. Designated clinical site staff evaluated study medication compliance by questioning the subject and evaluating the amount of study medication remaining at the end of each treatment period. The subject was asked to clarify any discrepancies.

Designated clinical site staff documented and re-instructed the subject after any significant Non-compliance was noted.

Safety
Safety was assessed by AEs, vital sign measurements, and 12-lead ECG results.

Ethics
This trial was designed and monitored in accordance with sponsor procedures, which comply with the ethical principles of Good Clinical Practice (GCP) as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki.

The efficacy parameters and subsequent analysis have previously been described for studies SUN101-301 and 302, the statistical plan for study SUN101-201 was generally similar in nature. The primary efficacy endpoint analysis is summarized below.

Primary Efficacy Analysis
The primary efficacy endpoint was the change from baseline in trough FEV1 approximately 24 hours after the morning dosing on Day 7. The change from baseline to trough was calculated for each treatment period as trough FEV1 minus baseline FEV1. Baseline was defined as the mean of the FEV1 values at 45 and 15 minutes prior to the morning dose on Day 1 for each respective treatment period. The average of the 2 spirometry values collected at 23 hours 15 minutes and at 23 hours 45 minutes after the morning dose on Day 7 of each treatment period was deemed the trough value and utilized for analyses.

The primary efficacy endpoint was analyzed for the efficacy population by means of an analysis of covariance (ANCOVA) model, with change from baseline in trough FEV1 as the response variable and with factors for treatment, period, treatment sequence, and the first-order carryover as fixed effects and baseline FEV1 as a covariate.

6 Review of Efficacy

Efficacy Summary

To support the proposed indication, the Applicant submitted data from two dose ranging studies (EP101-04 and SUN101-201) and two replicate 12-week confirmatory trials (SUN101-301 and SUN101-302). Study EP101-04 was a 28-day randomized, double blind, placebo-controlled, parallel group dose ranging study of glycopyrrolate (GP) in patients with moderate-to-severe COPD. Study SUN101-201 was a randomized, double-blind, placebo-controlled, open label, active control, 6-way crossover study with a 7-day treatment period and 5-7 day washout period. Studies SUN101-301 and SUN101-302 were replicate, 12-week, randomized, double-blind, placebo-controlled, multicenter studies to assess the efficacy and safety of GP 25 mcg and 50 mcg inhaled via the eflow CS nebulizer BID versus placebo in patients with moderate-to-severe COPD.

SUN101-301 and SUN101-302 enrolled adult male and female subjects aged ≥ 40 years of age with a clinical diagnosis of moderate-to-very severe COPD according to the GOLD 2014 guidelines. In addition, subjects were current or ex-smokers with ≥ 10 pack-year smoking history, with a post-bronchodilator (following inhalation of ipratropium bromide) FEV1 of < 80% of predicted normal and greater than 0.7 L, an FEV1/FVC ratio less than 0.70, and had the ability to perform reproducible spirometry according to the ATS/ERS guidelines. Patients were excluded at screening if there was concomitant clinically significant respiratory disease other than COPD (e.g., asthma, tuberculosis, bronchiectasis or other non-specific pulmonary disease), a recent history of COPD exacerbation requiring hospitalization or need for increased treatments for COPD within 6 weeks prior to screening, or use of daily oxygen therapy > 12 hours per day. Subjects were randomized to 1 of 3 treatments in a 1:1:1 ratio in studies SUN101-301 and SUN101-302, with approximately 430 subjects treated with either GP 25 mcg BID, GP 50 mcg BID, or placebo.

Baseline demographics were fairly balanced across treatment groups and were generally representative of the population in whom COPD is known to occur. The median age for the 2 studies ranged from 63-64 years, with a majority being white (86-92%) males (51-59%), <65 years of age (50-62%). These studies were conducted fully in the United States. Of the study population, 7 to 13% were black patients.

The primary endpoint in SUN101-301 and SUN101-302 was change from baseline in trough FEV1 at Week 12. The LS mean treatment difference for change from baseline in trough FEV1 was statistically significant for GP 25 mcg and GP 50 mcg versus placebo at 12 weeks (GP 25 mcg: 0.0961 L, 95% CI [0.0589, 0.1334], p<0.0001, GP 50 mcg: 0.1036 L, 95% CI [0.0663, 0.1409], p<0.0001 and GP 25 mcg: 0.0810 L, 95% CI [0.0416, 0.1204], p<0.0001, GP 50 mcg: 0.0736 L, 95% CI [0.0346, 0.1127], p=0.0002), respectively for both studies (SUN101-301 and SUN101-302).

The secondary endpoint SGRQ, when analyzed via a responder analysis, where a response was defined an improvement in score of 4 or more, demonstrated that all the results are in the direction to favor the GP treated groups in both studies and both dose levels. However, the logistic regression model analyses only demonstrated a statistically significant effect vs. placebo for the 25 mcg group in study SUN101-302 (SUN101-301 GP 25 mcg: 49.7% (OR: 1.486 [0.974, 2.267]), GP50: 44.1% (OR: 1.215 [0.791, 1.866]), Placebo: 39.7%. SUN101-302 GP 25 mcg: 43.7% (OR: 1.906 [1.220, 2.976]) GP 50 mcg: 39.4% (OR: 1.538 [0.985, 2.401]), Placebo 29.6%.)

Overall, the efficacy of GP for the treatment of COPD has been demonstrated. Two replicate 12-week lung function studies showed a statistically significant difference in the primary efficacy endpoint of trough FEV1.

6.1 Indication

The proposed indication for glycopyrrolate inhalation solution administered via the closed system (CS) nebulizer (PARI eFlow) is for the maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

6.1.1 Methods

The focus of this efficacy review is derived from Studies EP-101-04, SUN101-201, SUN101-301, SUN101-302 and SUN101-303.

6.1.2 Demographics

Studies SUN101-301 and SUN101-302

The demographics for the study population in studies SUN101-301 and SUN101-302 are displayed in Table 11.

Table 11. Demographics- SUN101-301 and SUN101-302

	Study SUN101-301			Study SUN101-302		
	GP 25 mcg BID N=217	**GP 50 mcg BID N=218**	**Placebo BID N=218**	**GP 25 mcg BID N=214**	**GP 50 mcg BID N=214**	**Placebo BID N=212**
Female n (%)	99 (45.6)	98 (45.0)	107 (49.1)	90 (42.1)	87 (40.7)	88 (41.5)
Age Categories in Years, n (%)						
Mean age (SD)	63.1 (8.78)	62.5 (8.09)	63.7 (8.37)	63.6 (8.66)	62.6 (9.20)	63.7 (9.26)
Race, n (%)						
White	200 (92.2)	198 (90.8)	196 (89.9)	185 (86.4)	188 (87.9)	192 (90.6)
Black	15 (6.9)	18 (8.3)	20 (9.2)	27 (12.6)	26 (12.1)	19 (9.0)
Asian	1 (0.5)	0	1 (0.5)	0	0	0
American Indian, Alaska Native	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.5)	0	0
Native Hawaiian Pacific Islander	0	1 (0.5)	0	0	0	1 (0.5)
Multi-Racial	0	0	0	1 (0.5)	0	0
Mean BMI kg/m2 (SD)	28.5 (7.11)	28.4 (6.59)	28.8 (6.95)	28.1 (6.78)	28.4 (6.3)	29.3 (6.85)
US site (%)	100%	100%	100%	100%	100%	100%

MBI= body mass index, SD= standard deviation
Source: Module 5.3.5.1, SUN101-301 CSR Page 80, Table 7, SUN101-302 CSR Page 74, Table 7

Baseline demographics were fairly balanced across treatment groups. The median age for the 2 studies ranged from 63-64 years, with a majority being white (86-92%) males (51-59%), <65 years of age (50-62%). These studies were conducted fully in the United States. Of the study population, 7 to 13% were black patients.

The baseline disease characteristics for the study population in studies SUN101-301 and SUN101-302 are displayed in Table 12.

Table 12. Baseline COPD Characteristics- SUN101-301 and SUN101-302

	Study SUN101-301			Study SUN101-302		
	GP 25 mcg BID N=217	**GP 50 mcg BID N=218**	**Placebo BID N=218**	**GP 25 mcg BID N=214**	**GP 50 mcg BID N=214**	**Placebo BID N=212**
Mean FEV_1 (L) pre-bronchodilator (SD)	1.29 (0.468)	1.36 (0.521)	1.31 (0.486)	1.31 (0.488)	1.33 (0.557)	1.33 (0.468)
Pre-Bronchodilator Percent Predicted FEV1(%) mean (SD)	44.8 (13.62)	45.5 (14.70)	45.8 (14.25)	44.6 (14.28)	43.9 (14.34)	45.0 (13.00)
+ COPD exacerbation in the previous year, n (%)	43 (19.8)	35 (16.1)	52 (23.9)	41 (19.2)	38 (17.8)	41 (19.3)
Number of COPD exacerbation in the previous year, n (%)	0.2 (0.53)	0.2 (0.48)	0.3 (0.68)	0.3 (0.59)	0.5 (3.40)	0.5 (3.74)
+ History of Oxygen Use, n (%)	11 (5.1)	11 (5.0)	9 (4.1)	21 (9.8)	7 (3.3)	11 (5.2)
+ LABA use at baseline, n (%)	66 (30.4)	68 (31.2)	63 (28.9)	69 (32.2)	67 (31.3)	69 (32.5)
+ ICS use at baseline, n (%)	62 (28.6)	63 (28.9)	60 (27.5)	64 (29.9)	59 (27.6)	67 (31.6)
Smoking history, n (%)						
Current smoker	124 (57.1)	121 (55.5)	112 (51.4)	116 (54.2)	105 (49.1)	106 (50.0)
Ex-smoker	93 (42.9)	97 (44.5)	106 (48.6)	98 (45.8)	109 (50.9)	106 (50.0)

LABA = long-acting β2 agonist, ICS= Inhaled Corticosteroid, FEV1 = forced expiratory volume in 1 second, SD= standard deviation
History of oxygen use was defined as oxygen use at or prior to baseline, as recorded on the concomitant medication log

Source: Module 5.3.5.1 SUN101-301 CSR Page 81, Tables 7, 8 and 9, SUN101-302 CSR Page 75, Tables 7, 8 and 9.

The COPD characteristics were fairly balanced (with the only exception being a wider spread in the history of exacerbations in the previous year for SUN101-301 GP 50 mcg 16 % vs. Placebo 24%) across treatment groups and typical of the chosen population. A majority of the patients had zero exacerbations in the previous year with mean FEV1 (L) pre-bronchodilator ranging 1.29-1.36 L as seen Table 12.

6.1.3 Subject Disposition

Subject disposition is described in Table 13.

Table 13. Disposition- SUN101-301 and SUN101-302

	Study SUN101-301			Study SUN101-302		
Disposition Reason	**GP 25 mcg BID N=217**	**GP 50 mcg BID N=218**	**Placebo BID N=218**	**GP 25 mcg BID N=214**	**GP 50 mcg BID N=214**	**Placebo BID N=212**
Randomized	217	218	218	214	214	213
Completed study on treatment, n (%)	194 (89.4)	191 (87.6)	176 (80.7)	183 (85.5)	190 (88.8)	177 (83.5)
Completed study, n (%)	203 (93.5)	201 (92.2)	191 (87.6)	193 (90.2)	199 (93.0)	188 (88.7)
Primary reason for early termination from treatment, n (%)						
Adverse Event	8 (3.7)	10 (4.6)	20 (9.2)	15 (7.0)	9 (4.2)	19 (9.0)
Lack of Efficacy	3 (1.4)	2 (0.9)	4 (1.8)	0	3 (1.4)	2 (0.9)
Pregnancy	0	0	0	0	0	0
Noncompliance with Study Medication	0	0	2 (0.9)	2 (0.9)	0	0
Protocol Violation	0	0	0	0	0	1 (0.5)
Other	12 (5.5)	15 (6.9)	16 (7.3)	14 (6.5)	12 (5.6)	13 (6.1)
Primary reason for early termination from study, n (%)						
Lost to Follow Up	2 (0.9)	3 (1.4)	3 (1.4)	6 (2.8)	3 (1.4)	2 (0.9)
Withdrawal by Subject	11 (5.1)	11 (5.0)	22 (10.1)	9 (4.2)	8 (3.7)	15 (7.1)
Death	0	1 (0.5)	0	0	0	0
Other	1 (0.5)	2 (0.9)	2 (0.9)	6 (2.8)	4 (1.9)	7 (3.3)

Source: Module 5.3.5.1, SUN101-301 CSR, Table 14.1.1, Page 2, SUN101-302 CSR, Table 14.1.1, Page 2

Most patients completed the study (88-94%) on treatment (81-89%). The number of patients who discontinued from treatment and the study was also fairly balanced, with higher premature discontinuations in the placebo group. The most common reason for premature discontinuation from the study was withdrawal by subject.

6.1.4 Analysis of Primary Endpoint(s)

The primary objective of the studies was to demonstrate the superiority of GP compared to placebo in terms of change from baseline in FEV_1 AUC0-12h at Week 12.

Table 14. LS Mean Difference in Change From Baseline in Trough FEV_1 (L)at Week 12 All Collected Data (ITT)– SUN101-301 and SUN101-302

		Treatment Difference			
Study Treatment	**CFB in Trough FEV_1 LS Mean (SE)**	**LS Mean (SE) Vs. Placebo**	**95% CI**	**p-value**	**Adjusted p-value [1]**
Study SUN101-301					
All Collected Data [a]					
GP 25 mcg BID N=217, n=202	0.0886 (0.01369)	0.0961 (0.01896)	(0.0589, 0.1334)	<0.0001	<0.0001
GP 50 mcg BID N=218, n=201	0.0961 (0.01371)	0.1036 (0.01900)	(0.0663, 0.1409)	<0.0001	-
Placebo N=218, n=194	-0.0075 (0.01397)	-	-	-	-
Study SUN101-302					
All Collected Data					
GP 25 mcg BID N=214, n=191	0.0921 (0.01446)	0.0810 (0.02006)	(0.0416, 0.1204)	<0.0001	0.0001
GP 50 mcg BID N=214, n=198	0.0847 (0.01423)	0.0736 (0.01989)	(0.0346, 0.1127)	0.0002	-
Placebo N=212, n=186	0.0111 (0.01452)	-	-	-	-

BID = twice daily; CFB = change from baseline; CI = confidence interval; FEV1 = forced expiratory volume in 1 second; ITT = intent to treat; L = liter(s); LS = least squares; MMRM = mixed model repeated measures; SE = standard error, N= ITT population, n= patients with data collected at baseline and week 12.

[a] All collected values were used for the analysis regardless of on-treatment/off-treatment or whether they were affected by other medication use.
[1]Adjusted p-value based on alpha level at 0.025 is obtained if the p-value of the comparison between SUN-101 50 mcg vs. placebo < 0.05.

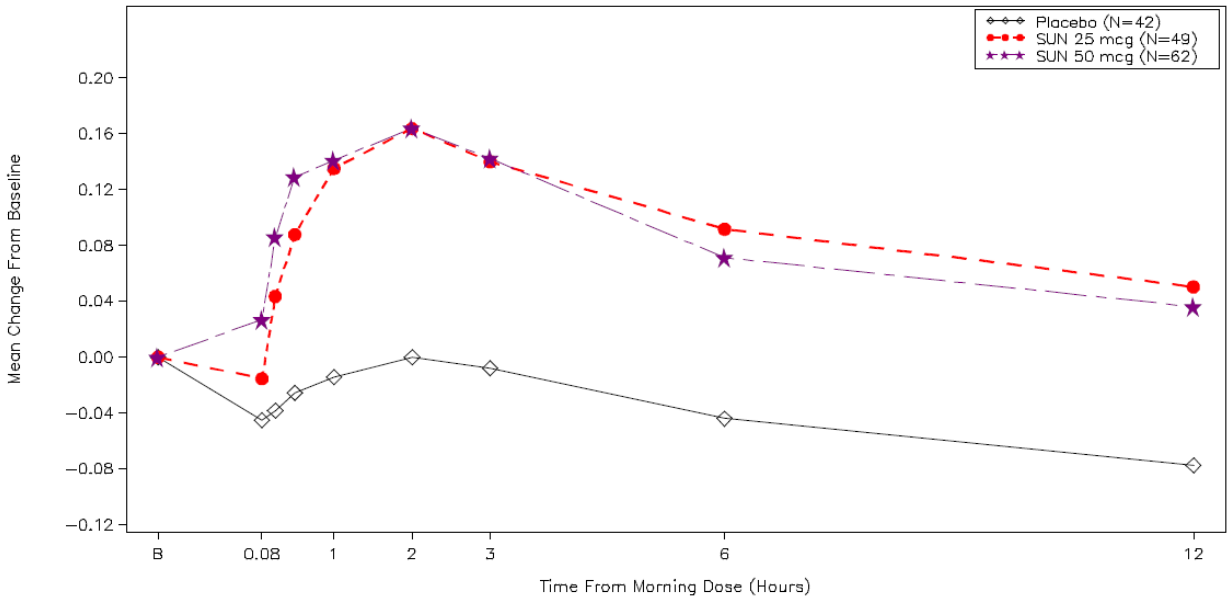
Note: Baseline is the average of the 45 and 15 minute pre-dose FEV1 values at Visit 2 (Week 0). Trough FEV1 is the average of the FEV1 values collected at the end of the dosing interval at each clinic visit. FEV1 = Forced Expiratory Volume in One Second, SD = Standard Deviation, SE = Standard Error, CFB = Change from Baseline. LS Means (Least Squares Means) are from a MMRM model with CFB in trough FEV1 at each visit as the response variable and with factors for treatment group, cardiovascular risk, week, background LABA use, and treatment by week interaction, with baseline FEV1 as a covariate. An unstructured covariance structure is used to model the intrasubject variability. Comparison LS Means are SUN-101 treatment change from baseline minus placebo change from baseline. All collected values are used for this analysis regardless of on-treatment/off-treatment or whether they are affected by other medication use. MMRM = Mixed Model with Repeated Measurements.

Source: Module 5.3.5.1, SUN101-301 CSR, Table 19, Page 100, Table 14.2.1.2, Page 216, SUN101-302 CSR, Table 14.2.1.2, Page 173

As described in Table 14, the LS mean treatment difference for change from baseline in trough FEV1 was statistically significant for GP 25 mcg and GP 50 mcg versus placebo at 12 weeks (GP 25 mcg: 0.0961 L, 95% CI [0.0589, 0.1334], p<0.0001, GP 50 mcg: 0.1036 L, 95% CI [0.0663, 0.1409], p<0.0001 and GP 25 mcg: 0.0810 L, 95% CI [0.0416, 0.1204], p<0.0001, GP 50 mcg: 0.0736 L, 95% CI [0.0346, 0.1127], p=0.0002), respectively for both studies (SUN101-301 and SUN101-302).

Serial spirometric evaluations throughout the 12-hour dosing interval were performed in a subset of subjects at Week 0 and Week 12 in study SUN101-301, and are displayed in Figure 6 and Figure 7. As seen in the figures, bronchodilation was maintained for 12 hours Week 0 (Day 1) and Week 12 for both GP doses.

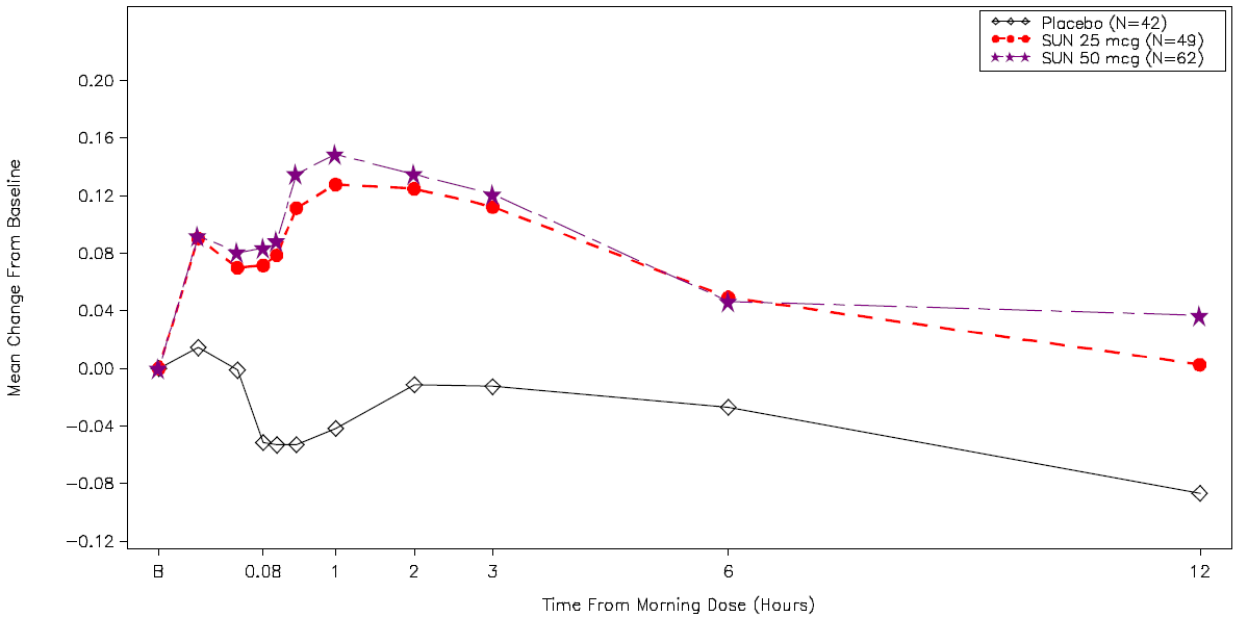
Figure 6. Mean Change from Baseline in FEV_1 (L) Over Time by Visit: All Collected Data (Sub-study Population) at Week 0 – Study SUN101-301



SUN 25= GP 25 mcg, SUN50 = GP 50 mcg, FEV1 = forced expiratory volume in 1 second.
Note: Baseline was the average of the 45- and 15-minute pre-dose FEV1 values on Visit 2 (Week 0). All collected values were used for this analysis regardless of on-treatment/off-treatment or whether they were affected by other medication use. This data was collected in a sub-study population.

Source: Module 5.3.5.1, SUN101-301 CSR, Figure 9, Page 111

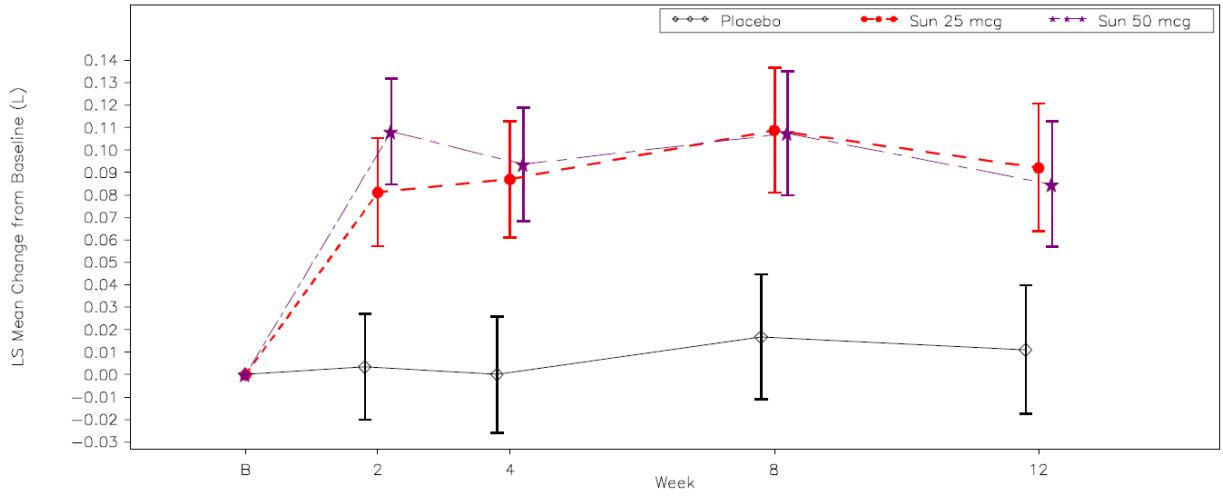
Figure 7. Mean Change from Baseline in FEV_1 (L) Over Time by Visit: All Collected Data (Sub-study Population) at Week 12 – Study SUN101-301



SUN 25= GP 25 mcg, SUN50 = GP 50 mcg, FEV1 = forced expiratory volume in 1 second.
Note: Baseline was the average of the 45- and 15-minute pre-dose FEV1 values on Visit 2 (Week 0). All collected values were used for this analysis regardless of on-treatment/off-treatment or whether they were affected by other medication use. This data was collected in a sub-study population.

Source: Module 5.3.5.1, SUN101-301 CSR, Figure 10, Page 111

Figure 8. Mean Change from Baseline in Trough FEV_1 (L) by Visit Week: All Collected Data- Study SUN101-302



Baseline is the average of the 45 and 15 minute pre-dose FEV1 values at Visit 2 (Week 0). Trough FEV1 is the average of the FEV1 values collected at the end of the dosing interval at each clinic visit. LS Means (Least Squares Means) are from a MMRM model with CFB in trough FEV1 at each visit as the response variable and with factors for treatment group, cardiovascular risk, week, background LABA use, and treatment by week interaction, with baseline FEV1 as a covariate. An unstructured covariance structure is used to model the intrasubject variability. All collected values are used for this analysis regardless of on-treatment/off-treatment or whether they are affected by other medication use. FEV1 = Forced Expiratory Volume in One Second, CFB = Change from Baseline, MMRM = Mixed Model with Repeated Measurements.

Source: SUN101-302 CSR Tables and Figures, Figure 14.2.1.3, Page 151

While serial spirometry was not conducted in SUN101-302, routine spirometry was conducted and Figure 8 demonstrates the bronchodilator effect of GP was maintained at Week 12.

6.1.5 Analysis of Key Secondary Endpoints(s)

FEV_1 AUC (0-12)h

Table 15. Standardized Change From Baseline at Week 12 in FEV_1 AUC (0-12)h in Liters– SUN101-301 (Sub-study Population)

		Treatment Difference			
Treatment	**CFB trough FEV_1 LS Mean (SE)**	**LS Mean (SE)**	**(95% CI)**	**p-value**	**Adjusted p-value[a]**
Study SUN101-301					
Trough FEV_1 AUC0-12					
GP 25 mcg BID N=49, n=45	0.058 (0.0301)	0.105 (0.0422)	(0.0219, 0.1888)	0.0137	0.0547
GP 50 mcg BID N=62, n=57	0.075 (0.0264)	0.122 (0.0400)	(0.0432, 0.2014)	0.0027	0.0162
Placebo N=42, n=33	-0.047 (0.0323)	-	-	-	-

CFB: change from baseline, AUC0-12 = area under the curve from 0 to 12 hours; BID = twice daily; CFB = change from baseline; CI = confidence interval; FEV1 = forced expiratory volume in 1 second; L = liter(s); LS = least squares; MMRM = mixed model repeated measures; SE = standard error.

[a] Adjusted P values are based on the Hochberg procedure.

Note: Data collected in a sub-study population. All collected values were used for the analysis regardless of on-treatment/off-treatment or whether they were affected by other medication use. Baseline is the average of the 45 and 15 minute pre-dose FEV1 values at Visit 2 (Week 0). LS Means (Least Squares Means) are from a MMRM model with FEV1 AUC(0-12) at each visit as the response variable and with factors for treatment group, week, cardiovascular risk, background LABA use, and treatment by week interaction, with baseline FEV1 as a covariate. An unstructured covariance structure is used to model the intra-subject variability. Comparison LS Means are GP treatment change from baseline minus placebo change from baseline.

Source: Module 5.3.5.1, SUN101-301 CSR, Table 21, Page 106 , Table 14.2.2.4.1, Page 851

As shown in Table 15, in the SUN101-301 sub-population, the standardized change from baseline at Week 12 in FEV_1 AUC0-12 resulted in improvements relative to placebo for GP 25 mcg BID, however, these differences did not reach statistical significance (0.1053 L, p=0.0547). Treatment with GP 50 mcg BID yielded a 0.1223L improvement from baseline at Week 12 in

FEV_1 AUC0-12 relative to placebo, which was statistically significant (p=0.0162). The results for FEV1 AUC0-12 at week 12 were likely affected by the small sample size (performed only in a sub population for study SUN101-301) and despite a lack of statistical significance for the 25 mcg dose, provide additional support for the primary endpoint.

Trough FVC

Table 16. LS Mean Difference in Change From Baseline in Trough FVC at Week 12: All Collected Data and On-treatment Data (ITT Population) – SUN101-301 and SUN101-302

		Treatment Difference			
Treatment	**CFB trough FEV_1 LS Mean (SE)**	**LS Mean (SE)**	**(95% CI)**	**p-value**	**Adjusted p-value[a]**
Study SUN101-301					
Trough FVC					
GP 25 mcg BID N=217, n=202	0.152 (0.0222)	0.137 (0.0309)	(0.0761, 0.1974)	<0.0001	<0.0001
GP 50 mcg BID N=218, n=201	0.148 (0.0223)	0.133 (0.0310)	(0.0720, 0.1936)	<0.0001	0.0002
Placebo N=218, n=194	0.015 (0.0227)	-	-	-	-
Study SUN101-302					
GP 25 mcg BID N=214, n=191, 192	0.135 (0.0224)	0.119 (0.0311)	(0.0580, 0.1800)	0.0001	0.0008
GP 50 mcg BID N=214, n=198	0.109 (0.0221)	0.093 (0.0308)	(0.0330, 0.1539)	0.0025	0.0101
Placebo N=212, n=186	0.016 (0.0225)	-	-	-	-

Note: Baseline is the average of the 45 and 15 minute pre-dose FVC values at Visit 2 (Week 0). Trough FVC is the average of the FVC values collected at the end of the dosing interval at each clinic visit. FVC = Forced Vital Capacity, SD = Standard Deviation, SE = Standard Error, CFB = Change from Baseline. LS Means (Least Squares Means) are from a MMRM model with CFB in trough FVC at each visit as the response variable and with factors for treatment group, cardiovascular risk, week, background LABA use, and treatment by week interaction, with baseline FVC as a covariate. An unstructured covariance structure is used to model the intra-subject variability. Comparison LS Means are GP treatment change from baseline minus placebo change from baseline. All collected values are used for this analysis regardless of on-treatment/off-treatment or whether they are affected by other medication use. MMRM = Mixed Model with Repeated Measurements.
[a] Adjusted p-values are based on the Hochberg procedure.

Source: Module 5.3.5.1, SUN101-301 CSR, Table 22, Page 107 , Table 14.2.2.1.1, Page 529, SUN101-302 CSR Table 21, Page 99, Table 14.2.2.1.1, Page 486

As seen in Table 16, the LS mean differences at Week 12 were 0.137 L and 0.133 L in the GP 25 mcg and GP 50 mcg groups in study SUN101-301 and 0.119 L and 0.093 L in the GP 25 mcg and GP 50 mcg groups in SUN101-302, respectively. These results provide additional data in support of the primary efficacy endpoint.

SGRQ

As seen in Table 17, the secondary endpoint, SGRQ, when analyzed via a responder analysis, where a response was defined an improvement in score of 4 or more, demonstrated that all the results are in the direction to favor the GP treated groups in both studies and both dose levels. However, the logistic regression model analyses only demonstrated a statistically significant effect vs. placebo for the 25 mcg group in study SUN101-302 (SUN101-301 GP 25 mcg: 49.7% (OR: 1.486 [0.974, 2.267]), GP50: 44.1% (OR: 1.215 [0.791, 1.866]), Placebo: 39.7%. SUN101-302 GP 25 mcg: 43.7% (OR: 1.906 [1.220, 2.976]) GP 50 mcg: 39.4% (OR: 1.538 [0.985, 2.401]), Placebo 29.6%.)

Table 17. SGRQ Responder Analysis at Week 12- SUN101-301 and SUN101-302

Study SUN101-301			
	Placebo BID (n = 218) n (%)	**GP 25 mcg BID (n = 217) n (%)**	**GP 50 mcg BID (n = 217) n (%)**
# of subjects with evaluable data	179	189	179
Responder	71 (39.7)	94 (49.7)	79 (44.1)
Non-responder	108 (60.3)	95 (50.3)	100 (55.9)
Odds Ratio (95% CI)		1.486 (0.974, 2.267)	1.215 (0.791, 1.866)
Study SUN101-302			
	Placebo BID (n = 212) n (%)	**GP 25 mcg BID (n = 217) n (%)**	**GP 50 mcg BID (n = 217) n (%)**
# of subjects with evaluable data	186	183	188
Responder	55 (29.6)	80 (43.7)	74 (39.4)
Non-responder	131 (70.4)	103 (56.3)	114 (60.6)
Odds Ratio (95% CI)		1.906 (1.220, 2.976)	1.538 (0.985, 2.401)

Source: Statistical Review Mingyu Xi, PhD.

Rescue Medication Use

Table 18. Change in Number of Rescue Medication Puffs per Day Over the 12-week, Double-blind Treatment Period (ITT Population) – SUN101-301 and SUN101-302

		Treatment Difference			
Treatment	**CFB trough FEV_1 LS Mean (SE)**	**LS Mean (SE)**	**(95% CI)**	**p-value**	**Adjusted p-value[a]**
Study SUN101-301					
Trough FVC					
GP 25 mcg BID N=217, n=212,193	-0.609 (0.1259)	0.024 (0.1700)	(-0.310, 0.357)	0.8896	>0.9999
GP 50 mcg BID N=218, n=216, 204	-0.815 (0.1234	-0.183 (0.1676)	(-0.512, 0.147)	0.2765	0.5529
Placebo N=218, n=213, 199	-0.632 (0.1257)	-	-	-	-
Study SUN101-302					
GP 25 mcg BID N=214, n=208, 192	-0.959 (0.1310)	-0.281 (0.1797)	(-0.634, 0.072)	0.1186	0.2371
GP 50 mcg BID N=214, n=212, 192	-0.845 (0.1311)	-0.167 (0.1797)	(-0.520, 0.186)	0.3544	0.7087
Placebo N=212, n=207, 183	-0.678 (0.1339)	-	-	-	-

Note: Baseline is the average of puffs per day during the run-in period. Puffs per day over 12 week double-blind treatment period is the average of puffs per day over the 12 week double-blind treatment period. SD = Standard Deviation, SE = Standard Error, CFB = Change from Baseline. LS Means (Least Squares Means) are from an ANCOVA model with CFB in rescue medication puffs per day as the response variable and with factors for treatment group, cardiovascular risk, and background LABA use and with baseline rescue medication puffs per day as a covariate. Comparison LS Means are GP treatment change from baseline minus placebo change from baseline. All collected values are used for this analysis regardless of on-treatment/off-treatment. ANCOVA = Analysis of Covariance.
[a] Adjusted p-values are based on the Hochberg procedure.

Source: Module 5.3.5.1, SUN101-301 CSR, Table 24, Page 109, Table 14.2.2.3.1, Page 777, SUN101-302 CSR Table 23, Page 101, Table 14.2.2.3.1, Page 734

As shown in Table 18, treatment with either dose of GP did not demonstrate a reduction in rescue medication use relative to placebo over the 12-week treatment period in studies SUN101-301 and SUN101-302.

6.1.6 Other Endpoints

Change From Baseline in Peak FEV_1 at Week 0 and Week 12 (Sub-study Population SUN101-301)

In the study SUN101-301 sub-study population, the mean change from baseline in peak FEV_1 in the placebo group was 0.0932 L (95% CI: 0.0331, 0.1533) at week 12. The peak change in FEV_1 was (0.2135 L [95% CI: 0.1511, 0.2759]) and (0.2354 L [95% CI: 0.1782, 0.2925]) for the GP 25 mcg and GP 50 mcg dose groups, respectively. These results provide further support of the primary endpoint.

Standardized Change From Baseline at Week 0 and Week 12 in FEV_1 AUC0-3 (Sub-study Population SUN101-301)

In the study SUN101-301 sub-study population, treatment with GP 25 mcg resulted in improvement from baseline in FEV_1 AUC0-3 compared with placebo at Week 0 (LS mean difference: 0.1325) and Week 12 (LS mean difference: 0.1450). Similar improvements were noted in the GP 50 mcg treatment group; at Week 0 (LS mean difference: 0.1436) and Week 12 (LS mean difference: 0.1632). These results are consistent with the results reported for the primary endpoint.

Number of Rescue Medication-free Days per Week

There were no meaningful changes from baseline in the number of rescue medication-free days for GP 25 mcg and GP 50 mcg in both studies SUN101-301 and SUN101-302.

Number and Percent of Subjects With Supplemental Ipratropium Use

During the screening period in study SUN101-301, ipratropium was used by 22 (10.1%) subjects in the placebo group, 26 (12.0%) subjects in the GP 25 mcg group, and 23 (10.6%) subjects in the GP 50 mcg group. During the treatment period, between Week 0 and Follow-Up, supplemental ipratropium use was similar in each treatment group (16 - 18 subjects per treatment group; 7.3% - 8.3%).

During the screening period in study SUN101-302, ipratropium was used by 17 (8.0%) subjects in the placebo group, 15 (7.0%) subjects in the GP 25 mcg group, and 16 (7.5%) subjects in the GP 50 mcg group. The overall use between Week 0 and Follow-up was similar for the placebo (18 [8.5%] subjects) and the GP 50 mcg (18 [8.4%] subjects) and slightly lower (14 [6.5%] subjects] for the GP 25 mcg group.

Incidence of COPD Exacerbations

From Week 0 to Follow-up, in study SUN101-301, 6% (13/217) of subjects in the GP 25 mcg group and 11% (24/218) of subjects in the GP 50 mcg group had COPD exacerbations. Exacerbations were classified as severe, moderate, and mild in the GP 25 mcg group; 0.9%, 4.6%, and 0.5%, respectively. Exacerbations in the GP 50 mcg group were similarly classified according to severity; severe 2.3%, moderate 8.3%, and mild 0.5%. The placebo group demonstrated similar results with 9.6% (21/218) of subjects experiencing a COPD exacerbation; 1.8% classified as severe, 6.9% classified as moderate, and 0.9% classified as mild.

From Week 0 to Follow-up, in study SUN101-302, 10.3% (22/214) of subjects in the GP 25 mcg group and 8.4% (18/214) of subjects in the GP 50 mcg group had COPD exacerbations. Exacerbations in the GP 25 mcg group were classified as severe, moderate and mild (0.9%, 7.9%, and 1.4%, respectively). In the GP 50 mcg group, exacerbations were classified as severe 1.4%, moderate 6.1%, and mild 0.9%. In the placebo group, 10.4% (22/212) of subjects had

COPD exacerbations; of these, 2.4% were severe, 7.5% were moderate, and 0.5% were mild in severity.

Overall, the incidences of mild, moderate, and severe COPD exacerbations were similar across the treatment groups with majority being moderate. There was a slight trend for a reduction in severe exacerbations in the GP 25 mcg group compared to GP 50 mcg and placebo groups.

Time to Onset of First COPD Exacerbation

In study SUN101-301, the median number of days to the onset of the first COPD exacerbation in subjects with at least one exacerbation were 31.0 days (range: 6 to 104 days) in the placebo group, 23.0 days (range: 2 to 70 days) in the GP 25 mcg group, and 32.0 days (range: 3 to 92 days) in the GP 50 mcg group.

In study SUN101-302, the median number of days to the onset of the first COPD exacerbation in subjects with at least one exacerbation were 31.0 days (range: 1 to 83 days) in the placebo group, 36.0 days (range: 1 to 85 days) in the GP 25 mcg group, and 42.0 days (range: 8 to 87 days) in the GP 50 mcg group.

Exacerbations were a rare event, with an incidence of 6-11%, and therefore it is difficult to draw further conclusions from the time to event data.

6.1.7 Subpopulations

The final statistical review was pending at the time of this review. Therefore, the following subgroup analysis was based on a preliminary statistical review of the data.

Subgroup analysis on the primary endpoint are shown by three demographic factors: age (< 65, 65-74, >=75), sex (F, M), and race (White, Non-White) and four baseline disease characteristics: baseline in-check PIFR (< 30, 30-60, 60-90, > 90), spirometry PIFR (<= 60, > 60-90, > 90-120, > 120-150, > 150-180, > 180-210, > 210), background LABA use (yes, no), and baseline COPD severity (< 30% Predicted, >= 30% to 50 % Predicted, >= 50% Predicted). Due to all the clinical trials being conducted in the US, there were no subgroup analyses on geographic region.

Subgroup analysis on the key secondary efficacy endpoint (change from baseline in trough FVC at week 12) are shown by the same three demographic factors: age (< 65, 65-74, >=75), sex (F, M), and race (White, Non-White) and one baseline disease characteristic: baseline COPD severity (< 30% Predicted, >= 30% to 50 % Predicted, >= 50% Predicted).

The tables and figures below summarize the efficacy results by subgroups for studies SUN101-301 and SUN101-302. In general, the subgroup analyses were consistent with the primary and key secondary results from the overall population. However, these studies were not designed or powered to detect differences in these specific groups.

Table 19. Subgroup Analysis on Primary Endpoint: Change from Baseline FEV1 at Week 12- SUN101-301

	Mean Difference of FEV1 25 mcg					Mean Difference of FEV1 50 mcg					Interaction Test p-value
	N	Est.	LL	UL	p-value	N	Est.	LL	UL	p-value	
----Age Group----	.	.	.	.	.	.	.	.	.	.	0.5122
< 65	122	0.076	0.025	0.127	0.0037	135	0.109	0.058	0.159	<0.0001	.
65 - 74	73	0.114	0.054	0.175	0.0002	66	0.078	0.016	0.140	0.014	.
>= 75	22	0.184	0.060	0.308	0.0037	17	0.197	0.067	0.328	0.0031	.
----Sex----	.	.	.	.		.	.	.	.		0.0795
F	99	0.106	0.052	0.159	0.0001	98	0.072	0.018	0.125	0.0090	.
M	118	0.086	0.035	0.137	0.0010	120	0.128	0.077	0.179	<0.0001	.
----Race----	.	.	.	.		.	.	.	.		0.1235
White	200	0.105	0.066	0.144	<0.0001	198	0.107	0.067	0.146	<0.0001	.
Non-white	17	-0.0005	-0.125	0.124	0.9932	20	0.077	-0.041	0.194	0.1994	.
----In-Check PIFR----	.		.	.	.	.		.	.	.	0.6007
< 30	9	0.108	-0.094	0.310	0.2937	7	0.226	0.012	0.441	0.0389	.
30 – 60	50	0.035	-0.042	0.112	0.3732	51	0.068	-0.010	0.146	0.0858	.
60 – 90	46	0.104	0.016	0.191	0.0204	49	0.137	0.051	0.222	0.0018	.
> 90	111	0.123	0.072	0.174	<0.0001	111	0.098	0.047	0.150	0.0002	.
----Spirometry PIFR----	.	.	.	.			.	.	.	.	0.0422
<= 60	16	0.129	-0.020	0.277	0.0889	10	0.122	-0.047	0.291	0.1544	
> 60 - 90	30	0.110	0.012	0.208	0.0284	29	0.083	-0.015	0.180	0.0984	.
> 90 - 120	40	0.123	0.040	0.206	0.0038	39	0.127	0.042	0.211	0.0036	.
> 120 - 150	45	0.144	0.050	0.237	0.0026	33	0.077	-0.023	0.176	0.1306	.
> 150 -180	26	-0.046	-0.163	0.071	0.4368	28	0.123	0.009	0.237	0.0341	.
> 180 -210	20	0.053	-0.082	0.189	0.4418	17	0.200	0.056	0.339	0.0063	.
> 210	15	0.104	-0.032	0.240	0.1340	19	0.084	-0.045	0.213	0.2004	.
---- Background LABA Use----	.	.	.	.		.	.	.	.	.	0.8372
Y	66	0.071	0.002	0.140	0.0433	68	0.081	0.012	0.149	0.0212	.
N	151	0.106	0.061	0.150	<0.0001	150	0.112	0.067	0.157	<0.0001	.
----COPD Severity----	.	.	.	.		.	.	.	.	.	0.3378
<30% Predicated	12	0.070	-0.090	0.230	0.3898	16	0.094	-0.058	0.246	0.2231	
>= 30% to 50% Predicated	83	0.067	0.005	0.128	0.0338	82	0.072	0.010	0.133	0.0223	
>= 50% Predicted	121	0.121	0.073	0.170	<0.0001	120	0.134	0.085	0.183	<0.0001	

Source: Statistical Review: Mingyu Xi, PhD.

Gender, Race, and Age

Table 19 summarizes the results of study SUN101-301 on the primary endpoint change from baseline of trough FEV1 at Week 12. The analysis population is all collected data of ITT. As seen in the table, there was a treatment-by-gender interaction effect with interaction p-value of 0.0795. Treatment with both doses of GP demonstrated improvements in trough FEV1 in both male and female subgroups at Week 12. The mean, placebo-adjusted trough FEV1 increased by 0.086 L and 0.128 L in male subjects in the GP 25 mcg and 50 mcg treatment groups, respectively. The mean, placebo-adjusted trough FEV1 increased by 0.106 L and 0.072 L in female subjects in the GP 25 mcg and 50 mcg treatment groups, respectively. Due to clinically

in-significant responses within and between the male and female subgroups, the gender subgroup results do not support an alternative dosing recommendation by gender for either the GP 25 mcg or 50 mcg doses.

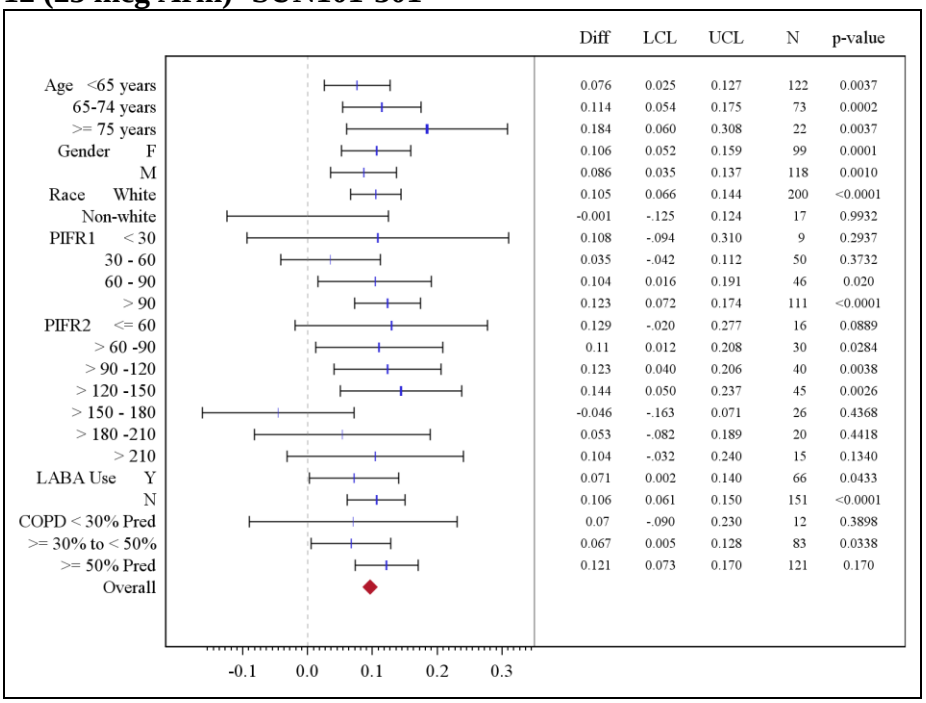
There were no treatment-by-age group interaction effects with interaction p-value of 0.5122 and no treatment-by-race interaction effects with interaction p-value of 0.1235.

Baseline Disease Characteristics

Subgroup analyses were performed on in-check PIFR, spirometry PIFR, background LABA use, and baseline COPD severity on the primary endpoint. Subgroup analyses were performed on baseline COPD severity on the key secondary endpoints.

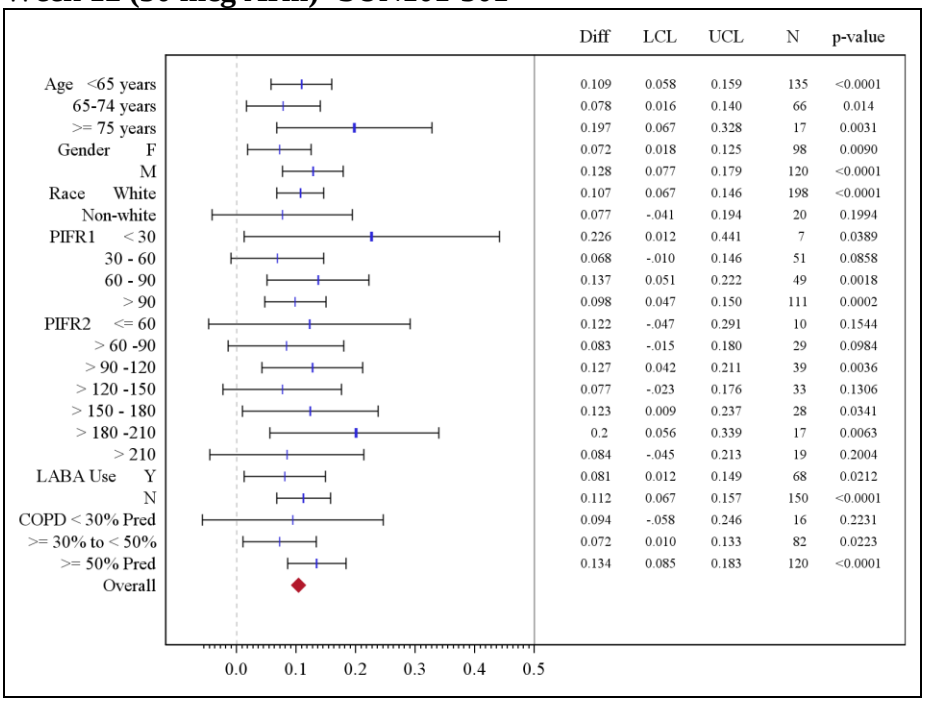
The analysis in Table 19 shows that there was no treatment-by-In-Check PIFR interaction effect with interaction p-value of 0.6007. However, there was a treatment-by-spirometry PIFR interaction effect with interaction p-value of 0.0422. Generally, the mean effects were consistent within each treatment group across the various categories, with the exception that the GP 25 mcg group had a spurious low mean of -0.048 L in the > 150 to 180 L/min category compared to a range of 0.063 to 0.1327 for the other categories, and that the GP 50 mcg group had a spurious high mean of 0.260 L in the > 180 to 210 L/min category compared to a range of 0.057 to 0.121 for the other categories. There was no treatment-by-background LABA interaction with the interaction p-value of 0.8372 and no treatment-by-COPD severity interaction effect with the interaction p-value of 0.3378. Treatment with both doses of GP showed improvements across different COPD severity categories.

Figure 9. Subgroup Analyses on Primary Endpoint: Change from Baseline FEV1 at Week 12 (25 mcg Arm)- SUN101-301



Source: Statistical Review: Mingyu Xi, PhD.

Figure 10. Subgroup Analyses on Primary Endpoint: Change from Baseline FEV1 at Week 12 (50 mcg Arm)- SUN101-301



Source: Statistical Review: Mingyu Xi, PhD.

Table 20. Subgroup Analyses on Primary Endpoint: Change from Baseline FEV_1 at Week 12- SUN101-302

	Mean Difference of FEV1 25 mcg					Mean Difference of FEV1 50 mcg					Interaction Test p-value
	N	Est.	LL	UL	p-value	N	Est.	LL	UL	p-value	
----Age Group----	.	.	.	.	.	.	.	.	.	.	0.7617
< 65	109	0.051	-0.004	0.105	0.0708	119	0.040	-0.013	0.094	0.1378	.
65 - 74	79	0.120	0.055	0.186	0.0004	74	0.136	0.070	0.202	<0.0001	.
>= 75	25	0.096	-0.018	0.210	0.0974	21	0.035	-0.083	0.152	0.5620	.
----Sex----	.	.	.	.		.	.	.	.	.	0.7329
F	89	0.075	0.015	0.136	0.0149	87	0.056	-0.006	0.117	0.0742	.
M	124	0.086	0.034	0.137	0.0012	127	0.086	0.035	0.136	0.0009	.
----Race----	.	.	.	.		.	.	.	.	.	0.2279
White	184	0.085	0.043	0.126	<0.0001	188	0.086	0.044	0.127	<0.0001	.
Non-white	29	0.046	-0.073	0.165	0.4479	26	-0.023	-0.146	0.099	0.7083	.
----In-Check PIFR----	.		.	.	.	.		.	.	.	0.3375
< 30	3	0.174	-0.150	0.497	0.2927	3	0.052	-0.246	0.351	0.7301	.
30 – 60	65	0.073	0.001	0.146	0.0465	70	0.104	0.033	0.175	0.0040	.
60 – 90	45	0.117	0.033	0.200	0.0062	51	0.032	-0.048	0.112	0.4373	.
> 90	100	0.066	0.008	0.125	0.0258	89	0.076	0.017	0.136	0.0120	.
----Spirometry PIFR----	.	.	.	.			.	.	.	.	0.5885
<= 60	8	0.152	-0.040	0.345	0.1201	17	0.120	-0.036	0.275	0.1313	.
> 60 - 90	29	0.030	-0.075	0.135	0.5721	26	0.022	-0.083	0.128	0.6798	.
> 90 - 120	38	0.145	0.054	0.236	0.0018	30	0.082	-0.014	0.178	0.0942	.
> 120 - 150	39	0.086	-0.008	0.180	0.0727	42	0.127	0.036	0.217	0.0062	.
> 150 -180	28	0.002	-0.107	0.111	0.9688	25	0.068	-0.045	0.181	0.2350	.
> 180 -210	16	0.154	0.003	0.304	0.0451	20	0.129	-0.014	0.272	0.0762	.
> 210	28	0.153	0.049	0.256	0.0041	27	0.038	-0.067	0.144	0.4774	.
---- Background LABA Use----	.	.	.	.		.	.	.	.	.	0.7733
Y	69	0.123	0.054	0.192	0.0005	67	0.085	0.015	0.155	0.0173	.
N	144	0.060	0.012	0.108	0.0151	147	0.069	0.021	0.116	0.0044	.
----COPD Severity----	.	.	.	.		.	.	.	.	.	0.1440
<30% Predicated	17	-0.085	-0.238	0.068	0.2752	19	-0.030	-0.178	0.119	0.6969	
>= 30% to 50% Predicated	72	0.054	-0.012	0.119	0.1096	76	0.063	-0.002	0.128	0.0557	
>= 50% Predicted	124	0.118	0.066	0.169	<0.0001	119	0.095	0.043	0.146	0.0003	

Source: Statistical Review: Mingyu Xi, PhD.

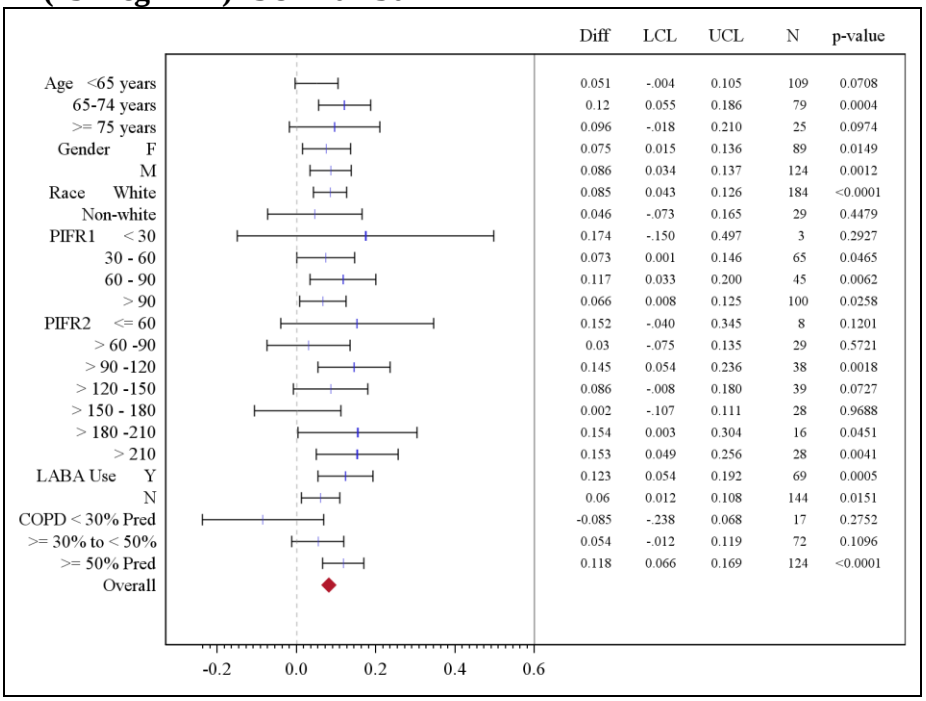
Gender, Race and Age

Table 20 summarizes the results of SUN101-302 on the primary endpoint change from baseline of trough FEV1 at Week 12. The analysis population is all collected data of ITT. There was no treatment-by-gender interaction effect with interaction p-value of 0.7329, no treatment-by-age group interaction effects with interaction p-value of 0.7617 and no treatment-by-race interaction effects with interaction p-value of 0.2279.

Baseline Disease Characteristics

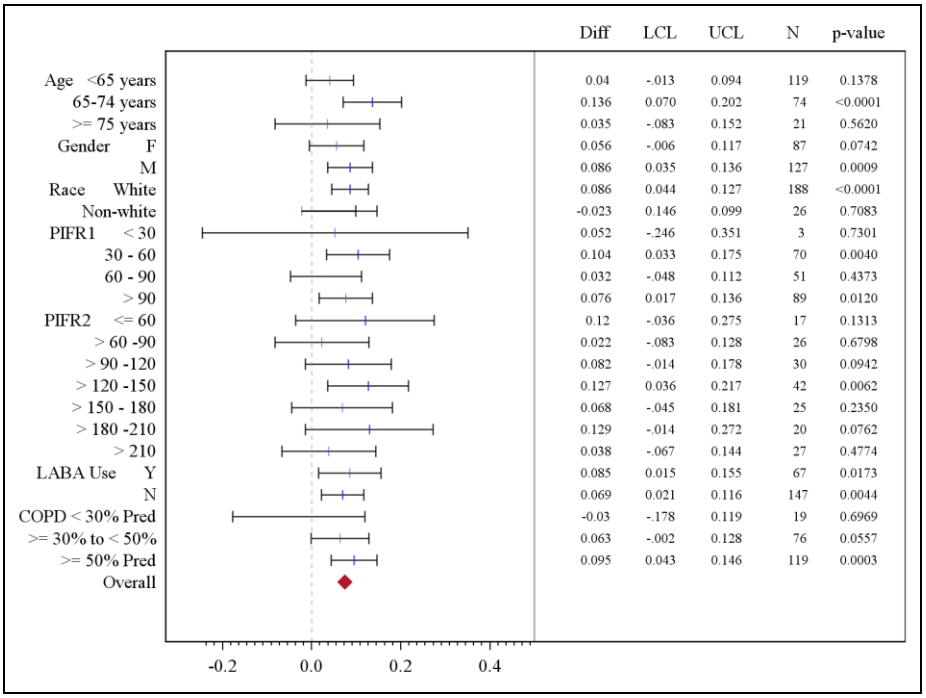
A seen in Table 20, there was no treatment-by-In-Check PIFR interaction effect with interaction p-value of 0.3375, no treatment-by-spirometry PIFR interaction effect with interaction p-value of 0.5885, no treatment-by-background LABA interaction with the interaction p-value of 0.7733 and no treatment-by-COPD severity interaction effect with the interaction p-value of 0.1440.

Figure 11. Subgroup Analyses on Primary Endpoint: Change from Baseline FEV_1 at Week 12 (25 mcg Arm)- SUN101-302



Source: Statistical Review: Mingyu Xi, PhD

Figure 12. Subgroup Analyses on Primary Endpoint: Change from Baseline FEV_1 at Week 12 (50 mcg Arm)- SUN101-302



Source: Statistical Review: Mingyu Xi, PhD

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Study EP-101-04

Study EP-101-04 was a randomized, double-blind, placebo-controlled, parallel group study. The study population consisted of subjects 35 to 75 years of age, with a diagnosis of moderate-to-severe COPD according to the GOLD 2011.

Upon confirmation that all study eligibility criteria were met at Visit 3, each subject was randomized to 1 of 5 treatment arms, stratified by inhaled corticosteroid (ICS) use (current ICS users versus non-ICS users) and by subject participation in extended spirometry assessments (yes/no). Subjects entered into a 28-day treatment period with the following treatment arms:

Table 21. Treatment Arms- Study EP-101-04

Treatment Arm	Treatment Regimen (BID Dosing)
1: SUN-101 Placebo	SUN-101 Placebo AM + SUN-101 Placebo PM
2: SUN-101 12.5 mcg	SUN-101 12.5 mcg AM + SUN-101 12.5 mcg PM
3. SUN-101 25 mcg	SUN-101 25 mcg AM + SUN-101 25 mcg PM
4. SUN-101 50 mcg	SUN-101 50 mcg AM + SUN-101 50 mcg PM
5. SUN-101 100 mcg	SUN-101 100 mcg AM + SUN-101 100 mcg PM

SUN101 = GP
Source: Module 5.3.5.1 EP-101-04 CSR, Page 20

The study population consisted of male and female subjects aged 35 through 75 years with a clinical diagnosis of moderate-to-severe COPD according to GOLD guidelines (GOLD-2011). Spirometry values consisted of the following; post-bronchodilator (following inhalation of ipratropium bromide MDI) FEV1 ≥ 30% and ≤ 70% of predicted normal value during the screening period and post-bronchodilator (following inhalation of ipratropium bromide MDI) FEV1/forced vital capacity (FVC) ratio < 0.70 during the screening period and post-bronchodilator (following inhalation of ipratropium bromide MDI) improvement in FEV1 ≥ 12% and ≥ 100 mL during the screening period.

The primary efficacy endpoint was the change from baseline in morning trough FEV1 on Day 28 (trough FEV1 was defined as the average of the 23.5 and 24 hour measurements collected after the in-clinic morning dose of study medication).

Baseline demographics were generally comparable across the treatment groups. The mean age was 60.5 years (range: 42 to 75 years) and were predominantly White (89.4%). Gender demonstrated some imbalance between the treatment groups; the 50 mcg group had the highest proportion of male subjects (57.9% males), compared to the remaining treatment groups (range: 42.4 to 49.1% males).

At baseline, the majority of subjects (81.9%) did not have any COPD exacerbations in the previous 12 months and 34.0% of subjects were receiving baseline treatment with inhaled corticosteroids. Approximately half (52.8%) of the subjects had ≥ 50% of predicted on the post-bronchodilator FEV1 at baseline and over half (60.3%) of subjects were considered current smokers at baseline. Subjects had smoked 52.9 pack-years on average (range: 10 to 144 pack-years).

Table 22. Subject Disposition- Study EP101-04

Disposition Reason	GP 12.5 mcg BID n (%)	GP 25 mcg BID n (%)	GP 50 mcg BID n (%)	GP 100 mcg BID n (%)	Placebo BID n (%)
Enrolled population[a]	60	59	62	61	
Completed run-in period, but did not enter double-blind period[b]	57 (95.0)	57 (96.6)	59 (95.2)	61 (100.0)	60 (100.0)
Safety population[c]	55 (91.7)	54 (91.5)	57 (91.9)	59 (96.7)	57 (95.0)
ITT population[d]	55 (91.7)	54 (91.5)	57 (91.9)	59 (96.7)	57 (95.0)
Completed double-blind period[e]	51 (92.7)	49 (90.7)	53 (93.0)	57 (96.6)	53 (93.0)
Discontinued during double-blind Period[e]	4 (7.3)	5 (9.3)	4 (7.0)	2 (3.4)	4 (7.0)
Adverse Event	3 (5.5)	4 (7.4)	3 (5.3)	2 (3.4)	2 (3.5)
Withdrawal by Subject	0	1 (1.9)	0	0	1 (1.8)
Lack of Efficacy	0	0	1 (1.8)	0	1 (1.8)
Other	1 (1.8)	0	0	0	0
Noncompliance	1 (1.8)	0	0	0	0

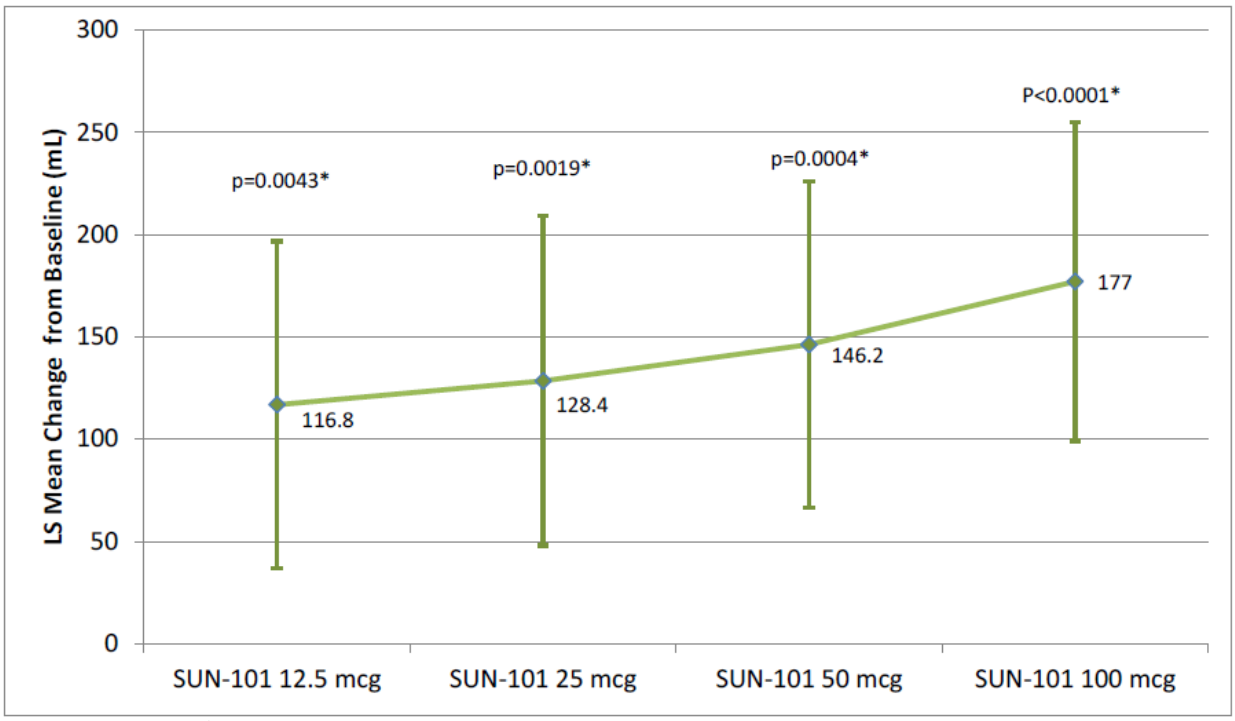
Abbreviations: BID = twice daily; PP = per-protocol; ITT = intent-to-treat.
[a] The enrolled population consisted of all subjects who participated in the run-in period.
[b] The denominator is the enrolled population.
[c] The safety population consisted of all subjects who were randomized to treatment and received at least 1 dose of double-blind study medication. It was expected that the safety population would be the same as the ITT population, although safety analyses were performed using the actual drug a subject received.
[d] The ITT population consisted of all subjects who were randomized to treatment and received at least 1 dose of double-blind study medication.
[e] The denominator is the ITT population.
Note: The treatment assignment for subjects enrolled, ITT population, and PP population is the randomized treatment.

Source: Module 5.3.5.1 Study EP1-04 CSR, Table 3, Page 48

As seen in Table 22, study completion and discontinuation due to adverse events was fairly balanced across the treatment groups.

Efficacy

Figure 13. Change from Baseline in Trough FEV1 on Day 28 Compared with Placebo (with 95% Confidence Intervals) (ITT Population)- Study EP101-04

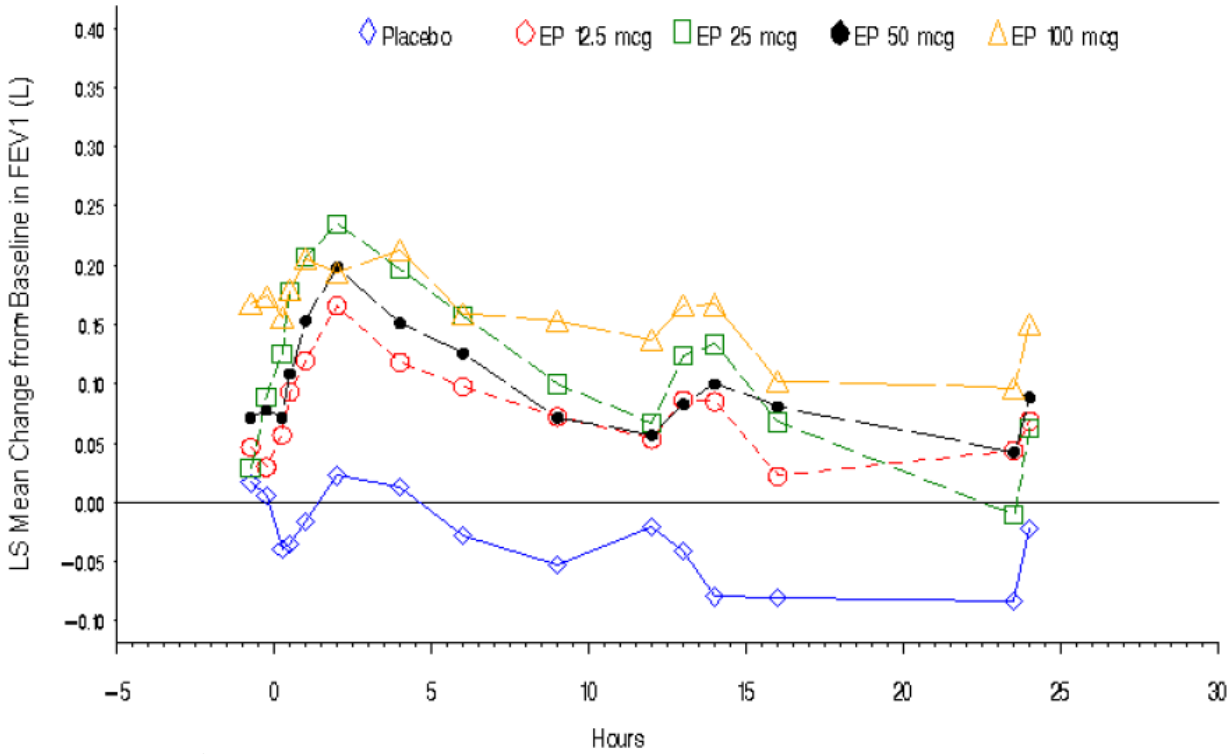


Abbreviations: FEV1 = forced expiratory volume in 1 second; ITT = intent-to-treat; LS Mean = least squares mean; mL = milliliter, SUN101 = GP.
Note: The comparison to placebo is active treatment change from baseline minus placebo change from baseline. A positive difference indicates a treatment effect over placebo.
Note: Statistics are from a mixed model for repeated measures with fixed factors for treatment, visit, inhaled corticosteroid use, sub-study participation, an interaction for visit by treatment; a covariate for baseline FEV1; and a random factor for subject. An unstructured covariance structure was used to account for the intra-subject variability.
Note: Alpha inflation is controlled through a gate-keeping methodology. Comparisons to placebo are considered using the highest dose level first. If that comparison has a p-value ≤ 0.05, then the next highest dose level can be considered. When a p-value is > 0.05 in a comparison, then no tests between lower doses and placebo can be considered. * indicates a p-value that is significant using the gateway methodology.

Source: Module 5.3.5.1 Study EP101-04 CSR, Figure 2, Page 61

As noted above, the EP101-04 study results demonstrate efficacy is achieved for all tested doses of GP, including the lowest dose 12.5 mcg BID. Therefore, study EP101-04 failed to adequately characterize the low end of the dose-response curve, which should include a dose which could be viewed as ineffective. The sponsor conducted a second study (Study SUN101-201) described below.

Figure 14. Change from Baseline in FEV1 Over Day 28 – Sub-Study Population (ITT Population)- Study EP101-04



Abbreviations: FEV1 = forced expiratory volume in 1 second; ITT = intent-to-treat; LS Mean = least squares mean, EP= GP
Note: Baseline is defined as the average of the 2 pre-dose FEV1 values at 45 and 15 minutes pre-dose on Day 1.
Note: The comparison to placebo is active treatment minus placebo. A positive difference indicates a treatment effect over placebo.
Note: Statistics are from an ANCOVA model with fixed factors for treatment, inhaled corticosteroid use, and a covariate for baseline FEV1. No adjustment for multiplicity was used for these results.
Note: The sub-study population is a subset of the ITT population who had measurements taken at 13, 14, and 16 hours.

Source: Module 5.3.5.1 Study EP101-04 CSR, Figure 3, Page 66

In the subset of subjects with extended spirometry measurements, the FEV1 response over 24 hours relative to placebo demonstrated the bronchodilator effect of GP and clear separation of all doses from placebo. In addition, the 24 hour curves effectively demonstrated that GP is a twice daily inhaled antimuscarinic agent.

Study SUN101-201

Study SUN101-201 was a randomized, 6-way crossover study designed to further evaluate the lower end of the GP dose response curve. The study was double-blind for GP and placebo and open-label for aclidinium bromide (hereafter also referred to as aclidinium). Following confirmation that all study eligibility criteria had been met, each subject was randomly allocated to a treatment sequence on Day 1 of Treatment Period 1. Each sequence comprised six 7-day treatment periods with a washout period of 5 to 7 days between each treatment period. Each subject was to receive each of 6 treatments. During each treatment period, study medications

were administered BID between 6:00 AM and 10:00 AM (morning dose) and between 6:00 PM and 10:00 PM (evening dose).

Each subject was to receive each of the following 6 treatments in a random order, BID:

- Placebo
- GP 3 mcg
- GP 6.25 mcg
- GP 12.5 mcg
- GP 50 mcg
- Aclidinium 400 mcg

GP and placebo were administered using the investigational high-efficiency eFlow CS nebulizer.

The study population consisted of male and female subjects between the ages of 40 to 65 years (inclusive) with a clinical diagnosis of moderate to severe COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (GOLD 2011). In addition, subjects were to be current smokers or ex-smokers; have post-bronchodilator (following inhalation of ipratropium) measurements during screening of forced expiratory volume in 1 second (FEV1) $\geq$ 40% and $\leq$ 70% of predicted normal, FEV1/FVC (forced vital capacity) ratio $\leq$ 0.70, and improvement in FEV1 $\geq$ 12% and $\geq$ 100 mL; and the ability to perform reproducible spirometry, and ability to participate in study assessments and/or procedures. All subjects had to be willing and able to remain at the clinical site for at least 24 hours at Day 7 of each treatment period.

The primary efficacy endpoint was the change from baseline in trough FEV1 at Treatment Visit Day 7 compared to placebo. Trough FEV1 was defined as the mean of FEV1 values obtained at 23 hours 15 minutes and 23 hours 45 minutes after the morning dose on Treatment Visit Day 7.

Baseline demographics were generally comparable across the treatment groups. The mean age was 54.6 years (range: 40 to 65 years) with 47.9% of subjects being male and predominantly white (89.6% subjects).

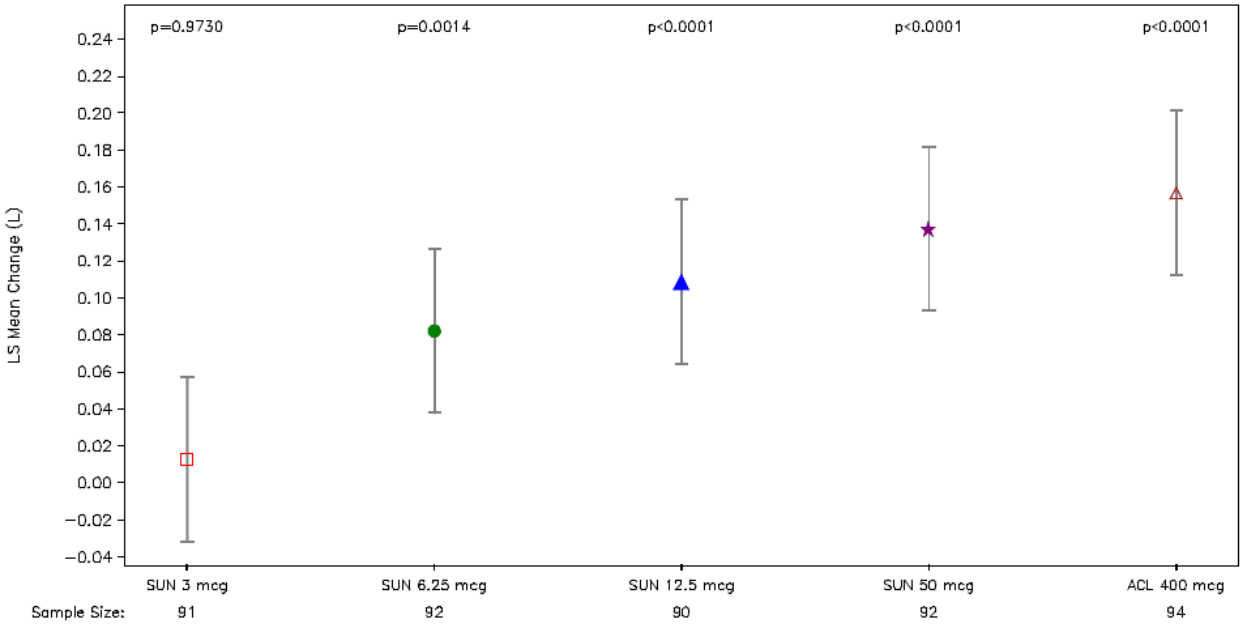
The majority of subjects (76.0%) did not have any COPD exacerbations in the previous 12 months. The mean (SD) number of COPD exacerbations within the 12 months prior to screening was 0.3 (0.62), with a range of 0 to 3 COPD exacerbations. The majority of subjects (63.5%) had FEV1 $\geq$ 50% of predicted and 5.2% of subjects had oxygen use during the study. A large majority of subjects were current smokers at screening (82.3%) with a mean 52.6 pack-years of smoking history.

A total of 164 subjects were screened, of which 68 subjects were screen failures. Ninety-six subjects were randomly assigned to a treatment sequence, of which [n=88 (91.7%)] subjects completed all treatments. A total of 8 subjects discontinued the study, [n=4 (4.2%)] subjects each during an in-clinic visit and the washout period. The reasons for discontinuation during the

study were S/AEs in [n=5 (5.2%)] of subjects, withdrawal by subject in [n=2 (2.1%)] of subjects, and death in [n=1 (1.1%)] of subjects.

Efficacy

Figure 15. Change from Baseline in Trough FEV1 on Day 7 Compared to Placebo (95% Confidence Intervals) (Efficacy Population)- Study SUN101-201



Abbreviations: ACL= aclidinium; FEV1= forced expiratory volume in 1 second; L= liter; LS= least square; SUN= GP.
Note: Comparison to placebo LS means are active treatment change from baseline minus placebo change from baseline based on a mixed effect analysis of covariance model with fixed factors for period, sequence, treatment, a covariate for baseline FEV1 and a random effect for subject nested within sequence. Dunnett's adjusted P values for GP treatment periods are displayed and unadjusted P value for aclidinium treatment period is displayed.

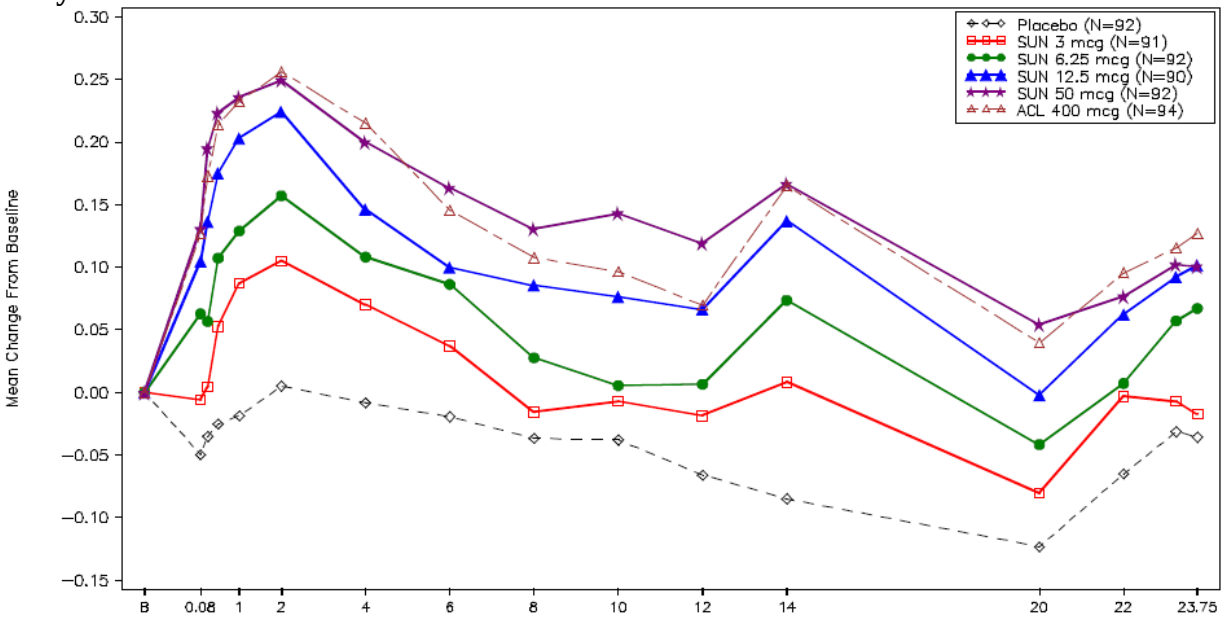
The efficacy population consisted of all subjects who were randomly assigned to treatment, received at least 1 dose of study medication, and had at least 1 trough FEV1 evaluation and the corresponding baseline FEV1 for at least
1 treatment period. The FEV1 values within 6 hours after the use of rescue medication were considered as missing. All efficacy summaries were performed on the efficacy population by treatments using the treatments assigned at the respective periods via the randomized treatment sequences.

Source: Module 5.3.5.1, SUN101-201 CSR, Figure 1, Page 63

Changes in trough FEV1 demonstrated increasing improvement with increasing doses of GP. The lowest dosing period, GP 3 mcg BID, did not show a treatment effect. The mean difference from the placebo period was 12.6 mL and failed to separate statistically from placebo. The GP 6.25 mcg BID treatment period was on the low end of the dose-response curve with an improvement in trough FEV1 of 82 mL, which was significantly different from placebo. The placebo-adjusted change in trough FEV1 for the GP 12.5 mcg BID treatment period was 108.8 mL and was statistically superior to placebo. There was a slightly larger improvement in trough FEV1 for the GP 50 mcg BID treatment period (137.5 mL), which was also significantly superior to placebo ($P < 0.0001$). The aclidinium treatment period (active control) demonstrated

a 156.7 mL improvement in trough FEV1 which was significantly greater than placebo and approximately 20 mL higher than the GP 50 mcg BID treatment period.

Figure 16. Mean Change From Baseline in FEV1 (L) Over Time (Efficacy Population)- Study SUN101-201



Abbreviations: ACL = aclidinium; B = baseline; FEV1 = forced expiratory volume in 1 second; L = liter.
Note: Baseline was the average of the 45- and 15-minute pre-dose FEV1 (L) values on Day 1.

Source: Module 5.3.5.1 SUN101-201 CSR, Figure 5, Page 69

All subjects in study SUN101-201 participated in serial spirometry measurements. Overall, the mean FEV1 response over 24 hours (unadjusted for placebo) demonstrated an improvement of 100 mL or greater during the first 4 hours after the morning dose for GP 6.25 and 12.5 mcg, during the first 8 hours for aclidinium, and during the first 12 hours for GP 50 mcg.

Upon review of the SUN101-201 data, the Division concluded that the lower end of the dose response curve had been adequately characterized and both the 25 and 50 mcg doses were reasonable to carry forward into Phase 3 studies.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The two replicate trials (SUN101-301 and SUN101-302) demonstrated persistence of response to GP over a 12 week treatment period. The spirometry endpoints in each controlled efficacy trial showed that GP 25 and 50 mcg BID resulted in bronchodilation which was maintained for 12 hours on Week 0 (Day 1) and week 12. Figure 6 and Figure 7, and Figure 8 discussed in Section 6.1.4 Analysis of Primary Endpoint(s), shows the trough FEV_1 through week 12 and

demonstrates separation of GP 25 mcg and 50 mcg compared to the placebo curves throughout the entire treatment period.

6.1.10 Additional Efficacy Issues/Analyses

None.

7 Review of Safety

Safety Summary

The safety evaluation of GP relies primarily on 3-month data from studies SUN101-301 and SUN101-302. Pooling of data across the two trials to examine the emergence of safety signals was deemed acceptable as these trials were similar in design/duration and the patient population was comparable in terms of demographics, baseline characteristics, and doses of GP received (25 and 50 mcg BID). Safety assessments in these 2 studies included adverse events (AEs), physical examinations, vital signs, ECGs, and clinical laboratory testing. In addition, a long term safety study, SUN101-303, was conducted and did not reveal any additional safety signals.

The 3-month safety database included 1,293 COPD patients; 431 treated with GP 25 mcg BID, 432 patients treated with GP 50 mcg BID, and 430 patients treated with placebo.

Few patients discontinued treatment prematurely in the GP development program. Study drug withdrawal occurred more frequently in the placebo group compared to GP 25 mcg and 50 mcg groups, respectively [n=40 (9.3%), n=22 (5.1%), n=17 (3.9%)]. The most common AE leading to discontinuation were events occurring in the respiratory, mediastinal and thoracic system organ class (SOC). Overall, adverse events were not a significant cause for patient discontinuation. Death was a rare occurrence, with one event (diastolic dysfunction, COPD exacerbation, pulmonary hypertension) occurring in the high dose (50 mcg) dose group in the 3-month studies.

The overall occurrence of SAEs was low and fairly balanced across GP 25 mcg and GP 50 mcg treatment groups, respectively [n=13 (3.0%), n=18 (4.2%)] with more events occurring in the placebo group [n=24 (5.6%)]. In general, the numbers of patients experiencing individual SAEs were small, without striking imbalances noted.

Adverse events of special interest (AESI) were identified by the Applicant based upon known class effects for anti-muscarinic drugs which included pneumonia, anticholinergic syndrome, cardiovascular, cerebrovascular, gastrointestinal obstruction, and glaucoma special interest events and adjudicated major adverse cardiovascular events (MACE). Pneumonia related events occurred slightly more frequently in the GP 50 mcg compared to the placebo arms, respectively [n=31 (7.2%), n=18 (4.2%)]. As expected, anticholinergic events (e.g. dry mouth, dizziness, blurred vison) were reported more frequently in the GP treatment arms compared to the placebo

arms and appeared to be dose-related. The most frequently reported anticholinergic AE was dry mouth [n=1 (0.2%) subject in the placebo group, n=4 [0.9%] subjects in the GP 25 mcg BID group, and 7 [1.6%] subjects in the GP 50 mcg BID group). Cardiovascular events of special interest occurred more frequently in the placebo group compared to the GP 25 mcg and 50 mcg treatment arms, respectively [n=11 (2.6%), n=7 (1.6%), n=9 (2.1%)]. MACE was reported in 5 subjects, which included 3 subjects (0.7%) who received GP 50 mcg, 2 subjects (0.5%) who received placebo, and 0 subjects who received GP 25 mcg. Cerebrovascular events were rare and fairly balanced across the treatment groups [GP 25mcg n=3 (0.7%), GP 50 mcg n=1 (0.2%), placebo n=2 (0.5%)]. Gastrointestinal obstruction AEs were reported for only 1 (0.2%) subject in the GP 25 mcg group (small intestinal obstruction), while no subjects in the placebo or GP 50 mcg BID groups reported an AE related to gastrointestinal obstruction. Glaucoma-related AEs were reported in 3 subjects with vision blurred in 2 (90.5%) subjects who received GP 25 mcg and eye pain in 1 (0.2%) subject who received 50 mcg. Overall, these differences were small and not clinically meaningful.

Adverse events were generally balanced between the GP and placebo groups. The most frequent AE was in the respiratory, thoracic, and mediastinal disorders SOC with the most frequently reported preferred terms being cough and COPD, both of which had the lowest incidence in the GP 25 mcg group. The findings from the long term safety study were consistent with the results seen for the primary 3 month safety database. No new safety signal was identified.

The safety database is adequate to assess the safety of GP. In summary, the safety data for the GP development program in COPD do not reveal any new safety concerns. Adverse events were few and generally those observed with similar approved anti-muscarinic products.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety data from the 3-month safety database are described here in Section 7. The long-term safety study did not reveal any new safety findings and is discussed when additional data is required for clarification. The protocols for the two studies that comprise the safety database along with the long-term safety study are reviewed in Section 5 Sources of Clinical Data.

The safety evaluation of GP relies primarily on 3-month data from SUN101-301 and SUN101-302. All analyses in this review were based on the pooled 3-month safety population, unless otherwise specified.

7.1.2 Categorization of Adverse Events

For pooled analyses of studies completed at various times, all AEs were presented using the MedDRA version 15.1.

AEs were evaluated by primary system organ class (SOC) and by preferred term (PT), and also according to severity (mild, moderate and severe) and according to the investigator's assessment of the possible relationship to study drug (possibly related or not related). They were classified as common AEs, SAEs including deaths, other significant AEs including AEs causing permanent discontinuation of study treatment, and AEs requiring additional therapy. In addition, AEs of special interest including pneumonia, anticholinergic syndrome, cardiovascular, cerebrovascular, gastrointestinal obstruction, glaucoma and adjudicated major adverse cardiovascular events (MACE) were also analyzed.

Most of the individual studies included in the integrated summary of safety (ISS) defined treatment-emergent AEs as those AEs that occurred on or after the first dose of study drug, those AEs with a missing start date and a stop date on or after the first dose of study drug, or those AEs with both a missing start and stop date. Adverse events were classified as on treatment events based on the following criteria; from the first date of study drug up to the last date of study drug + 7 days for non-serious AEs; from the first date of study drug up to the last date of study drug + 30 days for serious AEs and MACE.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The Applicant utilized multiple safety groupings for the safety analyses of this clinical development program. The Applicant defined a chronic-use studies pool (12 weeks of dosing) comprising 2 studies (SUN101-301 and SUN101-302). Analysis of the 3 month (12 week) safety data is the focus of the safety review. The sponsor also provided a long-term safety study pool comprising data from Study SUN101-303 (48 weeks of dosing) and this is also discussed in this review when relevant.

Pooling of data across trials to examine the emergence of safety signals was deemed acceptable as these trials were similar in design/duration and the patient population was comparable in terms of demographics, baseline characteristics, and dose of GP received.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The extent of exposure for the chronic use 3 month safety database (as defined above) is described in Table 23.

Table 23. Extent of exposure to GP: 3-month pooled safety database

	GP 25 mcg BID N=431	GP 50 mcg BID N=432	Placebo N=430
Duration of exposure (days)			
Mean (SD)	76.9 (21.34)	78.6 (17.58)	77.7 (19.55)
Person-years	90.7	93.0	87.0
Duration of exposure categories, n (%)			
1 Day to < 1 Week	17 (3.9)	4 (0.9)	14 (3.3)
1 Week to < 2 Weeks	4 (0.9)	8 (1.9)	12 (2.8)
2 Weeks to < 4 Weeks	12 (2.8)	8 (1.9)	16 (3.7)
4 Weeks to < 8 Weeks	13 (3.0)	17 (3.9)	22 (5.1)
8 Weeks to < 12 Weeks	81 (18.8)	90 (208)	86 (20.0)
12 Weeks to < 24 Weeks	304 (70.5)	305 (70.6)	280 (65.1)

Abbreviations: BID = twice daily; n/N = number of subjects; SD = standard deviation.
Note: Study drug exposure was calculated as the number of days from the first to the last dose date. For subjects who were lost to follow-up, and for whom the last dose date from the termination record was unknown, the maximum of the date of the last dose from the electronic diary and the date of the last available in-clinic dosing within each treatment period was used. Person-years of exposure was calculated by summing up the total exposure (in days) for all subjects within each treatment group, and dividing by 365 25. Subjects who participated in multiple studies had their exposure to study drug summarized for each treatment received.

Source: Module 5.3.5.3, ISS, Table 7, Page 48.

As shown in Table 23, the mean duration of exposure was similar across treatment groups, at approximately 77 days. Approximately 70% of GP (25 mcg and 50 mcg) treated patients and 65% of placebo treated patients were exposed to study drug for ≥ 12 weeks. The extent of exposure in the 3 month safety database was adequate to perform the safety evaluation for GP 25 mcg and 50 mcg BID in patients with COPD.

Demographics

Demographic information for the pooled 3-month safety database is summarized in Table 24.

Table 24. Demographics- 3-month pooled safety database			
	GP 25 mcg BID N=431	**GP 50 mcg BID N=432**	**Placebo N=430**
Female n (%)	189 (43.9)	185 (42.8)	195 (45.3)
Mean BMI kg/m2 (SD)	28.26 (6.94)	28.41 (6.45)	29.02 (6.90)
US site n (%)	100	100	100
Age Categories, n (%)			
Mean age (range)	63 (40-83)	62 (40-87)	64 (41-84)
<65 years	231 (53.6)	254 (58.8)	220 (51.2)
65-<75 years	153 (35.5)	140 (32.4)	169 (39.3)
≥75 years	47 (10.9)	38 (8.8)	41 (9.5)
Race, n (%)			
White	385 (89.3)	386 (89.4)	388 (90.2)
Asian	1 (0.2)	0	1 (0.2)
American Indian or Alaska Native	2 (0.5)	1 (0.2)	1 (0.2)
Native Hawaiian or Other Pacific Islander	0	1 (0.2)	1 (0.2)
Black	42 (9.7)	44 (10.2)	39 (9.1)
Source: Module 5.3.5.3, ISS, Table 20, Page74			

The mean age of the patient population was approximately 63 years and a larger proportion of the randomized population was male and Caucasian. The demographic parameters were fairly evenly split between the two treatment groups

Demographics SUN101-303 Long Term Study

Overall, the mean age was 63 years in the long-term safety study pool and approximately 10% subjects were 75 years of age or older. The majority of the subjects were male in each treatment group. Subjects were predominantly White (94%) and the majority of subjects were enrolled in the US (90.0% of subjects). There were no notable differences in subject demographics between treatment groups.

7.2.2 Explorations for Dose Response

Explorations for dose response were conducted by the Applicant prior to the phase 3 program; in addition, two doses (25 mcg and 50 mcg) were carried forward into the replicative phase 3 studies.

The efficacy results of the dose-ranging studies which led to dose selection in the phase 3 program are described in Section 5.1 Tables of Studies/Clinical Trials and in 6.1.8Analysis of Clinical Information Relevant to Dosing Recommendations.

The overall incidence of AEs was slightly higher in the GP 25 and 50 mcg compared to placebo in the dose ranging studies, however, these differences were small and not considered to be

clinically meaningful. In addition, when AEs were evaluated by preferred term, no clear safety signal was observed. However, given the known safety signal associated with other glycopyrrolate inhalation products, consisting of atrial fibrillation and flutter, both 25 and 50 mcg doses which demonstrated efficacy were carried forward into phase 3.

7.2.3 Special Animal and/or In Vitro Testing

No special animal and/or in vitro testing was conducted or required to further explore the safety profile of GP.

7.2.4 Routine Clinical Testing

The routine clinical testing in the development program for GP included: hematology, blood chemistry and urinalysis and ECGs.

7.2.5 Metabolic, Clearance, and Interaction Workup

Refer to section 4.4 Clinical Pharmacology.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

GP is an approved product NDA # 207923 12.5 mcg glycopyrronium, NDA # 012827 Robinul Forte 2 mg tablet/ Robinul 1 mg tablet, NDA # 017558 0.2mg/mL injection, NDA # 014764 0.2mg/mL injection, NDA # 012827 1mg tablet, ANDA # 202675 1 mg tablet, ANDA # 091522 1.5 mg tablet, ANDA # 091182 multiple strengths tablet, ANDA # 090963 0.2mg/mL injection, ANDA # 090195 multiple strengths tablet, ANDA # 090020 multiple strengths tablet, NDA # 089397 0.2 mg/mL injection, ANDA # 089393 0.2mg/mL injection, ANDA # 089335 0.2mg/mL injection, ANDA # 088475 0.2mg/mL, ANDA # 086947 0.2mg.mL injection, ANDA # 086902 1mg tablet, ANDA # 086900 2mg tablet, ANDA # 086178 2mg tablet, ANDA # 085563 2mg tablet, ANDA # 085562 1 mg tablet, ANDA # 081169 0.2mg/mL injection, ANDA # 040847 multiple strengths tablet, ANDA # 040844 multiple strengths tablet, ANDA # 040836 multiple strengths tablet, ANDA # 040821 multiple strengths tablet, ANDA # 040653 multiple strengths tablet, ANDA # 040568 multiple strengths tablet, NDA # 022571 Cuvposa 1mg/5mL oral solution) and is therefore not considered a new molecular entity (NME). GP is an anticholinergic and the adverse events that have been identified are common to other drugs in the class. The adverse events associated with anticholinergic agents consist of the following; xerostomia, decreased sweating, urinary hesitancy and retention, blurred vision, tachycardia, palpitations, dilatation of the pupil, cycloplegia, increased ocular tension, loss of taste, headaches, nervousness, mental confusion, drowsiness, weakness, dizziness, insomnia, nausea, vomiting, constipation, bloated feeling, impotence, suppression of lactation, severe allergic reaction or drug idiosyncrasies including anaphylaxis, urticaria and other dermal manifestations.

GP is also approved as part of a combination product (NDA # 201930 – Utibron Neohaler 12.5 mcg glycopyrronium + 27.5 mcg indacaterol and NDA# 208294- Bevespi Aerosphere 7.2 mcg of glycopyrronium + 4.8 mcg of formoterol fumarate).

7.3 Major Safety Results

7.3.1 Deaths

Deaths are summarized in Table 25.

Table 25. Deaths- Pooled 3 Month Safety Database

	GP 25 mcg BID N=431 n (%)	GP 50 mcg BID N=432 n (%)	Placebo N=430 n (%)
Deaths	0	1 (0.2)	0
Cardiovascular	0	1 (0.2)	0
Diastolic dysfunction	0	1 (0.2)	0
Respiratory, thoracic and mediastinal	0	1 (0.2)	0
COPD	0	1 (0.2)	0
Pulmonary Hypertension	0	1 (0.2)	0

Note: Adverse events are coded using MedDRA Version 15.1. This summary includes all AEs with onset date occurring on or after the first date of study drug. For the subject level calculations, a subject with multiple events in a given system organ class (SOC) or preferred term (PT) is counted only once per SOC or PT. Percentages are calculated based on the number of safety population subjects in each treatment group.

Source: Module 5.3.5.3, ISS, Table 15.3.1, Page 2211.

Death was a rare occurrence, with one event occurring in the high dose (50 mcg) dose group in the 3 month studies. The death occurred in a 61-year-old, white male. The cause of death was identified as worsening of diastolic dysfunction, worsening of COPD, and exacerbation of pulmonary hypertension, all reported starting on Day 43. The event was identified as an adjudicated MACE event, described in Section 7.3.5 Submission Specific Primary Safety Concerns. The small differences between treatment groups were not clinically significant.

While there was a higher frequency of deaths in the long-term 12 month safety database (described below in Table 26), events were fairly balanced across treatment groups. A total of 7 deaths occurred in the long-term safety study: 3 (0.5%) in the GP 50 mcg BID group and 4 (0.9%) in the tiotropium 18 mcg QD group. The 3 events in the GP 50 mcg group were classified as pancreatic carcinoma, pneumonia, dehydration, and hypokalemia. The 4 events identified in the tiotropium group were classified as cardiorespiratory arrest, arteriosclerosis, COPD exacerbation, and lung adenocarcinoma. Two of the events in the tiotropium treatment group were adjudicated as MACE events, which are discussed in section 7.3.5 Submission Specific Primary Safety Concerns.

Table 26. Deaths- Pooled 48-Week Safety Database

	GP 50 mcg BID N=620 n (%)	Spiriva (tiotropium) 18 mcg QD N=466 n (%)
Deaths	3 (0.5)	0
Infections and Infestations	1 (0.2)	0
Pneumonia	1 (0.2)	0
Metabolism and Nutrition	1 (0.2)	0
Dehydration	1 (0.2)	0
Hypokalemia	1 (0.2)	0
Neoplasms (benign, malignant)	1 (0.2)	0
Pancreatic Carcinoma	1 (0.2)	0
Lung Adenocarcinoma	0	1 (0.2)
Cardiac Disorders	0	1 (0.2)
Cardio Respiratory Arrest	0	1 (0.2)
Respiratory, Thoracic and Mediastinal	0	1 (0.2)
COPD	0	1 (0.2)
Vascular Disorders	0	1 (0.2)
Arteriosclerosis	0	1 (0.2)

Note: A treatment emergent adverse event is an AE with onset date occurring on or after the date of the first dose of study drug. Adverse events are coded using MedDRA 15.1. For the Subject level calculations, a subject with multiple events in a given system organ class (SOC) or preferred term (PT) is counted only once per SOC or PT. Percentages are calculated based on the number of safety population subjects in each treatment group. Tio=tiotropium

Source: Module 5.3.5.3 ISS, Table 15.4, Page 2213

7.3.2 Nonfatal Serious Adverse Events

An overview of serious adverse events (SAEs) is provided in Table 27 .

Table 27. Serious Adverse Events- Pooled 3-Month Safety Database			
	GP 25 mcg BID N=431 n (%)	**GP 50 mcg BID N=432 n (%)**	**Placebo N=430 n (%)**
Subjects with at least one SAE by SOC	13 (3.0)	18 (4.2)	24 (5.6)
Respiratory, thoracic and mediastinal disorders	2 (0.5)	8 (1.9)	5 (1.2)
Chronic obstructive pulmonary disease	2 (0.5)	6 (1.4)	4 (0.9)
Bronchitis	0	1 (0.2)	0
Pleural Effusion	0	1 (0.2)	0
Pulmonary Hypertension	0	1 (0.2)	0
Respiratory failure	0	1 (0.2)	0
Acute respiratory failure	0	0	1 (0.2)
Cardiac Disorders	2 (0.5)	2 (0.5)	5 (1.2)
Angina Pectoris	1 (0.2)	0	0
Angina Unstable	0	1 (0.2)	1 (0.2)
Coronary Artery Stenosis	1 (0.2)	0	0
Diastolic Dysfunction	0	1 (0.2)	0
Acute Myocardial Infarction	0	0	1 (0.2)
Atrial Fibrillation	0	0	2 (0.5)
Atrial Flutter	0	0	1 (0.2)
Cardiomyopathy	0	0	1 (0.2)
Ventricular Tachycardia	0	0	1 (0.2)
Infections and infestations	1 (0.2)	3 (0.7)	5 (1.2)
Pneumonia	0	2 (0.5)	3 (0.7)
Emphysematous Cholecystitis	0	1 (0.2)	0
Pyelonephritis	1 (0.2)	0	0
Septic Shock	0	1 (0.2)	0
Bronchitis	0	0	1 (0.2)
Lobar Pneumonia	0	0	1 (0.2)
Nervous System Disorders	3 (0.7)	1 (0.2)	1 (0.2)
Carotid Artery Stenosis	2 (0.5)	0	1 (0.2)
Lacunar Infarction	0	1 (0.2)	0
Subarachnoid Hemorrhage	1 (0.2)	0	0
Transient Ischemic Attack	0	1 (0.2)	0
Renal and Urinary	1 (0.2)	3 (0.7)	1 (0.2)
Nephrolithiasis	0	2 (0.5)	1 (0.2)
Obstructive Uropathy	1 (0.2)	0	0
Renal Failure Acute	0	1 (0.2)	0
General Disorders and Administration Site Conditions	1 (0.2)	2 (0.5)	0
Asthenia	1 (0.2)	0	0
Chest Pain	0	1 (0.2)	0
Noncardiac Chest Pain	0	1 (0.2)	0
Gastrointestinal Disorders	2 (0.5)	0	2 (0.5)

Nausea	1 (0.2)	0	0
Small Intestinal Obstruction	1 (0.2)	0	0
Gastric Ulcer	0	0	1 (0.2)
Gastrointestinal Hemorrhage	0	0	1 (0.2)
Pancreatitis Necrotizing	0	0	1 (0.2)
Injury, Poisoning, and Procedural Complications	0	2 (0.5)	2 (0.5)
Chest Injury	0	1 (0.2)	0
Intentional Overdose	0	1 (0.2)	0
Rib Fracture	0	1 (0.2)	0
Coronary Artery Restenosis	0	0	1 (0.2)
Subdural Hematoma	0	0	1 (0.2)
Metabolism and Nutrition Disorders	1 (0.2)	1 (0.2)	1 (0.2)
Dehydration	0	1 (0.2)	0
Obesity	1 (0.2)	0	0
Diabetes Mellitus Inadequate Control	0	0	1 (0.2)
Ear and Labyrinth Disorders	1 (0.2)	0	0
Vertigo	1 (0.2)	0	0
Hepatobiliary Disorders	0	1 (0.2)	1 (0.2)
Gallbladder Necrosis	0	1 (0.2)	0
Cholelithiasis	0	0	1 (0.2)
Musculoskeletal and Connective	0	1 (0.2)	1 (0.2)
	0	1 (0.2)	0
	0	0	1 (0.2)
Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps)	1 (0.2)	0	1 (0.2)
Lung Adenocarcinoma Stage IV	1 (0.2)	0	0
Malignant Neoplasm of Pleura Metastatic	0	0	1 (0.2)
Skin and subcutaneous tissue disorders	1 (0.2)	0	0
Hyperhidrosis	1 (0.2)	0	0
Blood and Lymphatic System Disorders	0	0	1 (0.2)
Hemorrhagic Anemia	0	0	1 (0.2)
Investigations	0	0	1 (0.2)
Antiphospholipid Antibodies	0	0	1 (0.2)

Abbreviations: BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; n/N = number of subjects; SAE = serious adverse event, SOC= system organ class. Note: Serious adverse events were coded using MedDRA version 15.1. This summary includes on-treatment SAEs with an onset date that occurred on or after the first date of study drug and within 30 days after the last date of study drug. A subject with multiple events per primary system organ class or per preferred term was counted only once per primary system organ class or preferred term. Percentages were calculated based on the number of safety population subjects in each treatment group.

Source: Module 5.3.5.3, ISS, Table 46, Page 146

The overall occurrence of SAEs was fairly balanced across GP 25 mcg and GP 50 mcg treatment groups, respectively [n=13 (3.0%), n=18 (4.2%)] with more events occurring in the placebo group [n=24 (5.6%)]. In general, the numbers of patients experiencing individual SAEs were small, without striking imbalances noted. Cardiac disorders were more common in the placebo arm compared to both GP 25 mcg and 50 mcg, respectively [n=5 (1.2%), n=2 (0.5%), n= 2 (0.5%)]. Similar findings were noted for the frequency of infections and infestations [n=5 (1.2%), n=1 (0.2%), n=3 (0.7%)]. No new safety signal was noted as a result of the SAE analysis by SOC or preferred terms.

7.3.3 Dropouts and/or Discontinuations

Adverse events (AEs) leading to study drug withdrawal are listed in Table 28.

Table 28. Adverse Events Leading to Study Drug Withdrawal During the On-treatment Period by System Organ Class and Preferred Term- Pooled 3-Month Safety Database

	GP 25 mcg BID N=431 n (%)	GP 50 mcg BID N=432 n (%)	Placebo BID N=430 n (%)
Patients ≥1 AE leading to study drug withdrawal	22 (5.1)	17 (3.9)	40 (9.3)
Respiratory, Thoracic, and Mediastinal Disorders	9 (2.1)	9 (2.1)	23 (5.3)
Cough	2 (0.5)	4 (0.9)	7 (1.6)
Dyspnea	4 (0.9)	2 (0.5)	4 (0.9)
COPD	3 (0.7)	1 (0.2)	5 (1.2)
Choking Sensation	0	1 (0.2)	0
Oropharyngeal Pain	0	1 (0.2)	0
Pleural Effusion	0	1 (0.2)	0
Bronchospasm	0	0	3 (0.7)
Hemoptysis	0	0	3 (0.7)
Respiratory Tract Congestion	0	0	1 (0.2)
Respiratory Tract Irritation	0	0	1 (0.2)
Wheezing	0	0	1 (0.2)
General Disorders and Administration Site Conditions	6 (1.4)	2 (0.5)	7 (1.6)
Fatigue	1 (0.2)	1 (0.2)	0
Irritability	1 (0.2)	1 (0.2)	0
Administration Site Pain	1 (0.2)	0	0
Asthenia	1 (0.2)	0	0

Chest Pain	1 (0.2)	0	0
Chills	1 (0.2)	0	0
Instillation Site Pain	1 (0.2)	0	3 (0.7)
Peripheral Edema	1 (0.2)	0	0
Adverse Drug Reaction	0	0	1 (0.2)
Chest Discomfort	0	0	2 (0.5)
Gait Disturbance	0	0	1 (0.2)
Gastrointestinal Disorders	2 (0.5)	3 (0.7)	3 (0.7)
Dry Mouth	0	2 (0.5)	0
Nausea	1 (0.2)	1 (0.2)	1 (0.2)
Diarrhea	0	1 (0.2)	0
Dysphagia	1 (0.2)	0	0
Glossodynia	0	1 (0.2)	0
Lip Pain	0	1 (0.2)	0
Abdominal Distension	0	0	1 (0.2)
Pancreatitis Necrotizing	0	0	1 (0.2)
Nervous System Disorders	3 (0.7)	1 (0.2)	3 (0.7)
Headache	1 (0.2)	1 (0.2)	2 (0.5)
Migraine	1 (0.2)	0	0
Tremor	1 (0.2)	0	1 (0.2)
Disturbance in Attention	0	0	1 (0.2)
Renal and Urinary Disorders	2 (0.5)	2 (0.5)	0
Hematuria	1 (0.2)	0	0
Nephrolithiasis	0	1 (0.2)	0
Urinary Retention	1 (0.2)	0	0
Urinary Tract Obstruction	0	1 (0.2)	0
Infections and Infestations	2 (0.5)	1 (0.2)	4 (0.9)
Bronchitis	0	1 (0.2)	0
Oral Candidiasis	1 (0.2)	0	0
Urinary Tract Infection	1 (0.2)	0	0
Lobar Pneumonia	0	0	1 (0.2)
Pneumonia	0	0	3 (0.7)
Musculoskeletal and Connective Tissue Disorders	1 (0.2)	1 (0.2)	2 (0.5)
Arthralgia	1 (0.2)	0	0
Pain In Extremity	0	1 (0.2)	0
Back Pain	0	0	1 (0.2)
Neck Mass	0	0	1 (0.2)
Psychiatric Disorders	1 (0.2)	1 (0.2)	3 (0.7)
Abnormal Behavior	0	1 (0.2)	0
Suicidal Ideation	1 (0.2)	0	0
Agitation	0	0	1 (0.2)
Anxiety	0	0	1 (0.2)
Insomnia	0	0	1 (0.2)
Skin and Subcutaneous Tissue Disorders	2 (0.5)	0	1 (0.2)
Rash	1 (0.2)	0	0

Urticaria	1 (0.2)	0	0
Pruritus	0	0	1 (0.2)
Cardiac Disorders	1 (0.2)	0	2 (0.5)
Angina Pectoris	1 (0.2)	0	0
Acute Myocardial Infarction	0	0	1 (0.2)
Atrial Flutter	0	0	1 (0.2)
Cardiomyopathy	0	0	1 (0.2)
Ear and Labyrinth Disorders	1 (0.2)	0	0
Tinnitus	1 (0.2)	0	0
Immune System Disorders	0	1 (0.2)	0
Hypersensitivity	0	1 (0.2)	0
Metabolism and Nutrition Disorders	1 (0.2)	0	0
Hypoglycemia	1 (0.2)	0	0
Vascular Disorders	1 (0.2)	0	0
Hypertension	1 (0.2)	0	0
Eye Disorders	0	0	1 (0.2)
Blepharospasm	0	0	1 (0.2)

Abbreviations: AE = adverse event; BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; n/N = number of subjects.
Note: Adverse events were coded using MedDRA version 15.1. This summary includes on-treatment AEs. On-treatment period was defined as the time from the first date of study drug until the last date of study drug + 7 days for nonserious AEs and until the last date of study drug + 30 days for serious AEs. A subject with multiple events per primary system organ class or per preferred term was counted only once per primary system organ class or preferred term. Percentages were calculated based on the number of safety population subjects in each treatment group.

Source: Module 5.3.5.3, ISS, Table 50, Page 169

Overall, few patients discontinued treatment prematurely in the GP development program and therefore, treatment withdrawal secondary to adverse events was also infrequent. Study drug withdrawal occurred more frequently in the placebo group compared to GP 25 mcg and 50 mcg groups, respectively [n=40 (9.3%), n=22 (5.1%), n=17 (3.9%)]. The most common AE leading to discontinuation was events occurring in the respiratory, mediastinal, and thoracic SOC. Overall, adverse events were not a significant cause for patient discontinuation.

7.3.4 Significant Adverse Events

Refer to Section 7.3.2 Nonfatal Serious Adverse Events.

7.3.5 Submission Specific Primary Safety Concerns

Adverse events of special interest included pneumonia, anticholinergic syndrome, cardiovascular, cerebrovascular, gastrointestinal obstruction, and glaucoma special interest events and adjudicated major adverse cardiovascular events (MACE).

Pneumonia-related Adverse Events of Special Interest

Table 29. Pneumonia-Related Adverse Events of Special Interest- Pooled 3 Month Safety Database

	GP 25 mcg BID N=431 n (%)	GP 50 mcg BID N=432 n (%)	Placebo N=430 n (%)
Any Pneumonia Special Interest Term	12 (2.8)	31 (7.2)	18 (4.2)
Respiratory Tract Infection (HLGT)	12 (2.8)	31 (7.2)	18 (4.2)
Upper Respiratory Tract Infection	6 (1.4)	15 (3.5)	4 (0.9)
Bronchitis	5 (1.2)	7 (1.6)	6 (1.4)
Pneumonia	0	6 (1.4)	5 (1.2)
Influenza	0	1 (0.2)	0
Lobar Pneumonia	0	1 (0.2)	1 (0.2)
Lower Respiratory Tract Infection	0	1 (0.2)	0
Respiratory Tract Infection	0	1 (0.2)	0
Viral Upper Respiratory Tract Infection	1 (0.2)	0	1 (0.2)
Tracheobronchitis	0	0	1 (0.2)
Lower Respiratory Tract Infection (HLT)	5 (1.2)	15 (3.5)	12 (2.8)
Bronchitis	5 (1.2)	7 (1.6)	6 (1.4)
Pneumonia	0	6 (1.4)	5 (1.2)
Lobar Pneumonia	0	1 (0.2)	1 (0.2)
Lower Respiratory Tract Infection	0	1 (0.2)	0

Note: Adverse events are coded using MedDRA Version 15.1. This summary includes on-treatment AEs. On-treatment period is defined as the time from the first date of study drug until the last date of study drug + 7 days for non-serious AEs and until the last date of study drug + 30 days for serious AEs. For the subject level calculations, a subject with multiple events in a given special interest term name or preferred term (PT) is counted only once per special interest term name or PT. Percentages are calculated based on the number of safety population subjects in each treatment group. HLT: High Level Term; HLGT: High Level Group Term

Source: Module 5.3.5.3, ISS Table 19.1.1, Page 2264

In the 3 month safety database, pneumonia-related events occurred slightly more frequently in the GP 50 mcg compared to the placebo arms, respectively [n=31 (7.2%), n=18 (4.2%)]. The most frequently reported pneumonia-related AE was upper respiratory tract infection; 25 subjects reported upper respiratory tract infections [n=4 (0.9%) subjects in the placebo group, n=6 (1.4%) subjects in the GP 25 mcg BID group, and n=15 (3.5%) subjects in the GP 50 mcg BID group]. Overall, these differences were small and not clinically meaningful.

Anticholinergic Adverse Events of Special Interest

Table 30. Anticholinergic Adverse Events of Special Interest: Pooled 3-Month Safety Database

	GP 25 mcg BID N=431 n (%)	GP 50 mcg BID N=432 n (%)	Placebo BID N=430 n (%)
Any Anticholinergic Specific Term	11 (2.6)	13 (3.0)	5 (1.2)
Anticholinergic Syndrome	11 (2.6)	13 (3.0)	5 (1.2)
Dry Mouth	4 (0.9)	7 (1.6)	1 (0.2)
Dizziness	2 (0.5)	1 (0.2)	1 (0.2)
Pyrexia	0	2 (0.5)	0
Somnolence	1 (0.2)	1 (0.2)	1 (0.2)
Vision Blurred	2 (0.5)	0	0
Dry Eye	1 (0.2)	0	0
Dysphagia	1 (0.2)	0	0
Pre-Syncope	0	1 (0.2)	0
Tachycardia	0	1 (0.2)	1 (0.2)
Urinary Retention	1 (0.2)	0	0
Agitation	0	0	1 (0.2)
Gait Disturbance	0	0	1 (0.2)

Note: Adverse events are coded using MedDRA Version 15.1. This summary includes on-treatment AEs. On-treatment period is defined as the time from the first date of study drug until the last date of study drug + 7 days for non-serious AEs and until the last date of study drug + 30 days for serious AEs. For the subject level calculations, a subject with multiple events in a given Standardized MedDRA Query (SMQ) name or preferred term (PT) is counted only once per SMQ or PT. Percentages are calculated based on the number of safety population subjects in each treatment group.

Source: Module 5.3.5.3, ISS Table 19.2.1, Page 2266

In the 3 month pooled safety database, anticholinergic events were reported more frequently in the GP treatment arms compared to the placebo arms and showed a dose response relationship. The most frequently reported anticholinergic AE was dry mouth [n=1 (0.2%) subject in the placebo group, n=4 (0.9%)] subjects in the GP 25 mcg BID group, and 7 (1.6%) subjects in the GP 50 mcg BID group]. This is an expected side effect of treatment with glycopyrrolate products.

Cardiovascular Events of Special Interest

Table 31. Cardiovascular Adverse Events of Special Interest: Pooled 3-Month Safety Database

	GP 25 mcg BID N=431 n (%)	GP 50 mcg BID N=432 n (%)	Placebo BID N=430 n (%)
Any Cardiovascular Special Interest Term	7 (1.6)	9 (2.1)	11 (2.6)
Any Ischemic Heart Disease (Narrow Terms)	5 (1.2)	1 (0.2)	3 (0.7)
Angina Pectoris	3 (0.7)	0	0
Angina Unstable	1 (0.2)	1 (0.2)	1 (0.2)
Coronary Artery Disease	1 (0.2)	0	1 (0.2)
Coronary Artery Stenosis	1 (0.2)	0	0
Coronary Artery Re-Stenosis	0	0	1 (0.2)
Cardiac Arrhythmia (Including Bradyarrhythmia and Tachyarrhythmia)	1 (0.2)	4 (0.9)	5 (1.2)
Atrial Flutter	0	1 (0.2)	1 (0.2)
Electrocardiogram QT Prolonged	1 (0.2)	0	0
Sinus Tachycardia	0	1 (0.2)	1 (0.2)
Supraventricular Extra Systoles	0	1 (0.2)	0
Supraventricular Tachycardia	0	1 (0.2)	0
Atrial Fibrillation	0	0	2 (0.5)
Ventricular Tachycardia	0	0	1 (0.2)
Arrhythmia Related Investigations, Signs and Symptoms	1 (0.2)	3 (0.7)	4 (0.9)
Electrocardiogram Abnormal	0	1 (0.2)	1 (0.2)
Palpitations	1 (0.2)	0	1 (0.2)
Syncope	0	1 (0.2)	1 (0.2)
Tachycardia	0	1 (0.2)	1 (0.2)
Cardiac Failure (Narrow Terms Only)	0	1 (0.2)	0
Pulmonary Edema	0	1 (0.2)	0
Torsade De Pointes/ QT Prolongation (Narrow Terms Only)	1 (0.2)	0	1 (0.2)
Electrocardiogram QT Prolonged	1 (0.2)	0	0
Ventricular Tachycardia	0	0	1 (0.2)
Myocardial Infarction (Narrow Terms Only)	0	0	1 (0.2)
Acute Myocardial Infarction	0	0	1 (0.2)

Note: Adverse events are coded using MedDRA Version 15.1. This summary includes on-treatment AEs. On-treatment period is defined as the time from the first date of study drug until the last date of study drug + 7 days for non-serious AEs and until the last date of study drug + 30 days for serious AEs. For the subject level calculations, a subject with multiple events in a given Standardized MedDRA Query (SMQ) name or preferred term (PT) is counted only once per SMQ or PT. Percentages are calculated based on the number of safety population subjects in each treatment group.

Source: Module 5.3.5.3, ISS Table 19.3.1, Page 2268

Cardiovascular events of special interest occurred more frequently in the placebo group compared to the GP 25 mcg and 50 mcg treatment arms, respectively [n=11 (2.6%), n=7 (1.6%), n=9 (2.1%)]. In the 3 month pooled safety database, the only cardiovascular AE reported by more than 2 subjects in any treatment group was angina pectoris [n=3 (0.7%) subjects in the GP 25 mcg group and no subjects in the placebo and GP 50 mcg groups]. Cardiac arrhythmia terms were reported by [n=5 (1.2%)] subjects in the placebo group, [n=1 (0.2%)] subject in the GP 25 mcg group, and [n=4 (0.9%)] subjects in the GP 50 mcg group; none of these events were reported for > 0.5% of any treatment group.

MACE Events

Table 32. Adjudicated MACE: Pooled 3-Month Safety Database

	GP 25 mcg BID N=431 n (%) TT=126.1		GP 50 mcg BID N=432 n (%) TT=128.5		Placebo BID N=430 n (%) TT=122.3	
	N (%)	IR	N (%)	IR	N (%)	IR
MACE Score	0	0	3 (0.7)	23.3	2 (0.5)	16.4
CV Death	0	0	1 (0.2)	7.8	0	0
Nonfatal MI	0	0	1 (0.2)	7.8	2 (0.5)	16.4
Nonfatal stroke	0	0	1 (0.2)	7.8	0	0

Note: This summary includes on-treatment adjudicated MACE events which occurred on or after the first date of study drug and up to 30 days after the last dose of study drug. The MACE Score is defined as the total number of subjects with adjudicated cardiovascular deaths, non-fatal myocardial infarctions, or non-fatal strokes. TT= Total Time in years. Total Time (TT) is defined as the time from the first date of study drug until 30 days after the last dose of study drug. Incidence Rate = n/TT x 1000. Percentages are calculated based on the number of safety population subjects in each treatment group. A subject is counted at most once per category.

Source: Module 5.3.5.3, ISS Table 18.1.2, Page 2254

In the pooled 3 month safety database, 5 subjects reported MACE: this included 3 subjects (0.7%) who received GP 50 mcg, 2 subjects (0.5%) who received placebo, and 0 subjects who received GP 25 mcg. The differences noted between the treatment arms were small and not clinically meaningful. In addition, the long term data was consistent with the results displayed for the 3 month data.

Cerebrovascular Adverse Events of Special Interest

Table 33. Cerebrovascular Adverse Events of Special Interest- Pooled 3 Month Safety Database

	GP 25 mcg BID N=431 n (%)	GP 50 mcg BID N=432 n (%)	Placebo BID N=430 n (%)
Any Cerebrovascular Special Interest Term	3 (0.7)	1 (0.2)	2 (0.5)
Ischemic Cerebrovascular Conditions	2 (0.5)	1 (0.2)	1 (0.2)
Carotid Artery Stenosis	2 (0.5)	0	1 (0.2)
Lacunar Infarction	0	1 (0.2)	0
Transient Ischemic Attack	0	1 (0.2)	0
Hemorrhagic Cerebrovascular Conditions	1 (0.2)	0	1 (0.2)
Subarachnoid Hemorrhage	1 (0.2)	0	0
Subdural Hematoma	0	0	1 (0.2)
Cerebrovascular Disorders Not Specified as Hemorrhagic or Ischemic	0	0	0

Note: Adverse events are coded using MedDRA Version 15.1. This summary includes on-treatment AEs. On-treatment period is defined as the time from the first date of study drug until the last date of study drug + 7 days for non-serious AEs and until the last date of study drug + 30 days for serious AEs. For the subject level calculations, a subject with multiple events in a given Standardized MedDRA Query (SMQ) name or preferred term (PT) is counted only once per SMQ or PT. Percentages are calculated based on the number of safety population subjects in each treatment group.

Source: Module 5.3.5.3, ISS Table 19.4.1, Page 2272

Cerebrovascular events were rare and fairly balanced across the treatment groups [GP 25mcg n=3 (0.7%), GP 50mcg n=1 (0.2%), Placebo n=2 (0.5%)].

Gastrointestinal Obstruction Adverse Events of Special Interest

Table 34. Gastrointestinal Obstruction Adverse Events of Special Interest: Pooled 3-Month Safety Database

	GP 25 mcg BID N=431 n (%)	GP 50 mcg BID N=432 n (%)	Placebo N=430 n (%)
Any Gastrointestinal Obstruction Special Interest Term	1 (0.2)	0	0
Gastrointestinal Obstruction	1 (0.2)	0	0
Small Intestinal Obstruction	1 (0.2)	0	0

Note: Adverse events are coded using MedDRA Version 15.1. This summary includes on-treatment AEs. On-treatment period is defined as the time from the first date of study drug until the last date of study drug + 7 days for non-serious AEs and until the last date of study drug + 30 days for serious AEs. For the subject level calculations, a subject with multiple events in a given standardized MedDRA Query (SMQ) name or preferred term (PT) is counted only once per SMQ or PT. Percentages are calculated based on the number of safety population subjects in each treatment group.

Source: Module 5.3.5.3, ISS Table 19.5.1, Page 2274

In the pooled 3 month safety database, gastrointestinal obstruction AEs were reported for only 1 (0.2%) subject in the GP 25 mcg group (small intestinal obstruction), while no subjects in the placebo or GP 50 mcg BID groups reported an AE related to gastrointestinal obstruction.

Glaucoma-related Adverse Events of Special Interest

Table 35. Glaucoma Adverse Events of Special Interest: Pooled 3-Month Safety Database

	GP 25 mcg BID N=431 n (%)	GP 50 mcg BID N=432 n (%)	Placebo BID N=430 n (%)
Any Glaucoma Special Interest Term	2 (0.5)	1 (0.2)	0
Glaucoma	2 (0.5)	1 (0.2)	0
Vision Blurred	2 (0.5)	0	0
Eye Pain	0	1 (0.2)	0

Note: Adverse events are coded using MedDRA Version 15.1. This summary includes on-treatment AEs. On-treatment period is defined as the time from the first date of study drug until the last date of study drug + 7 days for non-serious AEs and until the last date of study drug + 30 days for serious AEs. For the subject level calculations, a subject with multiple events in a given Standardized MedDRA Query (SMQ) name or preferred term (PT) is counted only once per SMQ or PT. Percentages are calculated based on the number of safety population subjects in each treatment group.

Source: Module 5.3.5.3, ISS Table 19.6.1, Page 2276

In the pooled 3-month safety database, 3 subjects reported glaucoma-related AEs: vision blurred in n=2 (0.5%) subjects who received GP 25 mcg and eye pain in n=1 (0.2%) subject who received 50 mcg. Overall, these events were rare and do not represent a new safety signal.

Hypersensitivity Reaction Events

In the pooled safety database, hypersensitivity reaction AEs were noted for 1 subject who received placebo (0.2%; urticaria), 1 subject who received GP 25 mcg (0.2%; urticaria), and 1 subject receiving GP 50 mcg (0.2%; hypersensitivity). There were no clinical observations that showed a pattern of hypersensitivity associated with GP.

Paradoxical Bronchospasm Events

No subject in the 3 month studies experienced paradoxical bronchospasm during study participation.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 36. Common Adverse Events (Adverse Events That Occurred in at Least 2% of Subjects in Any Treatment Group During the On-treatment Period by System Organ Class and Preferred Term, Pooled 3 Month Safety Database

System Organ Class Preferred Term	GP 25 mcg BID N=431 n (%)	GP 50 mcg BID N=432 n (%)	Placebo N=430 n (%)
Subjects with ≥ 1 AE	187 (43.4)	219 (50.7)	225 (52.3)
Respiratory, Thoracic, and Mediastinal Disorders	86 (20.0)	102 (23.6)	107 (24.9)
Cough	30 (7.0)	39 (9.0)	36 (8.4)
COPD	28 (6.5)	37 (8.6)	37 (8.6)
Dyspnea	21 (4.9)	14 (3.2)	13 (3.0)
Infections and Infestations	51 (11.8)	71 (16.4)	60 (14.0)
Upper Respiratory Tract Infection	6 (1.4)	15 (3.5)	4 (0.9)
Urinary Tract Infection	9 (2.1)	12 (2.8)	6 (1.4)
General Disorders and Administrative Site Conditions	27 (6.3)	24 (5.6)	27 (6.3)
Edema Peripheral	4 (0.9)	9 (2.1)	4 (0.9)
Chest Discomfort	5 (1.2)	4 (0.9)	9 (2.1)
Musculoskeletal and Connective Tissue Disorders	14 (3.2)	27 (6.3)	29 (6.7)
Arthralgia	3 (0.7)	9 (2.1)	5 (1.2)
Nervous System Disorders	20 (4.6)	21 (4.9)	15 (3.5)
Headache	7 (1.6)	8 (1.9)	10 (2.3)

Abbreviations: AE = adverse event; BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; n/N = number of subjects
Note: Adverse events were coded using MedDRA version 15 1 This summary includes on-treatment AEs On-treatment period was defined as the time from the first date of study drug until the last date of study drug + 7 days for non-serious AEs and until the last date of study drug + 30 days for serious AEs For the subject level calculations, a subject with multiple events in a given system organ class or preferred term was counted only once per system organ class or preferred term Percentages were calculated based on the number of safety population subjects in each treatment group

Source: Module 5 3 5 3, ISS, Table 35, Page 108

As shown in Table 36, common adverse events were generally balanced between the GP and placebo groups. The most frequent AE was in the respiratory, thoracic, and mediastinal disorders SOC with the most frequently reported preferred terms being cough and COPD, both of which had the lowest incidence in the GP 25 mcg group; 105 subjects reported cough (8.4% of subjects in the placebo group, 7.0% of subjects in the GP 25 mcg BID group, and 9.0% of subjects in the GP 50 mcg BID group), and 102 subjects reported COPD (8.6%, 6.5%, and 8.6%, respectively). All other AEs reported during the on-treatment period were seen in less than 5% of subjects in any treatment group.

7.4.2 Laboratory Findings

Overall, review of the clinical laboratory data did not reveal any clinically significant differences.

7.4.3 Vital Signs

Across studies, no clinically meaningful changes in vital sign parameters (heart rate and systolic and diastolic blood pressures) were observed after treatment with GP. The mean changes from baseline in all vital sign parameters were minimal and similar across the treatment groups

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were performed during studies for subjects in the 3 month pooled safety database (N=863 GP subjects, N=430 placebo subjects), and the long-term safety study pool (N=620 GP subjects, N=466 tiotropium subjects). No clinically meaningful differences were noted over time in the 3 month and long term studies. Few ECG changes were reported as AEs in either the 3 month chronic-use studies pool or the 48-week long-term safety study pool.

In Study SUN101-301, 24-hour Holter monitoring was performed at Visit 1 for all subjects and at Visit 6 (Week 12) for the sub-study population. Holter monitor results were centrally reviewed, with a comment from the reviewing cardiologist for all abnormal results. Baseline and Week 12 post-dosing assessments were available for N=33 (78.6%), N=46 (93.9%), and N=57 (91.9%) subjects in the placebo, GP 25 mcg BID, and GP 50 mcg BID dosing groups.

In the placebo group, 3 (12.0%) of the sub-study subjects with normal baseline Holter results were classed as abnormal at Week 12, with sustained bradycardia, periods of ectopic atrial rhythm, and runs of atrial fibrillation. One of these subjects had a recording time of < 18 hours, which may have resulted in an abnormal reading at follow-up. All 8 placebo subjects with abnormal baseline Holter results had normal findings at follow-up. One subject had a normal sinus rhythm but an incomplete recording at Baseline (later deemed to be normal, even though < 18 hours in duration), and 1 subject with normal sinus rhythm had an inaccurate scan number (later found to be incorrect, with a normal tracing at both baseline and follow-up visits). Thus,

there were only 6 placebo subjects with shifts of abnormal-to-normal Holter results from baseline to Week 12.

In the GP 25 mcg BID group, 7 (17.5%) sub-study subjects with normal baseline Holter results were reported as abnormal at Week 12. The reported abnormalities included; sinus tachycardia (2 subjects), sinus arrhythmia (1 subject), sustained bradycardia (1 subject), and tachycardia (1 subject). One of these subjects had a normal sinus rhythm reported at Week 12, but due to < 18 hours of monitoring, the findings were considered abnormal. Six subjects had abnormal baseline Holter results with 2 normal reports at Week 12. One of these subjects had sinus rhythm and ventricular tachycardia of ≥ 3 beats at baseline with normal sinus rhythm at Week 12, while another had normal sinus rhythm with non-sustained supraventricular beats at baseline with normal sinus rhythm at Week 12.

In the GP 50 mcg BID group, 7 (14.6%) sub-study subjects had normal Holter results at baseline and abnormal results at Week 12. Abnormal findings at Week 12 included; 1 subject with a blocked atrial beat, 1 subject with a recording time of < 18 hours (however, the available cardiac monitoring was categorized as a normal sinus rhythm), 1 subject with sustained bradycardia (> 30 bpm, but < 40 bpm), 1 subject with runs of atrial fibrillation, 1 subject with ventricular tachycardia (consisting of ≥ 3 beats), and 2 subjects with single blocked P waves. Of the 7 subjects with abnormal Holter findings at baseline, 2 subjects had no shift to normal findings at Week 12; 1 subject had sinus bradycardia at Baseline that was still noted at Week 12; the other subject had normal sinus rhythm and junctional rhythm (relative distribution not defined) and at Week 12 it was noted that the subject had normal sinus rhythm and occasional junctional rhythm.

There was a slight increase in abnormal Holter results captured in the GP arms compared to placebo, however, the sample size was small, differences were minor and did not demonstrate a dose response relationship.

7.4.5 Special Safety Studies/Clinical Trials

There were no special safety studies conducted as part of this NDA.

7.4.6 Immunogenicity

Immunogenicity is not applicable to this small molecule drug product.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Refer to section 7.2.2 Explorations for Dose Response.

7.5.2 Time Dependency for Adverse Events

See sections describing AEs in the 3-month pooled safety database vs. the long-term safety study.

7.5.3 Drug-Demographic Interactions

Across the 3 month and long-term (48 week) safety studies, the relationships between AE occurrence and specific demographic groups (gender, age, race, COPD severity, and geographical region [long-term safety study pool only]) were evaluated.

When AE rates were evaluated based on subject gender, slightly more female subjects reported AEs in the chronic-use studies pool with an overall frequency of AEs for males (placebo 50.6%, GP 25 mcg 39.7%, GP 50 mcg 46.2%) and females (placebo 54.4%, GP 25 mcg 48.1%, GP 50 mcg 56.8%). Similar findings were noted in the long-term safety study pool GP 50 mcg BID group (males 67.1%, females 72.2%) and tiotropium 18 mcg QD (males 64.2%; females 70.4%). While females did experience a higher incidence of AEs, this trend was also noted in the tiotropium arm of the 48 week study and more importantly, the incidence of SAEs in the 3 month studies (placebo: males 6.0%, females 5.1% and GP total: males 3.7%, females 3.5%) and discontinuation due to AEs by gender (placebo: males 8.9%, females 9.7% and GP total: males 3.5%, females 5.9%) were similar for both genders.

When AE rates were evaluated based on subject age, a difference was noted between the chronic-use safety studies pool and the long-term safety study pool. The overall incidence of AEs was slightly higher for subjects 65 to 74 years of age in the chronic-use studies pool GP total group, while in the 48 week long term study the AE incidence was highest for subjects who were ≥ 75 years of age, however, the incidence of AEs was higher for the tiotropium 18 mcg QD group than for the GP 50 mcg BID group. Evaluation of SAEs showed no meaningful difference in the 3 month chronic-use studies, while in the 48 week long-term safety study pool a greater percentage of the subjects ≥ 75 years of age treated with tiotropium experienced SAEs. The incidence of AEs leading to study drug withdrawal in the chronic-use studies pool was similar in subjects across the age groups, while subjects aged ≥ 75 years who received GP in the long-term safety study pool had the greatest study drug discontinuation rate when compared with the other age groups (≥ 75 years: GP 50 mcg 20.3% and tiotropium 18 mcg 6.3%, < 65 years: GP 50 mcg 8.5% and tiotropium 18 mcg 2.3%, 65 to 74 years: GP 50 mcg 9.5% and tiotropium 18 mcg 2.5%). However, due to the small sample size in the ≥ 75 years age category; direct comparisons are difficult. Overall, no clear pattern in AEs leading to withdrawal was noted.

When placebo was compared with GP 25 mcg BID in the 3 month studies, the point estimates for the differences in SAE rates consistently favored GP 25 mcg BID in all subgroups. No trend was noted when placebo was compared with GP 50 mcg BID.

Most of the subjects in the 3 month and 48 week studies pool were white patients with severe COPD residing in the United States; making AE comparisons by race, disease severity and geographic region of limited value.

7.5.4 Drug-Disease Interactions

In the 3 month use studies, the greatest proportion of subjects had COPD severity of ≥ 50% predicted (i.e., moderate disease), followed by COPD severity of ≥ 30% to < 50% predicted (ie, severe disease), with fewest subjects with COPD severity of < 30% predicted (i.e., very severe disease), with limited value in the direct comparison of AEs by COPD severity. The percentages of subjects who experienced AEs were similar across the COPD severity groups for GP (45.3% to 47.5%) and placebo (47.7% to 58.3%). Similar findings were noted in the long term study.

With increasing COPD severity, the rate of SAEs in the 3 month studies also increased in both the placebo group (4.7%, 6.5%, and 8.3% for moderate, severe, and very severe disease subgroups, respectively) and the GP total group (2.9%, 4.1%, and 6.3%, for moderate, severe, and very severe disease subgroups, respectively). Similar findings were noted in the long term study with the greatest incidence of SAEs across COPD severity groups seen in the very severe disease subgroup.

Similar incidences of AEs leading to study drug withdrawal were noted in the 3 month studies for all GP doses in all COPD severity categories (ranged from 2.9% to 6.9%). While in the long term study, in the GP 50 mcg BID group, the highest study drug discontinuation rate was for the very severe disease subgroup (21.6%) followed by the severe disease subgroup (9.8%) and the moderate disease subgroup (8.9%). However, for the tiotropium 18 mcg QD group, the highest study drug discontinuation rate was for the moderate disease subgroup (3.3%) followed by the severe disease subgroup (2.4%) and the very severe disease subgroup (0%).

There are no known effects of GP on liver blood flow or liver metabolizing enzymes.

Renal elimination of GP accounts for about 60% to 70% of total clearance of systemically available GP; the remaining 30% to 40% of clearance is partially accounted for by biliary clearance, but the majority of non-renal clearance is thought to be due to metabolism. As GP is largely renally eliminated, GP should be used with caution in patients with renal impairment.

Inhibition of the hERG current was observed with glycopyrrolate only at concentrations significantly higher than the maximum human exposure at the recommended clinical dose. Anticholinergic drugs are known to be associated with cardiovascular AEs, such as arrhythmias (including supraventricular tachycardia and atrial fibrillation), angina, nonspecific chest pain, and edema. However, review of the cardiovascular AE data in the chronic-use and long-term safety studies, provide support for the overall cardiovascular safety of GP 25 mcg.

Pharmacological studies showed parasympathetic inhibition in multiple species after systemic administration of GP. Observations included mydriasis and antitremorine activity in mice,

inhibition of gastric secretion in rats and dogs, inhibition of salivary secretion in dogs, blocked lacrimation in rats, and decreased intestinal tone and motility of intestinal contractions in dogs. Overall, anticholinergic special interest events were infrequent in clinical studies with GP.

In pharmacological studies evaluating parasympathetic inhibition in multiple species after systemic administration of GP, no effects on blood pressure or respiration and no central effects in mice were observed.

7.5.5 Drug-Drug Interactions

Nonclinical studies have not been performed to specifically evaluate potential interactions of GP with drugs that may be co-administered with GP. The maximum concentration for GP at the maximum intended clinical dose of GP (50 mcg BID [ie, total daily dose of 100 mcg]) is 69.4 pg/mL (0.17 nM) (Study SUN101-201). At these low systemic concentrations, the potential for GP to be a perpetrator of drug-drug interactions with cytochrome 450 or transporter substrates is remote and the potential for GP to be a victim of cytochrome P450 or transporter inhibitors, given the mechanisms by which the drug is cleared, is also remote.

The concurrent use of GP with other anticholinergics or medications with anticholinergic activity, such as phenothiazines, anti-Parkinson's drugs, or tricyclic antidepressants, may intensify the antimuscarinic effects and result in an increase in anticholinergic side effects.

In the Phase 3 studies, the only disallowed medications were LAMAs, short-acting β-agonists (except for rescue use of albuterol), and theophylline; parenteral corticosteroids were prohibited at study entry. In the clinical studies, concurrent administration of GP and other drugs commonly used in the treatment of COPD including sympathomimetics (long- and short-acting β2 agonists), anticholinergics (short-acting anti-muscarinic antagonists), and oral and inhaled steroids showed no increases in adverse drug reactions.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Following chronic (6-month) inhalation administration of GP to rats, no neoplastic or pre-neoplastic changes were observed at dose levels that resulted in systemic exposures greater than 14,000-fold higher than those anticipated following repeated administration at the maximum intended clinical dose. Consistent with the recommendation received from the Division at the pre-investigational new drug (IND) meeting (FDA, pre-IND meeting minutes, 16 Mar 2011) and confirmed at the End of Phase 2 Meeting (FDA, End of Phase 2 meeting minutes, 17 Oct 2013), no carcinogenicity studies were conducted in support of the clinical development of GP. In addition, studies conducted in support of the clinical development of NVA237 (Seebri Neohaler, 15.6 mcg of glycopyrrolate inhaled BID for the treatment of COPD, Approved October 29, 2015), no glycopyrrolate-related neoplastic findings were observed after inhalation

administration for 2 years in Wistar rats or oral gavage administration for 26-weeks in wild-type and CByB6F1-Tg(HRAS)2jic transgenic mice.

GP has been shown to be non-genotoxic in vitro (Ames mutagenicity assay and chromosomal aberration assay in human peripheral blood lymphocytes) and in vivo (rat bone marrow micronucleus test).

7.6.2 Human Reproduction and Pregnancy Data

No GP related effects on male fertility parameters were noted in rats. Decreased corpora lutea and implantation sites were noted in female rats. Dietary administration of GP to rats resulted in diminished rates of conception in a dose-related manner. Embryo-fetal development studies with GP in rats and rabbits revealed no teratogenic effects; dose-related decreased pup survival was noted in rats. No effects on peri- or postnatal development were observed in rats.

7.6.3 Pediatrics and Assessment of Effects on Growth

N/A in COPD.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No AEs of overdose of GP have been reported in clinical studies. An overdose of GP may lead to anticholinergic signs and symptoms, such as nausea, vomiting, dizziness, lightheadedness, blurred vision, increased intraocular pressure (causing pain, vision disturbances, or reddening of the eye), obstipation, and difficulties in voiding.

In COPD patients, orally inhaled administration of GP at a total daily dose of 200 mcg for 28 consecutive days (maximum of 1 mg) was well tolerated. Pharmacokinetic results from several studies conducted in COPD patients showed that a single well-tolerated dose of 1000 mcg had a peak (maximum) plasma concentration (Cmax) of 1534 pg/mL and an area under the concentration-time curve from time zero to infinity (AUC0–∞) of 5271 pg·hr/mL. These values are approximately 44- and 21-fold higher, respectively, than the estimated daily Cmax of 34.5 pg/mL and AUC0–∞ of 255 pg·hr/mL for a GP 25 mcg BID dose regimen at steady state.

7.7 Additional Submissions / Safety Issues

7.7.1 120 Day Safety Update

The updated safety information provided in the 120-Day update includes information for the reporting period of March 25, 2016 through October 10, 2016. The submission includes new safety information from the completed study, SUN101-105, evaluating a single dose of GP 50 mcg QD. The primary objective of the study was to determine the extent of pulmonary absorption of glycopyrrolate following dosing via eFlow nebulizer and Seebri Breezhaler with and without activated charcoal in subjects with moderate to severe COPD.

Overall, there were no new safety signals identified in this safety update. There were no deaths or serious adverse events reported during the study. Overall, AEs were reported by 6 (20.7%) to 11 (40.7%) subjects across treatments, with a consistently higher incidence in the charcoal groups. The most commonly reported events (higher in the charcoal groups) occurred in the gastrointestinal disorders SOC (preferred terms: abdominal discomfort, abdominal pain, and upper abdominal pain) and nervous system disorders SOC (preferred terms: headache, migraine). Other than the events noted in the charcoal group, the type and frequencies of events reported in this 4-month Safety Update were consistent with those reported at the time of the NDA submission and therefore confirmed a similar safety profile for GP dosing.

7.7.2 Long Term Safety

The findings from the 48 week safety study were consistent with the results seen for the chronic use 3 month safety database. No new safety signal was identified. Results of the long-term safety trial are embedded within the 3-month safety database review, with details provided, as needed.

8 Postmarket Experience

SUN-101 (GP) has not been granted regulatory approval in any country or territory. Therefore, there is no post-marketing clinical experience or safety data available.

9 Appendices

9.1 Literature Review/References

1. NDA 21936, Medical Review by Dr. Robert Lim
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/021936Orig1s000MedR.pdf

2. Robert A. Wise. Tiotropium Respimat Inhaler and the Risk of Death in COPD. NEJM October 17, 2013 vol. 369 no. 16

9.2 Labeling Recommendations

Suggested Revisions to Proposed Labeling

While the labeling has not been finalized at the time this review is being completed, we have proposed the following general recommendations as summarized below.

(b) (4)

(b) (4)

9.3 Advisory Committee Meeting

The risk-benefit assessment of the use of anticholinergic medications in the treatment of COPD is well-established; further, GP is not a NME. Therefore, an advisory committee was neither convened, nor required, for this application.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ERIKA N TORJUSEN
04/27/2017

BANU A KARIMI SHAH
04/27/2017

MEDICAL OFFICER FILING REVIEW
Division Of Pulmonary and Allergy Products (HFD-570)

APPLICATION:	NDA 208437	**TRADE NAME:**	Lonhala Magnair
APPLICANT/SPONSOR:	Sunovion	**USAN NAME:**	Glycopyrrolate
MEDICAL OFFICER:	Erika Torjusen, M.D., MHS.		
TEAM LEADER:	Banu Karimi-Shah, M.D.	**CATEGORY:**	Long-acting anticholinergic
DATE:	October 11, 2016	**ROUTE:**	Inhalation via closed system nebulizer (eFlow, PARI)

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
July 29, 2016	July 29, 2016	NDA 208437	Original NDA

REVIEW SUMMARY: This is a medical officer 45-day Filing Review of a 505(b)(2) NDA 208437 for the drug-device combination product, glycopyrrolate inhalation solution delivered via closed system nebulizer (eFlow, PARI). Sunovion has developed glycopyrrolate inhalation solution as a long-term, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema. The proposed dose of glycopyrrolate is 25 mcg BID. Glycopyrrolate (ie, glycopyrronium bromide), a quaternary ammonium compound, is a muscarinic antagonist in the anticholinergic class of drugs that has been in clinical use for longer than 30 years and approved for systemic (intravenous [IV] or intramuscular [IM]), and oral administration (Robinul and Robinul Forte), oral solution (Cuvposa), and as a dry powder for oral inhalation (Seebri Neohaler and in combination with indacaterol as Utibron Neohaler). The key studies for this NDA includes two dose ranging studies (EP-101-04 and SUN101-201), two 12-week confirmatory phase 3 safety and efficacy studies, (SUN101-301 and SUN101-302) and one 48-week long-term safety study (SUN101-303). The submission is provided in eCTD format.

The Applicant has included the necessary elements (21 CFR 314.50) in this NDA, and therefore the submission is fileable. Based upon a preliminary review of the application, no data integrity concerns were identified. An evaluation of effect size by site did not reveal any sites which enrolled a disproportionally large number of patients and/or had a treatment effect that was much different than the overall treatment effect. This was a large clinical development program that enrolled relatively small numbers of patients at each clinical site. Therefore, it is unlikely that one clinical site would drive the treatment effect. In addition, glycopyrrolate is known clinical entity (as stated above). For all these reasons, we have concluded that an OSI inspection will not be required/conducted for this application.

The filing meeting was held on September 20, 2016. Background information is provided in the filing meeting slides included in this review.

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS:	**FILEABLE___X___**	**NOT FILEABLE_____**	
	APPROVAL_____	**APPROVABLE_____**	**NOT APPROVABLE_____**
OTHER ACTION:	**COMMENTS FOR SPONSOR_____**		

1. Items Required for Filing

The following items pertinent to a clinical review are included in the submission.

- Application form (FDA 356h): 1.1.2
- Index : eCTD
- Summary 2.7 (clinical summary)
- Clinical study reports
    - Study reports 5.3.5.1
    - Reports of analyses of data from more than one study: 5.3.5.3
    - Integrated summary of efficacy 5.3.5.3
    - Integrated summary of safety 5.3.5.3
    - Good Clinical Practice: within the body of each CSR
    - Debarment certification: 1.3.3
    - Pediatric use: 1.9.1 (full waiver request)
- Labeling: 1.14
- Case report forms: 5.3.5.1
- Financial disclosure 1.3.4

2. Pediatric Development

Sunovion requested a full waiver in pediatric patients aged 0 to 17 years because studies would be impossible or highly impractical. A proposed Pediatric Study Plan (PSP) was submitted within 60 days of the End-of-Phase 2 meeting (IND 110,663, Sequence 0038; November 12, 2013). FDA reviewed the proposed PSP with the Pediatric Review Committee (PeRC) and notified Sunovion (FDA Correspondence dated February 6, 2014) that they were in agreement with proposed PSP. In accordance with FDASIA, the agreed upon initial PSP noting the waiver was submitted within 90 days of the FDA correspondence (IND 110,663, Sequence 0043; February 21, 2014).

3. Review Timeline

Submission/Rec'd date:	July 29, 2016
Filing date:	September 27, 2016
74-Day Letter:	October 11, 2016
File/Plan meeting:	September 20, 2016
MCR meeting:	December 19, 2016
WU meeting:	April 18, 2017
Primary review:	April 27, 2017
Secondary review:	May 1, 2017
PeRC:	TBD
CDTL memo:	May 8, 2017
DD memo:	May 29, 2017
PDUFA date:	**May 29, 2017**

4. Filing Checklist

On initial overview of the NDA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	x			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	x			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	x			
10	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			
11	Has the applicant submitted a benefit-risk analysis for the product?	x			
12	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	x			Robinul® Injectable (NDA 17558), Robinul® Oral (NDA 12827), Cuvposa® oral solution (NDA 22571), Seebri™ Neohaler® (NDA 207923)

	Content Parameter	Yes	No	NA	Comment
DOSE					
13	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: EP-101-04 Study Title: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, DOSE-RANGING STUDY OF THE EFFICACY AND SAFETY OF EP-101 IN SUBJECTS WITH MODERATE-TO-SEVERE CHRONIC OBSTRUCTIVE PULMONARY DISEASE: GOLDEN-2 (GLYCOPYRROLATE FOR OBSTRUCTIVE LUNG DISEASE VIA ELECTRONIC NEBULIZER) Sample Size: 263 Arms: R 1:1:1:1:1 ratio x 28 d Placebo BID GP 12.5 mcg BID GP 25 mcg BID GP 50 mcg BID GP 100 mcg BID All via eFlow CS nebulizer Study Number: SUN101-201 Study Title: A DOSE-RANGE FINDING STUDY OF SUN-101 IN SUBJECTS WITH MODERATE TO SEVERE COPD: GOLDEN 6 (GLYCOPYRROLATE FOR OBSTRUCTIVE LUNG DISEASE VIA ELECTRONIC NEBULIZER) Sample Size: 88 (6 way CO) Arms: Placebo BID GP 3 mcg BID GP 6.25 mcg BID GP 12.5 mcg BID GP 50 mcg BID	x			

	Content Parameter	Yes	No	NA	Comment
	Aclidinium 400 mcg BID GP and Pbo via eFlow CS nebulizer Aclidinium via Tudorza Pressair DPI				
EFFICACY					
14	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: SUN101-301 Pivotal Study #2: SUN101-302 Supportive Study #3: SUN101-303 Indication: Long-term, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema	x			
15	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
16	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			
17	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			x	
SAFETY					
18	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
19	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	x			
20	Has the applicant presented a safety assessment based on all current worldwide knowledge	x			

	Content Parameter	Yes	No	NA	Comment
	regarding this product?				
21	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	x			
22	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	
23	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	x			
24	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
25	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			
OTHER STUDIES					
26	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			
27	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			
ABUSE LIABILITY					
29	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	Content Parameter	Yes	No	NA	Comment
30	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			x	
DATASETS – per stats					
31	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
32	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
33	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
34	Are all datasets to support the critical safety analyses available and complete?	x			
35	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	x			
CASE REPORT FORMS					
36	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	
FINANCIAL DISCLOSURE					
38	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
39	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ____Yes____

5. Comments for the 74-day letter

Provide the SGRQ results (or its location within the NDA) evaluated as a responder analysis (i.e. the proportion of subjects achieving a -4.0 unit reduction, including Odds Ratios and 95% CI) across treatments by study for studies SUN101-301 and SUN101-302.

6. Filing meeting slides

NDA 208437
Glycopyrrolate Inhalation Solution
Long Acting Anticholinergic
Sunovion Pharmaceuticals, Inc.

Erika Torjusen, MD, MHS
Filing Meeting
9/20/16
Clinical Review

Introduction

- 505(b)(2)
- **Recommendation:** Fileable
- **Products:** Glycopyrrolate (GP) (not an NME)
- **Class:** Long Acting Anticholinergic
- **Route:** Inhalation via closed system nebulizer (eFlow, PARI)
- **Indication:** Long-term, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema
- **Dose:** 25 mcg BID
- Drug-device combination product

Reference Products:
Robinul® Injectable (NDA 17558),
Robinul® Oral (NDA 12827),
Cuvposa® oral solution (NDA 22571),
Seebri™ Neohaler® (NDA 207923)
Published literature

Key Regulatory History

Interaction	Date	Highlights
Pre-IND	3/16/11	Agreed relying on information of reference products to support NDA acceptable
Type C WRO	6/20/12	Data only support BID dosing Guidance on doses/study design for P2 EP-101-04 study
Type B EOP2	10/17/13	Agreed completed clinical pharmacology studies adequate Agreed systemic levels GP inhalation solution are lower than approved RLDs SUN-101 studies no increase in QTc intervals- formal QTc study not required EP-101-04 data not sufficient to characterize the dose response Rec study SUN101-201 to support doses for P3 and characterize lower end of dosing curve, including dose likely ineffective
Type C TCON	10/8/14	Agreed data SUN101-201 support 2 doses in P3 25 mcg and 50 mcg BID Long-term safety study (50 mcg BID) not unreasonable for investigation
Type B pre-NDA	5/11/16	Agreed clinical study report for SUN101-105 could be provided without integrated analyses in the 120 day safety update

Module 1.6.2, Table 1, Page 3 Meetings

3

Key Dose Selection Trials

Study	Design	Duration	N	Treatment	1° Endpoint
P2 Dose Ranging					
EP-101-04	R, DB, PG, PC Mod- severe COPD	28 days	R:282 Comp: 263	R 1:1:1:1:1 ratio x 28 d Placebo BID GP 12.5 mcg BID GP 25 mcg BID GP 50 mcg BID GP 100 mcg BID All via eFlow CS nebulizer	Δ from baseline in placebo-adjusted trough FEV1 on Day 28
SUN101-201	R, DB,PC, 6-way CO, OL Active Control 7 day treatment; 5-7 day W/O between doses Mod- severe COPD	7 days each separated by 5-7 day W/O	R: 96 Comp: 88	Placebo BID GP 3 mcg BID GP 6.25 mcg BID GP 12.5 mcg BID GP 50 mcg BID Aclidinium 400 mcg BID GP and Pbo via eFlow CS nebulizer Aclidinium via Tudorza Pressair DPI	Δ from baseline in placebo-adjusted trough FEV1 on treatment Day 7

Module 2.7.5 Table 1, Page 15, ISE
Reference Products: Robinul® injectable (NDA 17-555), Robinul® Oral (NDA 12-827), Cuvposa® oral solution (NDA 22-571), glycopyrrolate as an inhalation powder (Sozbin™ Neohaler®) for the treatment of patients with COPD and published literature.

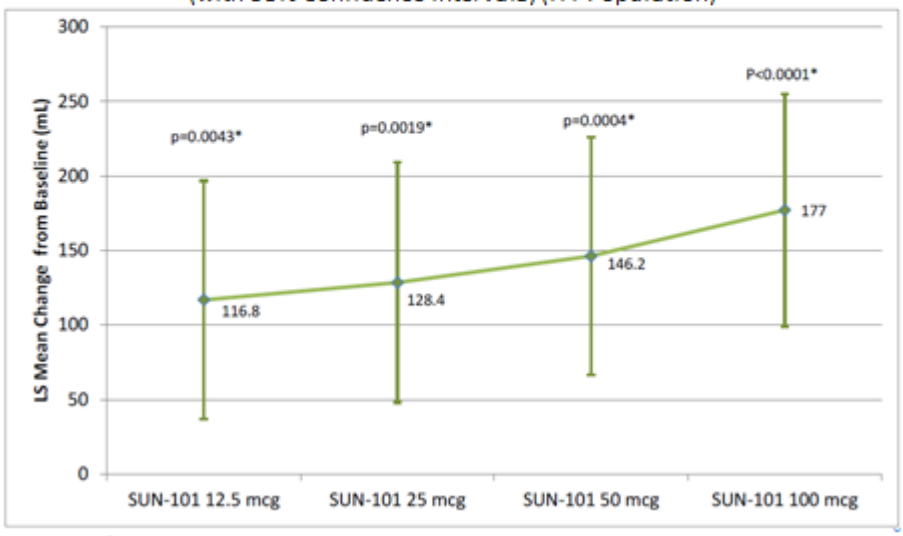
Key Clinical Trials

Study	Design	Duration	N	Treatment	1° Endpoint
P3 Confirmatory S/E Trials					
SUN101-301	R, DB, PG, PC Mod- severe COPD	12 weeks	R: 653 Comp: 595 Sub Study Enroll: 153 Comp: 144	1:1:1 ratio: SUN-101 50 mcg BID SUN-101 25 mcg BID Placebo BID All via eFlow CS nebulizer	Trough FEV1 at Week 12 (CFB)
SUN101-302	R, DB, PG, PC Mod- severe COPD	12 weeks	R: 641 Comp: 580	1:1:1 ratio: SUN-101 50 mcg BID SUN-101 25 mcg BID Placebo BID All via eFlow CS nebulizer	Trough FEV1 at Week 12 (CFB)
SUN101-303	R, OL, PG, AC Moderate-very severe COPD	48 weeks	R: 1087 Comp: 838 Substudy Enroll: 102 Compl: 85	4:3 ratio: SUN 101 50 mcg BID Spiriva (tiotropium) 18 mcg QD Via eFlow CS nebulizer or Handihaler	Safety Secondary/supportive efficacy: Trough FEV1 over 48 weeks (CFB)

Module 2.7.5, Table 1, Page 17, ISE

Dose Evaluation EP-101-04

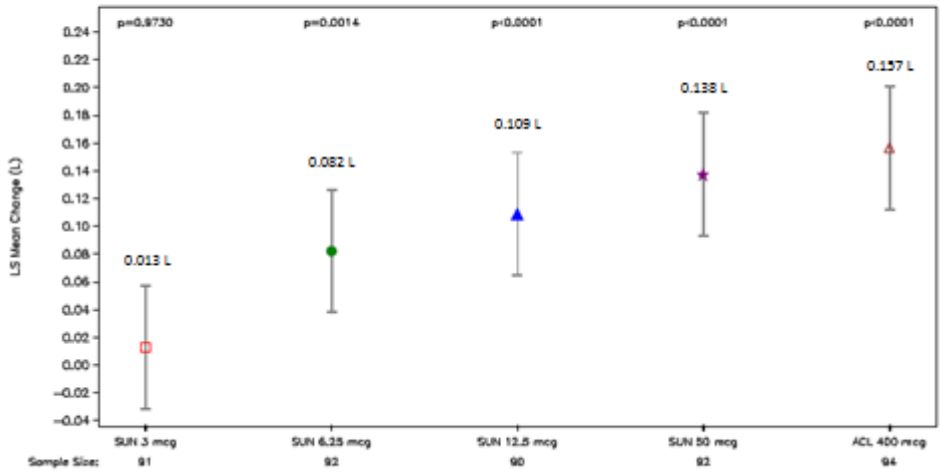
Change from Baseline in Trough FEV1 on Day 28 Compared with Placebo
(with 95% Confidence Intervals) (ITT Population)



CSR EP 101 04, Figure 2, Page 61

Dose Evaluation SUN101-201

Change from Baseline in Trough FEV1 on Day 7 Compared to Placebo
(95% Confidence Intervals) (Efficacy Population)



CSR SUN101-201, Figure 1, Page 65

Primary Efficacy

Primary and Key Secondary Efficacy Endpoints:
On-treatment Data (SUN101-301 ITT and SUN101-302 ITT Population)

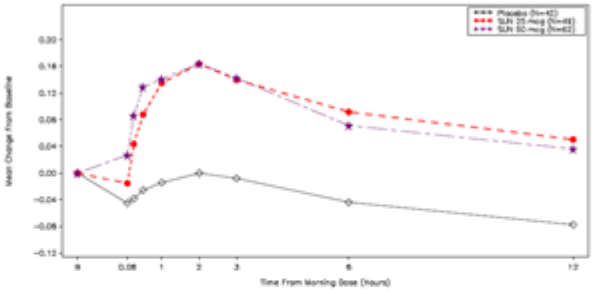
Parameter	Comparison to Placebo	Study SUN101-301				Study SUN101-302			
		SUN-101 25 mcg BID N = 217		SUN-101 50 mcg BID N = 218		SUN-101 25 mcg BID (N =214)		SUN-101 50 mcg BID (N = 214)	
	Statistic	CFB	Order[a]	CFB	Order[a]	CFB	Order[a]	CFB	Order[a]
Trough FEV_1 at Week 12	LS Mean Diff (SE)	0.1052 (0.02060)		0.1264 (0.02076)		0.0840 (0.02069)	NA	0.0820 (0.02055)	NA
	95% CI	(0.0647, 0.1457)	NA	(0.0856, 0.1672)	NA	(0.0433, 0.1246)		(0.0417, 0.1224)	
	Adjusted *P* Value	0.0001[b]		<0.0001[b,c]		0.0001[b]		<0.0001[b,c]	
FEV_1 AUC_{0-12} at Week 12 (Substudy Population)	LS Mean Diff (SE)	0.1024 (0.04541)		0.1235 (0.04259)		NA	NA	NA	NA
	95% CI	(0.0125, 0.1922)	2	(0.0392, 0.2078)	3				
	Adjusted *P* Value	0.1034		0.0264[b]					
Trough FVC at Week 12	LS Mean Diff (SE)	0.1494 (0.03302)		0.1667 (0.03329)		0.1301 (0.03264)	3	0.1126 (0.03241)	3
	95% CI	(0.0845, 0.2142)	4	(0.1013, 0.2321)	4	(0.0659, 0.1942)		(0.0489, 0.1762)	
	Adjusted *P* Value	<0.0001[b]		<0.0001[b]		0.0005[b]		0.0033[b]	
SGRQ at Week 12/EOS/EOT[d]	LS Mean Diff (SE)	-3.072 (1.1250)		-1.848 (1.1395)		−3.585 (1.1231)	2	−3.557 (1.1159)	2
	95% CI	(-5.282, -0.862)	3	(-4.087, 0.390)	2	(−5.791, −1.379)		(−5.749, −1.365)	
	Adjusted *P* Value	0.0392[b]		0.4053		0.0060[b]		0.0061[b]	
Rescue Medication Use Over 12-week, Treatment Period	LS Mean Diff (SE)	0.006 (0.1730)		-0.217 (0.1703)		−0.305 (0.1812)	1	−0.140 (0.1800)	1
	95% CI	(-0.333, 0.346)	1	(-0.552, 0.117)	1	(−0.661, 0.051)		(−0.494, 0.214)	
	Adjusted *P* Value	>0.9999		0.4053		0.1853		0.8744	

Module 2.5, Clinical Overview, Table 2, Page 14

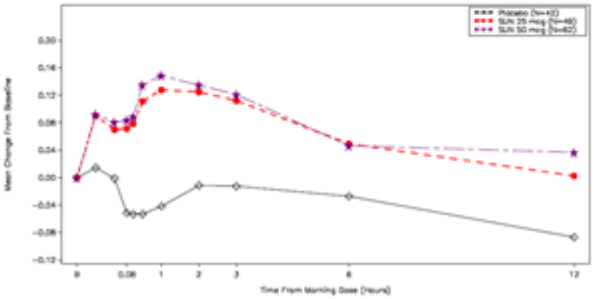
8

Change from Baseline in FEV1 (L) Over Time (0-12h)

Week 0



Week 12



CSR GP501 Figures 9 and 10, Page 111

9

Safety Population

- Chronic-Use Safety Pool:
  - SUN101-301 & SUN101-302 (12 week studies)
    - Placebo (N = 430)
    - GP 25 mcg BID (N = 431)
    - GP 50 mcg BID (N = 432)
      - GP Total (N = 863)
- Long Term Safety Pool:
  - SUN101-303 (48 week study)
    - GP 50 mcg BID (N = 620)
    - Tiotropium 18 mcg QD (N = 466)

10

Disposition

	12 week				48 week	
	Placebo N (%)	GP 25 mcg BID N (%)	GP 50 mcg BID N(%)	Total GP N (%)	GP 50 mcg BID N (%)	Tio 18 mcg QD N (%)
Total treated	430	431	432	863	620	466
Completed Study	379 (88.1)	396 (91.9)	400 (92.6)	796 (92.2)	436 (70.3)	402 (86.3)
Withdrawal of Study Drug	77 (17.9)	54 (12.5)	51 (11.8)	105 (12.2)		
Primary Reason for Withdrawal of Study Drug						
AE	39 (9.1)	23 (5.3)	19 (4.4)	42 (4.9)		
Lack of Efficacy	6 (1.4)	3 (0.7)	5 (1.2)	8 (0.9)		
Protocol Violation	1 (0.2)	0	0	0		
Pregnancy	0	0	0	0		
Noncompliance	2 (0.5)	2 (0.5)	0	2 (0.2)		
Other	29 (6.7)	26 (6.0)	27 (6.3)	53 (6.1)		
Discontinuation from Study	51 (11.9)	35 (8.1)	32 (7.4)	67 (7.8)	184 (29.7)	64 (13.7)
Primary Reason for Discontinuation from Study						
AE					63 (10.2)	15 (2.8)
Lost to Follow-up	5 (1.2)	8 (1.9)	6 (1.4)	14 (1.6)		
W/D by Subject	37 (8.6)	20 (4.6)	19 (4.4)	39 (4.5)	78 (12.5)	32 (6.9)
Lack of efficacy					13 (2.1)	3 (0.6)
Protocol Violation					3 (0.5)	2 (0.4)
Non Compliance					3 (0.5)	1 (0.2)
Death	0	0	1 (0.2)	1 (0.1)	2 (0.3)	2 (0.4)
Other	9 (2.1)	7 (1.6)	6 (1.4)	13 (1.5)	22 (3.5)	11 (2.4)

SCS Table 6, Page 27 and Table 7 Page 29 SCS

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Demographics

	12 week				48 week	
	Placebo N (%)	GP 25 mcg BID N (%)	GP 50 mcg BID N(%)	Total GP N (%)	GP50 mcg BID N (%)	Tiotropium 18 mcg QD N (%)
Total treated	450	451	452	865	820	466
Age (years)						
Mean (SD)	65.7 (8.81)	65.5 (8.71)	62.6 (8.64)	62.9 (8.68)	63.3 (8.46)	63.3 (8.97)
Median	64.0	65.0	62.0	65.0	64.0	65.0
Minimum, Maximum	41, 84	40, 85	40, 87	40, 87	43, 86	41, 89
Age Category N (%)						
< 65 Years	220 (51.2)	251 (55.6)	254 (56.2)	485 (56.2)	530 (55.2)	256 (54.9)
65 – 74 Years	169 (59.5)	155 (35.5)	140 (32.4)	295 (34.0)	251 (37.5)	162 (34.8)
≥ 75 Years	41 (9.5)	47 (10.9)	38 (8.8)	85 (9.8)	39 (9.5)	48 (10.3)
Gender – N (%)						
Male	255 (54.7)	242 (56.1)	247 (57.2)	489 (56.7)	550 (56.5)	260 (55.8)
Race – N (%)						
White	388 (90.2)	385 (89.5)	386 (89.4)	771 (89.5)	582 (95.9)	436 (93.6)
Black or African American	39 (9.1)	42 (9.7)	44 (10.2)	86 (10.0)	35 (5.6)	27 (5.8)
Cardiovascular Risk – N (%)						
Low	152 (35.3)	156 (36.2)	157 (36.3)	313 (36.3)	219 (35.5)	169 (36.3)
High	278 (64.7)	275 (63.8)	275 (63.7))	550 (63.7)	401 (64.7)	297 (63.7)
Geographic Region – n (%)						
US	(100)	(100)	(100)	(100)	556 (89.7)	421 (90.5)

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COPD Characteristics

	12 week			
	Placebo N (%)	GP 25 mcg BID N (%)	GP 50 mcg BID N(%)	Total GP N (%)
Total treated	450	451	452	865
COPD Exacerbations within 12 Months, N (%)				
Yes	95 (21.6)	84 (19.5)	73 (16.9)	157 (18.2)
# COPD Exacerbations within 12 Mo				
Mean (SD)	0.4 (2.67)	0.2 (0.56)	0.3 (2.42)	0.3 (1.75)
FEV1 Reversibility (% Imp)				
Mean (SD)	17.1 (15.26)	15.6 (15.04))	17.0 (14.11)	17.5 (14.60)
Post-bronch FEV1, N (%)				
< 50% predicted	24 (5.6)	29 (6.7)	55 (6.1)	64 (7.4)
≥ 50% - < 80% pred	155 (35.6)	156 (36.2)	158 (36.6)	314 (36.4)
≥ 80% predicted	255 (58.6)	245 (56.8)	259 (59.5)	484 (56.1)
Missing	0	1 (0.2)	0	1 (0.2)
History of Tobacco Use, n (%)				
Current	218 (50.7)	240 (55.7)	226 (52.5)	466 (54.0)
Past	212 (49.3)	191 (44.3)	206 (47.7)	397 (46.0)
Background LABA Use N (%)				
Yes	152 (50.7)	155 (51.5)	155 (51.5)	270 (51.5)
ICS Use N (%)				
Yes	127 (29.5)	126 (29.2)	122 (28.2)	248 (28.7)

Module 2.7.4, Table 5, Page 24 SCS

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Adverse Events Primary Safety Database

	12 week				48 week	
	Placebo N (%)	GP 25 mcg BID N (%)	GP 50 mcg BID N(%)	Total GP N (%)	GP 50 mcg BID N(%)	Tio 18 mcg QD N (%)
Total treated	430	431	432	863	620	466
Any AE	225 (52.3)	189 (43.9)	219 (50.7)	408 (47.3)	430 (69.4)	312 (67)
AE leading to drug DC	40 (9.3)	22 (5.1)	17 (3.9)	39 (4.5)	62 (10.0)	13 (2.8)
Any SAE	24 (5.6)	15 (3.5)	18 (4.2)	33 (3.8)	76 (12.3)	49 (10.5)
AE leading to Death	0	0	1 (0.2)	1 (0.1)	3 (0.5)	4 (0.9)
Table 9.3, Page 840 ISS, Table 6, Page 31 SCS						

Deaths

Chronic Use (12 week): 1 GP 50 mcg (diastolic dysfunction, COPD exac, Pulm HTN)

Long Term (48 week): 3 GP 50 mcg (pancreatic ca, PNA, dehydration and hypokalemia)

4 Tio (cardio resp arrest, arteriosclerosis, COPD exacerbation, lung adenocarcinoma

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Adverse Events
≥ 2.0% of Subjects (12 week data)

	12 week			
	Placebo N (%)	GP 25 mcg BID N (%)	GP 50 mcg BID N(%)	Total GP N (%)
Total treated	430	431	432	863
Any AE	225 (52.3)	189 (43.9)	219 (50.7)	408 (47.3)
Respiratory, Thoracic, Mediastinal D/O	107 (24.9)	86 (20.0)	102 (23.6)	188 (21.8)
Cough	30 (6.4)	30 (7.0)	39 (9.0)	69 (8.0)
COPD	37 (8.6)	28 (6.5)	37 (8.6)	65 (7.5)
Dyspnoea	15 (3.0)	21 (4.9)	14 (3.2)	35 (4.1)
Infections and Infestations	60 (14.0)	51 (11.8)	71 (16.4)	122 (14.1)
URI	4 (0.9)	6 (1.4)	15 (3.5)	21 (2.4)
UTI	6 (1.4)	9 (2.1)	12 (2.8)	21 (2.4)
General D/O, Admin Site Conditions	27 (6.3)	27 (6.3)	24 (5.6)	51 (5.9)
Edema Peripheral	4 (0.9)	4 (0.9)	9 (2.1)	13 (1.5)
Chest Discomfort	9 (2.1)	5 (1.2)	4 (0.9)	9 (1.0)
Musculoskeletal/Connective Tissue D/O	29 (6.7)	14 (3.2)	27 (6.3)	41 (4.8)
Arthralgia	5 (1.2)	3 (0.7)	9 (2.1)	12 (1.4)
Nervous System Disorders	15 (3.5)	20 (4.6)	21 (4.9)	41 (4.8)
Headache	10 (2.3)	7 (1.6)	8 (1.9)	15 (1.7)
Module 2.7.4, Table 9 Page 34 SCS				

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MACE 12 Week Data

MACE Category	12 week								48 week			
	Placebo N=430 TT=122.3		GP 25 mcg BID N=431 TT=126.1		GP 50 mcg BID N=432 TT=128.5		Total GP N=863 TT=254.6		GP 50 mcg BID N=620 TT = 467.4		TIO 18 mcg QD N=466 TT = 394.3	
	N (%)	IR	N (%)	IR	N (%)	IR	N (%)	IR	N (%)	IR	N (%)	IR
MACE Score	2 (0.5)	16.4	0	0	3 (0.7)	23.3	3 (0.3)	11.8	3 (0.5)	6.4	8 (1.7)	20.3
CV Death	0	0	0	0	1 (0.2)	7.8	1 (0.1)	3.9	1 (0.2)	2.1	2 (0.4)	5.1
Nonfatal MI	2 (0.5)	16.4	0	0	1 (0.2)	7.8	1 (0.1)	3.9	2 (0.3)	4.3	5 (1.1)	12.7
Nonfatal stroke	0	0	0	0	1 (0.2)	7.8	1 (0.1)	3.9	0	0	1 (0.2)	2.5

Module 2.7.4 SCS Table 17, page 51 and Table 18, page 52
TT total time, IR = incidence rate per thousand person-years

Summary includes on-treatment adjudicated MACE events which occurred on or after the first date of study drug and up to 30 days after the last dose of study drug. MACE score defined as the total number of subjects with adjudicated cardiovascular deaths, nonfatal myocardial infarctions, or nonfatal strokes. Total time defined as the time from the first date of study drug until 30 days after the last dose of study drug, in years. Incidence rate = n/TT x 1000. Percentages calculated based on the number of safety population subjects in each treatment group. A subject was counted at most once per category.

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Labeling

(b) (4)

Summary

- Fileable
- No plans for advisory committee
- Standard review clock
- No additional consults
- OSI inspections: d/w stats to determine which sites to investigate
- Proposed tradename -Lonhala Magnair "conditionally acceptable"
- Nothing identified to communicate to the sponsor in the filing letter

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Mid Cycle Deliverables

- Complete protocol reviews
- Efficacy/safety review
- Preliminary review of the label
- Review non-pooled SGRQ data

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ADMINISTRATION

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ERIKA N TORJUSEN
10/11/2016

BANU A KARIMI SHAH
10/11/2016