CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208437Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	208437
Submission Date	07/29/2016
Submission Type	505(b)(2)
Generic Name	Glycopyrrolate Inhalation Solution
OCP Review Team	Clinical Pharmacology Reviewers - Bhawana Saluja, Ph.D., Anshu Marathe Ph.D. (Team Leader) Pharmacometric Reviewers - Chao Liu, Ph.D., Jingyu Yu, Ph.D. (Team Leader)
OCP Division	Clinical Pharmacology 2
OND Division	Division of Pulmonary, Allergy, and Rheumatology Products
Applicant	Sunovion Respiratory Development Inc.
Dosage Form and Strength	Solution for oral inhalation, each 1 mL unit-dose single-use vial contains 25 mcg of glycopyrrolate (25 mcg/mL)
Proposed Dosing Regimen	Inhalation of the contents of one vial (25 mcg/mL strength) twice-daily via a portable nebulizer closed-system (CS) eFlow® nebulizer
Relevant IND/NDA	IND 110663
Proposed Indication	Maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including emphysema and/or chronic bronchitis

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1. Executive Summary

Sunovian has submitted NDA 208437 (glycopyrrolate solution for inhalation) under 505(b)(2) pathway seeking the marketing approval for Lonhala Magnair for the proposed indication of "*long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema*". The proposed dosing regimen is oral inhalation of the contents of one vial (each 1 mL vial contains 25 mcg glycopyrrolate) twice daily using a closed-system (CS) eFlow® nebulizer.

The Sponsor supports this NDA submission with 6 clinical pharmacology studies. The PK of glycopyrrolate inhalation solution was evaluated in one Phase 1 (SUN101-105) and four Phase 2 studies (EP-101-01, EP-101-02, EP-101-03 and SUN101-201). All these studies were conducted in patients with moderate to severe COPD. It should be noted, however, that studies EP-101-01, EP-101-02 and EP-101-03 did not use the to-be-marketed device, i.e., CS eFlow® nebulizer. The following are the major findings from the current review:

1) Following administration of glycopyrrolate inhalation solution via CS eFlow® nebulizer, the median T_{max} for glycopyrrolate occurs around approximately 20 minutes and the elimination half-life is approximately 5 hours. (Study SUN101-105)

2) The dosing regimen for glycopyrrolate inhalation solution has been adequately explored. Prior to the confirmatory phase 3 trials, two pivotal dose ranging trials (EP-101-04 and SUN101-201) were conducted in patients with COPD exploring total daily doses from 3 mcg to 100 mcg administered twice daily (BID) (Table 2). Glycopyrrolate inhalation solution at 25 and 50 mcg BID dosing regimen demonstrated a clinically meaningful (>0.100 L) difference in trough FEV1compared to placebo. Therefore, glycopyrrolate inhalation solution at 25 and 50 mcg BID were selected for confirmation in the Phase 3 program.

3) The systemic exposure following single-dose administration of glycopyrrolate inhalation solution (50 mcg) in subjects with moderate to severe COPD (Study SUN101-105) 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).

1.1. Recommendations

The Office of Clinical Pharmacology has reviewed the clinical pharmacology information provided within NDA 208437 and finds the application acceptable.

1.2. Post Marketing Requirement

None

1.3. Summary of Important Clinical Pharmacology Findings

Glycopyrrolate (i.e., glycopyrronium bromide) is a quaternary ammonium compound which belongs to the anti-cholinergic class of drugs and is classified as a muscarinic antagonist. Glycopyrrolate has been in clinical use for over 30 years for several conditions, including COPD. Table 1 lists all the approved glycopyrrolate brand products approved in the United States.

Table 1 Approved glycopyrrolate drug products in the United States

Drug Product	Application Number	Approval Date	Indication(s)
Utibron® Neohaler#	207930	10/29/2015	Long-term, maintenance treatment of airflow obstruction in patients COPD
Seebri® Neohaler	207923	10/29/2015	Long-term, maintenance treatment of airflow obstruction in patients COPD
Cuvposa® Oral Solution	022571	07/28/2010	Reduce chronic severe drooling in patients aged 3-16 years
Robinul® Injection	017558	02/06/1975	In anesthesia: For use as a preoperative antimuscarinic In peptic ulcer: For use in adults as adjunctive therapy for the treatment of peptic ulcer
Robinul® and Robinul® Forte Tablets	012827	08/11/1961	For use as adjunctive therapy in the treatment of peptic ulcer

in combination with indacaterol

Sunovian has developed glycopyrrolate inhalation solution for delivery to the lung using CS eFlow®, using Robinol® injection (NDA 017558), Robinol® Oral Tablet (NDA 012827), Cuvposa® Oral Solution (NDA 022571) and Seebri® Neohaler (NDA 207923) as the reference products. The glycopyrrolate inhalation solution is being proposed "for the maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema." The proposed dosing regimen is oral inhalation of the contents of one vial (each 1 mL vial contains 25 mcg glycopyrrolate) twice daily (BID) using the CS eFlow® nebulizer.

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 sponsor 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).

Dosing Regimen Selection

The dosing regimen of glycopyrrolate inhalation solution has been explored in two pivotal phase 2 dose-ranging studies in patients with COPD prior to proceeding to the two Phase 3 efficacy and safety studies in patients with COPD. Glycopyrrolate inhalation solution at doses of 25 and 50 mcg BID was selected for confirmation in the Phase 3 program.

- In Study EP-101-04, all treatment groups (glycopyrrolate inhalation solution 12.5, 25, 50, and 100 mcg BID) showed an increase in trough FEV1 from baseline over the 28-day treatment period with a trend of dose-response (Table 5 and Figure 2). In the comparison of placebo, clinically meaningful change (>0.001 L) in trough FEV1 on Day 28 was observed for all treatment groups.

- In Study SUN101-201, which included four glycopyrrolate treatment groups (i.e., glycopyrrolate inhalation solution 3, 6.25, 12.5 and 50 mcg BID), the treatment groups of 12.5 and 50 mcg BID showed a clinically meaningful increase in trough FEV1 from baseline over the 7-day treatment period with a trend of dose-response (Table 6 and Figure 3). The 3 mcg BID treatment group was

not different from placebo, and the 6.25 mcg BID group failed to achieve clinically meaningful increase in trough FEV1 on Day 7.

Pharmacokinetics

Population Pharmacokinetic Analysis
Population PK models were developed to describe the systemic exposure of glycopyrrolate inhalation solution in subjects with COPD and to determine if any intrinsic factors influence the systemic exposure.

Age and Body Weight
Age and body weight had no relevant effect on drug exposure following administration of glycopyrrolate inhalation solution.

Race/Ethnicity
Race/ ethnicity had no relevant effect on drug exposure following administration of glycopyrrolate inhalation solution.

Hepatic Impairment
No dedicated clinical studies with glycopyrrolate inhalation solution in patients with hepatic impairment have been conducted.

Renal Impairment
No dedicated clinical studies with glycopyrrolate inhalation solution in patients with renal impairment have been conducted. However, population PK analysis indicated that patients with mild (N=41) and moderate (N=67) renal impairment would have 17.2% and 27.6% greater dose-normalized AUC at steady state as compared with patients with normal renal function (N=67).

2. Question-Based Review

Sunovian submitted NDA 208437 (glycopyrrolate inhalation solution) under 505(b)(2) pathway referencing Robinol® injection (NDA 017558), Robinol® Oral Tablet (NDA 012827), Cuvposa® Oral Solution (NDA 022571) and Seebri® Neohaler (NDA 207923). The intent of PK assessment in the dose ranging Phase 2 studies and a Phase 1 PK study was to characterize the PK of the proposed glycopyrrolate inhalation solution in patients with chronic obstructive lung disease (COPD). Only relevant information based on studies submitted in the NDA will be reviewed in this document.

2.1. Regulatory history

Glycopyrrolate (i.e., glycopyrronium bromide) is a muscarinic antagonist and belongs to the anti-cholinergic class of drugs. Sunovian submitted NDA 208437 (glycopyrrolate inhalation solution) under 505(b)(2) pathway on July 29, 2016, seeking the marketing approval for Lonhala Magnair. The proposed product is indicated "*for the maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema*." The sponsor supports the NDA submission with 6 clinical pharmacology studies.

2.2. List the in vitro and in vivo Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA

The clinical pharmacology studies submitted under NDA 208437 are summarized in Table 2, including one PK study (SUN101-105) and two key dose-ranging studies (EP-101-104 and SUN101-201). In addition, the applicant also submitted three additional dose-ranging studies (EP-101-01, EP-101-02 and EP-101-103) with an OS eFlow® nebulizer prior to proceeding with the two key dose-ranging studies (i.e., EP-101-104 and SUN101-201).

Table 2 Summary of clinical pharmacology studies

	Study ID	Objectives	Population	Study Design	Treatment and Device
PK study	SUN101-105	PK	Moderate to severe patients (40-70 yrs) with COPD (n=26 completed)	Rand, OL, 5-period, crossover, SD	GIS 50 mcg SD CS Nebulizer GIS 50 mcg SD CS Nebulizer with activated charcoal Seebri® Breezhaler Inhalation powder (Non-US approved product) Seebri® Breezhaler Inhalation powder with activated charcoal (Non-US approved product) Glycopyrrolate injection 50 mcg (Non-US approved product)
Exploratory Dose Ranging Studies (OS Nebulizer)	EP-101-01	Dose-ranging, PK, tolerability and safety	Moderate to severe patients (40-75 yrs) with COPD (n=12 completed)	Part 1 - R, OL, parallel SAD, 2 cohorts Part 2 - R, DB, parallel, PC, SD	Part 1 – SD of GIS (25 mcg, 75 mcg, 200 mcg, 500 mcg, and 1000 mcg) OS nebulizer Part 2 - SD GIS 200 mcg OS nebulizer or placebo via general purpose nebulizer
	EP-101-02	Dose-ranging, PK, tolerability and safety	Moderate to severe patients (40-75 yrs) with COPD (n=35 completed)	R, DB, 6-way crossover, PC, SD 5-12 day washout	Placebo GIS 12.5 mcg OS nebulizer GIS 50 mcg OS nebulizer GIS 100 mcg OS nebulizer GIS 200 mcg OS nebulizer GIS 400 mcg OS nebulizer
	EP-101-03	Dose-ranging, PK, efficacy, safety	Male and Female subjects (40-75 yrs) with moderate to severe COPD (n=126 completed)	R, DB, PC, 7-arm incomplete block, crossover Active control (OL) 7-day treatment, 5-7 day washout	Placebo QD OS nebulizer GIS 25 mcg QD OS nebulizer GIS 50 mcg QD OS nebulizer GIS 100 mcg QD OS nebulizer GIS 200 mcg QD OS nebulizer Tiotropium bromide 18 mcg QD (Spiriva® Handihaler) Ipratropium bromide 500 mcg inhalation solution TID
Pivotal Dose-Ranging Studies (CS Nebulizer)	EP-101-04	Dose-ranging, safety and efficacy	Moderate to severe patients (35-75 yrs) with COPD (n=263 completed)	R, DB, parallel, PC 28-day treatment	Placebo BID CS Nebulizer GIS 12.5 mcg BID CS Nebulizer GIS 25 mcg BID CS Nebulizer GIS 50 mcg BID CS Nebulizer GIS100 mcg BID CS Nebulizer
	SUN101-201	Dose-ranging, PK, safety and efficacy	Moderate to severe patients (40-65 yrs) with COPD (n=88 completed)	R, DB (placebo and GIS), 6-way crossover Active control (OL) 7-day treatment, 5-7 day washout	Placebo BID CS Nebulizer GIS 3 mcg BID CS Nebulizer GIS 6.25 mcg BID CS Nebulizer GIS 12.5 mcg BID CS Nebulizer GIS 50 mcg BID CS Nebulizer Aclidinium 400 mcg BID (Tudorza® Pressair®)

Abbreviations - CS: closed system eFlow®; DB: double blind; OL: open label; OS: open system eFlow®; PC: placebo controlled; PK: pharmacokinetics; QD: once daily; R: randomized; SAD: single ascending dose; SD: single dose; GIS: glycopyrrolate inhalation solution

(Source – Adapted from NDA 208437, Module 5.2, Tabular Listing of All Clinical Studies)

Key Phase 3 studies for glycopyrrolate inhalation solution are summarized in Table 3.

Table 3 Overview of clinical development program

	Study ID	Objectives	Population	Study Design	Treatment and Device
Pivotal Phase 3 Studies	SUN101-301	Safety and efficacy	Moderate to very severe patients (≥ 40 yr) with COPD (n=595 completed)	R, DB, parallel PC 12-week treatment	Placebo GIS 25 mcg BID CS nebulizer GIS 50 mcg BID CS nebulizer
	SUN101-302	Safety and efficacy	Moderate to very severe patients (≥ 40 yr) with COPD (n=580 completed)	R, DB, parallel PC 12-week treatment	Placebo GIS 25 mcg BID CS nebulizer GIS 50 mcg BID CS nebulizer
	SUN101-303	Safety and efficacy	Moderate to very severe patients (≥ 40 yr) with COPD (n=838 completed)	R, OL, parallel Active control 48-week treatment	GIS 50 mcg BID CS nebulizer, or Spiriva 18 mcg QD via Handihaler in a 4:3 ratio

Abbreviations - BID: twice daily; CS: closed system eFlow®; DB: double blind; OL: open label; PC: placebo controlled; PK: pharmacokinetics; QD: once daily; R: randomized; SD: single dose; GIS: glycopyrrolate inhalation solution
(Source – Adapted from NDA 208437, Module 5.2, Tabular Listing of All Clinical Studies

2.3. General Attributes of the Drug

2.3.1. What are the highlights of the chemistry and physico-chemical properties of the drug substance and the formulation of the drug product?

Drug Substance

Glycopyrrolate (glycopyrronium bromide) is a small molecule with the molecular structure as shown in Figure 1. It is a white powder with a molecular formula of $C_{19}H_{28}NO_3$.Br and a molecular weight of 398.33 Da.

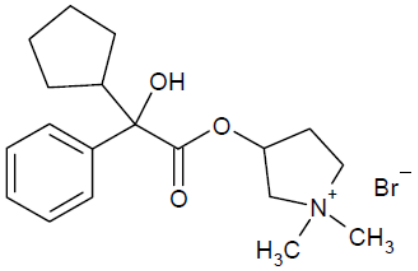


Figure 1 Molecular structure of glycopyrronium bromide (glycopyrrolate)

Drug Product

The drug product is a drug-device combination product containing glycopyrrolate as the active ingredient administered by a CS eFlow® nebulizer. The glycopyrrolate 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. (b) (4) The strength is expressed as the amount of

glycopyrrolate, USP (glycopyronium bromide) in the one mL vial: 25 mcg/mL. The composition of glycopyrrolate inhalation solution is presented in Table 4.

Table 4 Quantitative composition of glycopyrrolate inhalation solution

Ingredient	Function	Amount per mL
Glycopyrrolate, USP	Active ingredient	25 mcg
Citric Acid Monohydrate, USP Sodium Chloride, USP	(b) (4)	
Sodium Hydroxide, NF	pH adjusting agent	Adjust to pH 4.0
Hydrochloric Acid, Ph. Eur.	(b) (4)	(b) (4)
Water for Injection, Ph. Eur.	Diluent	q.s. to 1 mL

(Source – NDA 208437, Module 3.2.P.1, Description and Composition of the Drug Product)

2.3.2. What are the proposed mechanism of action and therapeutic indications?

Glycopyrrolate (i.e., glycopyrronium bromide) is a muscarinic antagonist and belongs to the anti-cholinergic class of drugs.

The proposed product is indicated "*for the maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema*".

2.3.3. What are the proposed dosages and routes of administration?

Glycopyrrolate inhalation solution is supplied in LDPE unit dose vials, each containing 1.0 mL of the solution. The strength of the proposed product is expressed as the amount of glycopyrrolate, USP (glycopyronium bromide) in the one mL vial. The proposed product will be supplied as a single strength (25 mcg/mL), and is intended for oral inhalation.

2.4. General Clinical Pharmacology

2.4.1. What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

The clinical development program included two pivotal dose-ranging studies to establish the appropriate doses of glycopyrrolate inhalation solution before proceeding to Phase 3 program. Two dose levels of 25 mcg BID and 50 mcg glycopyrrolate BID were assessed in Phase 3 program. The two pivotal dose-ranging studies are described below.

- Study EP-101-04 is a randomized, double-blind, parallel, placebo-controlled, dose-ranging study to assess the efficacy and safety of glycopyrrolate inhalation solution (via CS eFlow® nebulizer) in subjects with moderate-to-severe COPD. The evaluated dosing regimens for glycopyrrolate inhalation solution included –
    - BID: 12.5 mcg, 25 mcg, 50 mcg and 100 mcg
- Study SUN101-201 is a randomized, 6-way crossover study, active-control, dose-ranging study to assess the efficacy and safety of glycopyrrolate inhalation solution in subjects with moderate to severe COPD. The evaluated dosing regimens included –

- BID: 3 mcg, 6.25 mg, 12.5 mcg, and 50 mcg

The clinical pharmacology and biopharmaceutics studies supporting this NDA and their design features are listed under Section 2.2 (Table 2).

2.4.2. What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

Trough FEV1 was selected as the primary efficacy endpoint in Phase 2 dose-ranging studies (i.e., Studies EP-101-04 and SUN101-201). Trough FEV1 was selected as the primary endpoint for the Phase 3 studies. This clinical endpoint has previously been used in the development programs of other LAMAs for COPD.

2.4.3. Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameter and exposure response relationships?

In all relevant studies, only glycopyrronium concentrations were measured. No metabolites were quantified because the metabolites of glycopyrronium are not active, and are not known to be associated with efficacy or safety.

2.5. Dose-Exposure/Response

2.5.1. What are the characteristics of the exposure-response relationship for effectiveness?

For inhaled glycopyrrolate, the systemic exposure is not directly related to clinical response (FEV1).

2.5.2. Has the dosing of glycopyrrolate inhalation solution been adequately explored?

Phase 2 dose-ranging Studies –

The dosing for glycopyrrolate inhalation solution has been explored in two pivotal Phase 2 dose-ranging trials in patients with COPD. Two dosing regimens of 25 mcg and 50 mcg BID were further tested in Phase 3 studies in patients with COPD.

Study EP-101-04 - In Study EP-101-04, all treatment groups (glycopyrrolate inhalation solution 12.5, 25, 50, and 100 mcg BID) showed an increase in LS mean FEV1 from baseline over the 28-day treatment period. In the comparison of placebo versus each glycopyrrolate dose, the change from baseline in trough FEV1 over the 28-day treatment period was clinically relevant (>0.100 L) for all treatment groups (Table 5 and Figure 2).

Table 5 Primary and secondary efficacy results (ITT) – Phase 2 dose-ranging study EP-101-04

Endpoint	Statistic	Glycopyrrolate BID			
		12.5 mcg (n=55)	25 mcg (n=54)	50 mcg (n=57)	100 mcg (n=59)
Change from Baseline in Trough FEV1 (L) Day 28 Compared to Placebo (Primary)	LS Mean (SE)	0.1168 (0.04055)	0.1284 (0.04089)	0.1462 (0.04037)	0.1770 (0.03953)
	95% CI	0.0369, 0.1966	0.0479, 0.2089	0.0667, 0.2257	0.0992, 0.2548
	P value	0.0043	0.0019	0.0004	<0.0001
Change from Baseline in FEV1 $AUC_{0\text{-}12\,h}$ (L) on Day 28 Compared to Placebo (Secondary)	LS Mean (SE)	0.1357 (0.03296)	0.1632 (0.03312)	0.1054 (0.03255)	0.1831 (0.03213)
	95% CI	0.0709, 0.2005	0.0982, 0.2283	0.0415, 0.1694	0.1199, 0.2462
	P value	<0.0001	<0.0001	0.0013	<0.0001

Abbreviations – CI: confidence interval; FEV1: forced expiratory volume in 1 second; L: liter; LS: least square; SE: standard error

[Source – Adapted from NDA 208437, Module 5.3.5.1, Study Report Body for EP-101-04 – 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)]

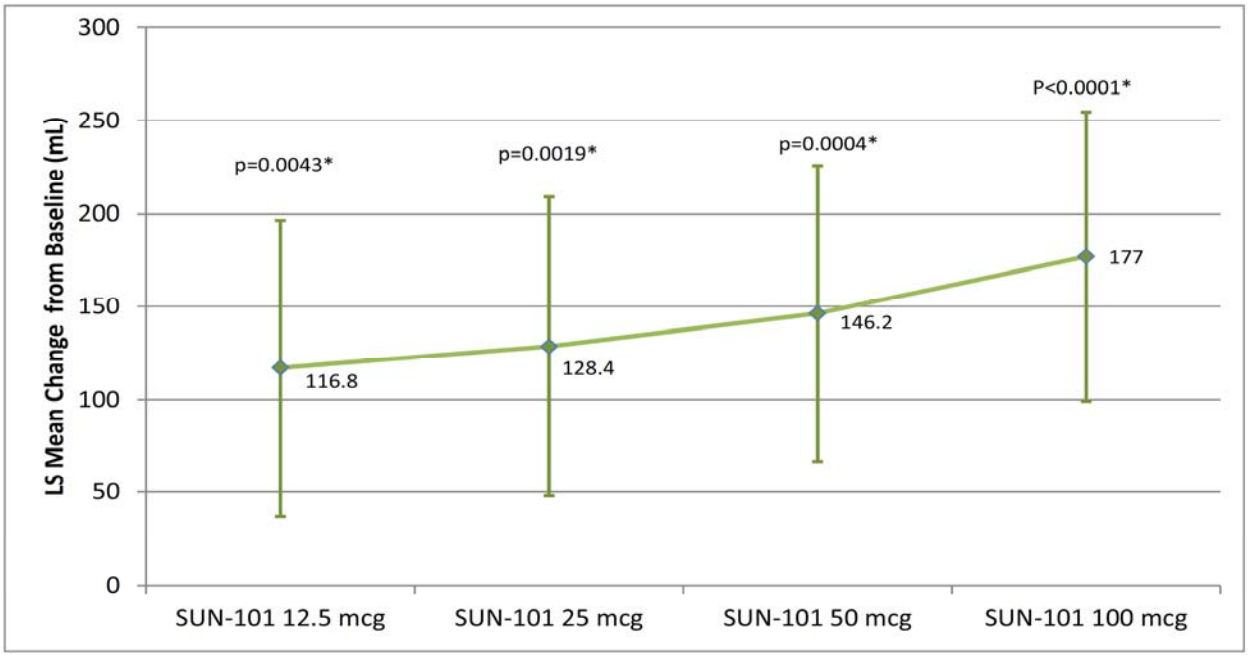


Figure 2 Change from Baseline in Trough FEV1 on Day 28 Compared to Placebo (Study EP-101-04)

[Source –NDA 208437, Module 5.3.5.1, Study Report Body for EP-101-04 – 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)]

Study SUN101-201 - In Study SUN101-201, the change from baseline in trough FEV1 for two treatment groups of 12.5 and 50 mcg BID glycopyrrolate inhalation solution were both clinically relevant (>0.100L) and statistically significant as compared to placebo. Although the treatment group of 6 mcg BID glycopyrrolate inhalation solution was associated with statistically significant improvement in trough FEV1 as compared to placebo, it failed to achieve clinical relevance. The treatment group of 3 mcg BID glycopyrrolate inhalation solution was not different from placebo.

Table 6 Primary and secondary efficacy results (ITT) – Phase 2 dose-ranging study SUN101-201

Endpoint	Statistic	Glycopyrrolate BID				ACL 400 mcg (n=94)
		3 mcg (n=91)	6.25 mcg (n=92)	12.5 mcg (n=90)	50 mcg (n=92)	
Change from Baseline in Trough FEV1 (L) on Day 7 Compared to Placebo (Primary)	LS Mean (SE)	0.0126 (0.0225)	0.0822 (0.0225)	0.1088 (0.0226)	0.1375 (0.0226)	0.1567 (0.0226)
	95% CI	(-0.0318, 0.0569)	(0.0380, 0.1264)	(0.0644, 0.1532)	(0.0931, 0.1818)	(0.1121, 0.2012)
	P value	0.9370	0.0014	<0.0001	<0.0001	<0.0001
Change from Baseline in FEV1 $AUC_{0\text{-}12\,h}$ (L) on Day 7 Compared to Placebo (Secondary)	LS Mean (SE)	0.0526 (0.0184)	0.0842 (0.0185)	0.1255 (0.0186)	0.1963 (0.0184)	0.1902 (0.0186)
	95% CI	(0.0163, 0.0888)	(0.0478, 0.1206)	(0.0890, 0.1621)	(0.1601, 0.2325)	(0.1537, 0.2268)
	P value	0.0046	<0.0001	<0.0001	<0.0001	<0.0001

Abbreviations – ACL: aclidinium; CI: confidence interval; FEV1: forced expiratory volume in 1 second; L: liter; LS: least square; SE: standard error

[Source –Adapted from NDA 208437, Module 5.3.5.1, Study Report Body for SUN101-201 – 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)]

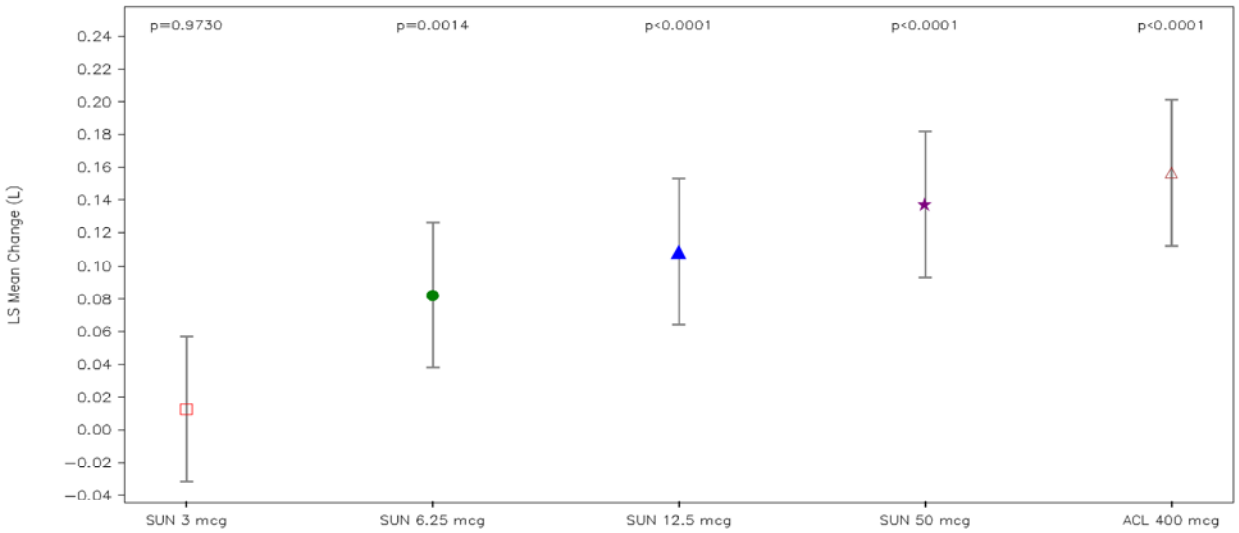


Figure 3 Change from Baseline in Trough FEV1 on Day 7 Compared to Placebo (Study SUN101-201)

[Source – NDA 208437, Module 5.3.5.1, Study Report Body for SUN101-201 – 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)]

In the two pivotal dose-ranging studies EP-101-04 and SUN101-201, twice-daily dosing with 50 mcg glycopyrrolate inhalation solution improved trough FEV1 by 0.146 L (28 day treatment) and 0.138 L (7 day treatment), respectively. Additionally, the trough FEV1 improvement was 0.118 L and 0.128 L on Day 7 and Day 28, respectively, for the 25 mcg BID dose treatment group in the EP-101-04 study. The results for the Phase 2 dose-ranging studies were discussed at a Type C meeting on September 15, 2014. The Agency stated that the choice of 25 and 50 mcg BID doses for the Phase 3 studies is not unreasonable based on the findings of the two pivotal dose-ranging studies. In addition, at the Type B EOP2 meeting on September 18, 2013, the Agency indicated that a dose of 100 mcg BID may be too high and potentially dangerous, due to death of a 52 year-old man with COPD who received a total daily dose of 200 mcg glycopyrrolate from a myocardial infarction. Since a trend in dose response was observed in both pivotal dose-ranging studies, and 100 mcg BID dose had a potential safety signal, the choice of 25 and 50 mcg BID dose for Phase 3 drug development appears reasonable.

Phase 3 Safety and Efficacy Studies –

Studies SUN101-301 and SUN101-302 were Phase 3, 12-week, multi-center, randomized, double-blind, parallel-group, placebo-controlled studies in subjects with moderate to very severe COPD.

The primary efficacy endpoint for the two studies was the change from baseline in placebo adjusted trough FEV1 at Week 12. The primary efficacy endpoint results are provided in Table 7, and shown in Figure 4 and 5.

Table 7 Summary of primary efficacy endpoints (ITT) (Studies SUN101-301 and SUN101-302)

Parameter	Statistic	Study SUN101-301		Study SUN101-302	
		25 mcg BID	50 mcg BID	25 mcg BID	50 mcg BID
Trough FEV1 (L) at Week 12 Compared to Placebo	n	217	218	214	214
	LS Mean (SE)	0.1052 (0.02060)	0.1264 (0.02076)	0.0840 (0.02069)	0.0820 (0.0255)
	95% CI	(0.0647, 0.1457)	(0.0856, 0.1672)	(0.0433, 0.1246)	(0.0417, 0.1224)
	P value	0.0001	<0.0001	0.0001	<0.0001

Abbreviations - BID: twice daily; CI: confidence interval; FEV1: forced expiratory volume in 1 second; LS: least squares; NA: not applicable; SE: standard error; SUN-101: glycopyrrolate inhalation solution via CS eFlow® nebulizer
(Source: Adapted from NDA 208437, Module 2.5, Clinical Overview)

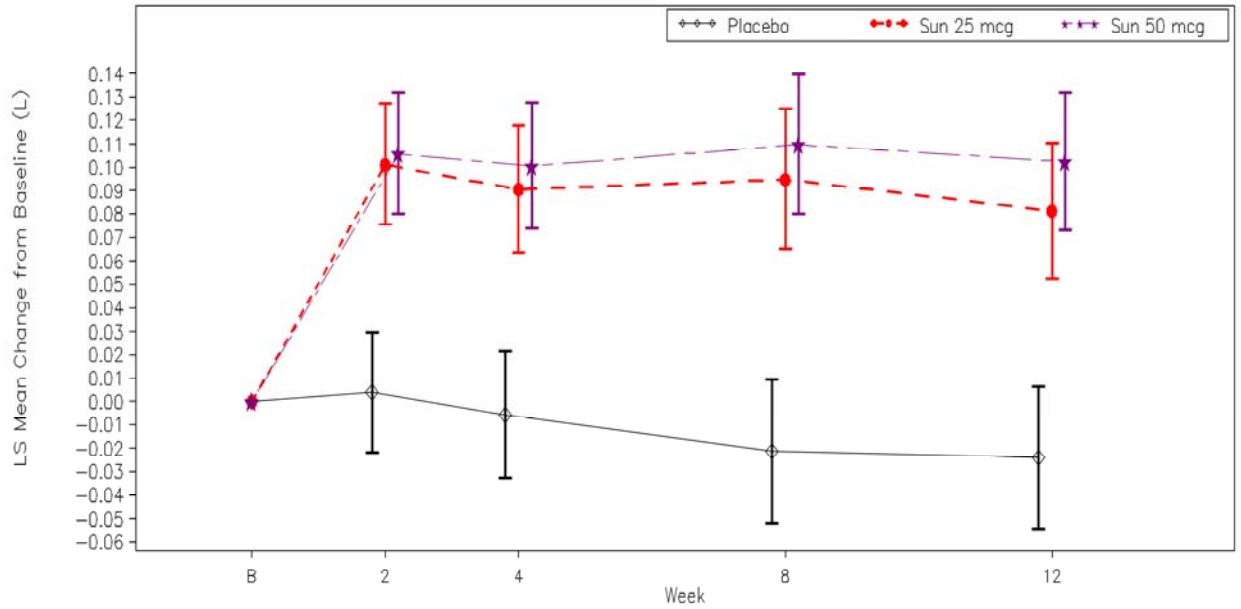


Figure 4 Mean change from baseline in trough FEV1 by visit week (Study SUN101-301)
Abbreviations - FEV1: forced expiratory volume in 1 second; LS: least squares; NA: not applicable; SE: standard error; SUN-101: glycopyrrolate inhalation solution via CS eFlow® nebulizer
(Source – NDA 208437, Module 2.5, Clinical Overview)

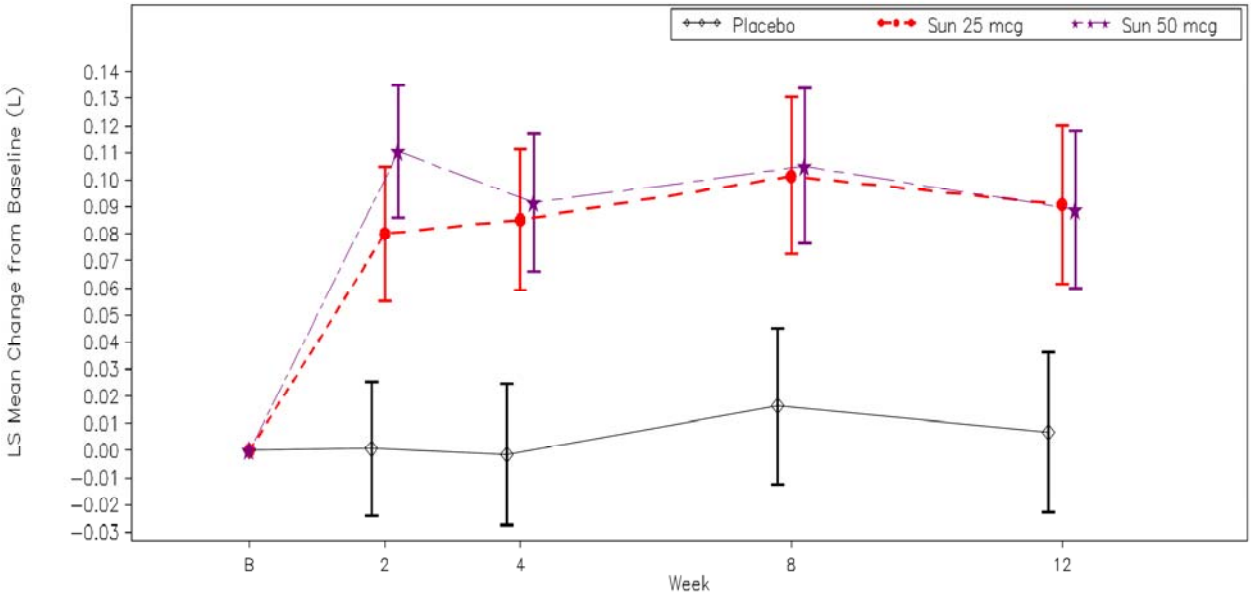


Figure 5 Mean change from baseline in trough FEV1 by visit week (Study SUN101-302)
Abbreviations - FEV1: forced expiratory volume in 1 second; LS: least squares; NA: not applicable; SE: standard error; SUN-101: glycopyrrolate inhalation solution via CS eFlow® nebulizer
(Source – NDA 208437, Module 2.5, Clinical Overview)

In Study SUN101-301, for all collected data (i.e., including pulmonary function test results from retrieved dropouts who may have received marketed COPD medications after discontinuing from the double-blind study drug), the treatment with 25 mcg and 50 mcg BID glycopyrrolate inhalation solution resulted in statistically significant improvements in the primary endpoint of change from baseline in trough FEV1 compared with placebo. As shown in Table 7, a slight numerical increase in response is observed with 50 mcg BID compared to 25 mcg BID.

In Study SUN101-302, for all collected data (i.e., including pulmonary function test results from retrieved dropouts who may have received marketed COPD medications after discontinuing from the double-blind study drug), the treatment with 25 mcg and 50 mcg BID glycopyrrolate inhalation solution resulted in statistically significant improvements in the primary endpoint of change from baseline in trough FEV1 compared with placebo. As shown in Table 7, the response was similar between the two doses.

From an efficacy standpoint, given similar response between the two doses (i.e., 25 mcg BID and 50 mcg BID) in Study SUN101-302, and a slight numerical increase observed in the 50 mcg BID treatment group in Study SUN101-301, the proposed dose of 25 mcg BID for long-term, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema, is reasonable.

Please refer to the Clinical Review by Dr. Erika Torjusen and the Statistical Review by Dr. Mingyu Xi regarding the final risk/benefit assessment for the proposed doses of glycopyrrolate inhalation solution based on the efficacy and safety analyses of Phase 3 studies.

2.6. What are the PK characteristics of the drug?

2.6.1. What are the PK parameters of glycopyrrolate inhalation solution in subjects with COPD following single and multiple-dose administration?

Single-Dose Study

SUN101-105 evaluated the PK parameters of glycopyrrolate inhalation solution via CS eFlow® nebulizer in subjects with COPD following a single dose administration. Study SUN101-105 was a randomized, open-label, single-dose, five-way crossover study in subjects 40 to 70 years of age with moderate to severe COPD. After single dose administration of 50 mcg glycopyrrolate inhalation solution via CS eFlow® nebulizer in subjects with COPD, the median T_{max} for glycopyrrolate occurs around approximately 20 minutes and the elimination half-life for glycopyrrolate is approximately 5 hours.

Table 8 Key PK parameters of glycopyrrolate inhalation solution (50 mcg) in subjects with moderate to severe COPD (Study SUN101-105)

C_{max} (pg/mL)	$AUC_{(0-24)}$ (pg/mL*hr)	$AUC_{(0-\infty)}$ (pg/mL*hr)	$t_{1/2}$ (hr)	T_{max} (hr)
Mean (SD)	Mean (SD)	Mean (SD)	Median	Median
61.46 (39.415)	273.47 (442.436)	292.94 (237.338)	4.658	0.317

(Source – Adapted from NDA 208437, Module 2.7.2, Summary of Clinical Pharmacology)

Multiple-Dose Study

SUN101-201 evaluated the PK parameters of glycopyrrolate inhalation solution via CS eFlow® nebulizer in subjects with COPD following multiple-dose administration. Study SUN101-201was a randomized, 6-way crossover study in subjects 40 to 65 years old with moderate to severe COPD. Glycopyrrolate inhalation solution via CS eFlow® nebulizer was administered at doses of 3 mcg, 6.25 mg, 12.5 mcg, and 50 mcg BID for 7 days. Mean plasma concentration-time profiles of glycopyrrolate on Day 7 are presented in Figure 6. In this study, the median T_{max} for glycopyrrolate occurred within 0.5 hour post-dose and appeared to exhibit more than dose-proportional PK (C_{max} and AUC_{0-12}) across the dose range of 3 to 50 mcg BID (Table 9). However, in another study (Study EP-101-01, see Appendix), the PK appeared to be linear across the dose range of 200 to 1000 mcg glycopyrrolate.

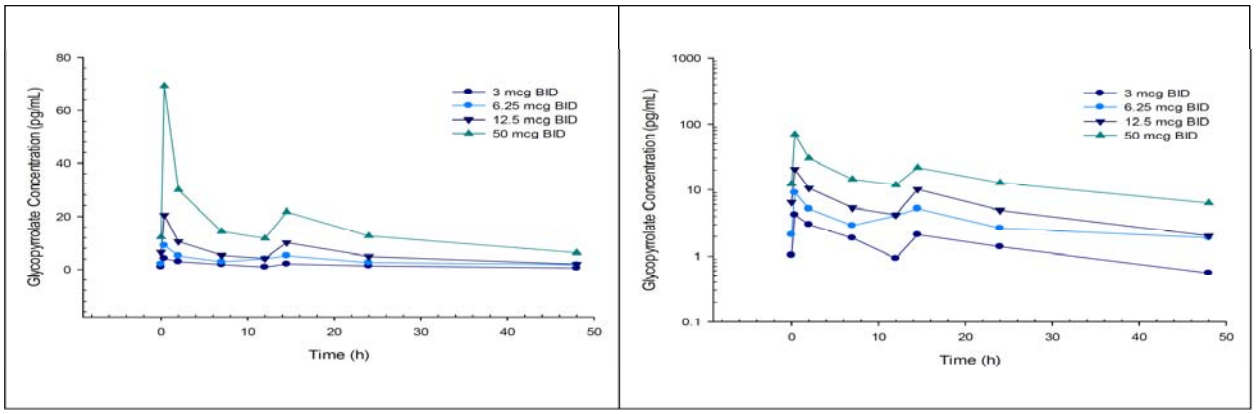


Figure 6 Plasma concentration-time profiles in linear and logarithmic scales on day 7 after 3 to 50 mcg bid administration of glycopyrrolate inhalation solution (Study SUN101-201)
(Source – NDA 208437, Module 2.7.2, Summary of Clinical Pharmacology), Results reported are for the glycopyrrolate (glycopyrronium bromide)

Table 9 Key PK parameters in subjects with moderate to severe COPD on Day 7 following daily administration of 3, 6.25, 12.5 or 50 mcg BID of glycopyrrolate inhalation solution (Study SUN101-201)

Treatment	C_{max} (pg/mL)	$AUC_{(0\text{-}tau)}$ (pg/mL*hr)	$t_{1/2}$ (hr)	T_{max} (hr)	Accumulation Index
	Mean (SD)	Mean (SD)	Mean	Median	Mean
3 mcg BID	5.623 (3.948)	32.714 (19.131)	6.383	0.47	1.385
6.25 mcg BID	9.407 (6.299)	51.314 (39.931)	9.830	0.47	1.770
12.5 mcg BID	20.538 (16.486)	88.684 (59.751)	12.244	0.47	2.051
50 mcg BID	69.381 (40.343)	255.471 (137.343)	6.536	0.43	1.398

(Source – Adapted from NDA 208437, Module 5.3.3.5, Study 101-900: Pop-PK Report)

2.6.2. How does the systemic exposure of glycopyrrolate inhalation solution compare to the listed drug(s)?

The mean $AUC_{0\text{-}inf}$ and C_{max} following a single-dose administration of glycopyrrolate inhalation solution (50 mcg) in subjects with moderate to severe COPD administered via the CS eFlow® nebulizer were 292.94 pg/mL*hr and 61.46 pg/mL, respectively (Study SUN101-105, Table 10).
As shown in Table 10, the systemic exposure ($AUC_{0\text{-}inf}$ and C_{max}) in subjects with moderate to severe COPD following single-dose administration of glycopyrrolate inhalation solution (50 mcg) 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).[1]

[1] Maximum recommended dose is 0.1 mg/kg three times daily, not to exceed 1.5-3 mg per dose based upon weight. It is recommended to be administered at least one hour before or two hours after meals.

Table 10 Comparison of $AUC_{0-\infty}$ and C_{max} following single dose administration of glycopyrrolate inhalation solution and Cuvposa® Oral Solution (cross-study comparison)

PK Parameter (Mean)	Cuvposa® Oral Solution* (fasted, 2 mg)	Glycopyrrolate inhalation Solution# (50 mcg)
	Single Dose	Single Dose
$AUC_{(0-\infty)}$ (ng/mL*hr)	1.81	0.292
C_{max} (ng/mL)	0.318	0.061

*From Drug product PI for Cuvposa® Oral Solution (NDA022571, Section 12.3)
#From Study SUN101-105 [NDA 208437, Module 5.3.3.2, Study Report Body for Study SUN101-105: A CROSSOVER CLINICAL PHARMACOLOGY STUDY TO EVALUATE THE TOTAL SYSTEMIC EXPOSURE AND LUNG BIOAVAILABILITY OF SUN-101 AND SEEBRI® BREEZHALER® ADMINISTERED WITH AND WITHOUT ACTIVATED CHARCOAL IN SUBJECTS WITH MODERATE TO SEVERE CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) (GOLDEN-7))]

2.6.3. What is the relative bioavailability of glycopyrrolate inhalation solution given with oral activated charcoal relative to without oral activated charcoal?

SUN101-105 evaluated the relative bioavailability of glycopyrrolate inhalation solution given with oral activated charcoal relative to without oral activated charcoal. Study SUN101-105 was a randomized, open-label, single-dose, five-way crossover study in subjects 40 to 70 years of age with moderate to severe COPD. Co-administration of glycopyrrolate inhalation solution via CS eFlow® nebulizer with activated charcoal, given as an oral suspension prior to the inhaled glycopyrrolate, led to a reduction in both C_{max} and $AUC_{0-\infty}$ of glycopyrrolate, as compared with glycopyrrolate inhalation solution administered via eFlow® nebulizer alone (Table 11).

Table 11 Key PK parameters of glycopyrrolate inhalation solution (50 mcg) via CS eFlow® nebulizer in subjects with moderate to severe COPD with and without activated charcoal (Study SUN101-105)

PK Parameters Mean (SD)	Without Charcoal	With Charcoal
C_{max} (pg/mL)	61.46 (39.415)	57.51 (36.322)
$AUC_{(0-\infty)}$ (pg/mL*hr)	292.94 (237.338)	179.56 (75.637)

(Source – Adapted from NDA 208437, Module 2.7.2, Summary of Clinical Pharmacology)

2.7. Intrinsic Factors

2.7.1. What are the major intrinsic factors responsible for the inter-subject variability in exposure in patients with the target disease and how much of the variability is explained by the identified covariates?

Population PK models were developed to describe systemic exposure for glycopyrrolate inhalation solution in patients with COPD. Please see Pharmacometrics Review in Appendix 4.2 for additional details.

There was no evidence of 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 effects.

Population PK analysis suggested the apparent glycopyrrolate clearance (CL/F) increases with greater dose levels. For further discussion on this from individual studies based on NCA analysis, see Section 2.6.1.

In addition, renal function was identified as a significant factor for patient clearance (CL/F). Patients with mild (N=41) and moderate (N=67) renal impairment would have 17.2% and 27.6% greater dose-normalized AUC at steady state as compared with patients with normal renal function (N=67). This finding was consistent with that observed for Seebri Neohaler (NDA 207923). Seebri Neohaler's prescribing label states that 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]".

No dedicated study(s) was conducted in renal or hepatic impairment patients in this NDA.

2.8. Extrinsic Factors

No dedicated study(s) was conducted to determine the effect of extrinsic factors on systemic exposure of glycopyrrolate inhalation solution.

2.9. General Biopharmaceutics

2.9.1. How is the proposed to-be-marketed formulation linked to the clinical formulation?

The proposed commercial formulation and device were used in PK study SUN101-201, SUN101-105 and all Phase 3 studies.

2.10. Analytical Section

2.10.1. How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?

The summary of bioanalytical method validation studies used in clinical development program for glycopyrrolate inhalation solution is shown in Table 12.

Table 12 Listing of bioanalytical method validation studies and supported clinical studies

Bioanalytical Validation Report No.	Method Brief Description	Validation Reort Location	Supported Clinical Study No.
RD 311/24784HV	Validation of LC-MS/MS method, curve range 25.0 – 10,000 pg/mL; liquid-liquid extraction with ion-pairing agent heptafluorobutyric acid Human plasma volume: 0.200-mL	5.3.1.4	EP-101-01 EP-101-02
RD 311/25162HV	Validation of LC-MS/MS method, curve range 10.0 – 5,000 pg/mL; solid phase extraction Human plasma volume: 0.200-mL	5.3.1.4	EP-101-03
SUN-R3081*R1*	Validation of LC-MS/MS method, curve range 0.500 – 250 pg/mL; solid phase extraction Human plasma volume: 0.500-mL	5.3.1.4	SUN101-201
SUN-R4511	Validation of LC-MS/MS method, curve range 4.00 – 2,000 pg/mL; solid phase extraction Human plasma volume: 0.200-mL	5.3.1.4	SUN101-105

(Source – Adapted from NDA 208437, Module 2.7.1, Summary of Biopharmaceutic Studies and Associated Analytical Methods)

As the proposed commercial products were used in PK study SUN101-201, SUN101-105 and all Phase 3 studies, only the method validation reports SUN-R3081R1 and SUN-R4511 are summarized below (Table 13 and 14).

Table 13 Method validation report SUN-R3081R1

Method description		Method BTM-1765-R0 is an LC-MS/MS method for the determination of glycopyrrolate in human plasma using d_3-glycopyrrolate iodide as the internal standard (IS). Glycopyrrolate and the internal standard were extracted using solid phase extraction from human plasma. Reversed-phase HPLC separation was achieved with an Agilent Pursuit 5 PFP, column (150 x 2.0 mm, 5 micron). MS/MS detection was set at transitions of m/z 318.3→116.1 for glycopyrrolate, and 321.3→119.1 for the IS in TIS positive mode.	
Biological matrix		Human plasma (Lithium heparin)	
Sample volume		500 µL	
Regression		Linear regression	
Weighting factor		$1/x^2$	
Dynamic range		0.500 – 250 pg/mL	
QC concentrations		0.500 pg/mL (LLOQ), 1.50 pg/mL (Low), 80.0 pg/mL (Mid), and 180 pg/mL (High), Dilution QCs: 900 pg/mL and 3,600 pg/mL	
Analytes		glycopyrrolate	
Internal standards		d_3-glycopyrrolate iodide	
Linearity		$R^2 \geq 0.9948$	
Lower limit of quantitation (LLOQ)		0.500 pg/mL	
Average recovery of the Analyte (%)		88.8 %	
Average recovery of the IS (%)		Per SOP BIO-201 guidelines, because stable isotope labeled IS was used, the recovery established for the unlabeled analyte will be sufficient. Recovery for the stable isotope labeled IS will not be required.	
QC Level		LLOQ	QC (Low, Mid, High)
QC Intra-run accuracy (%CV)	Run 1	16.3	2.0 to 4.3
	Run 2	19.1	1.3 to 5.8
	Run 3	14.5	1.8 to 8.0
QC Intra-run accuracy (%Bias)	Run 1	-2.8	-13.3 to -3.9
	Run 2	7.0	-4.7 to -3.3
	Run 3	16.2	-6.1 to 12.7
QC Inter-run precision range (%CV)		17.3	1.7 to 13.0
QC Inter-run accuracy range (%Bias)		7.4	-4.6 to -2.0
QC sample bench-top stability		6 hours at room temperature	
Processed sample stability		124 hours at room temperature	
Re-injection reproducibility		93 hours at room temperature	
QC sample freeze/thaw stability		3 freeze (–20 °C)/thaw (RT) cycles	
Long-term Stability in matrix		115 days at -20 °C 115 days at -70 °C	
Dilution integrity		900 pg/mL diluted 5-fold; 3,600 pg/mL diluted 20-fold	
Stock Solution Stability in diluent (ACN/H_2O 50:50)		6 hours under white light at room temperature 92 days at -20 °C	
Spike Solution Stability in diluent (ACN/H_2O 50:50)		17 hours under white light at room temperature 77 days at -20 °C	
Matrix Effect		IS-normalized Matrix factor = 1.16±0.10 at 1.50 pg/mL with %CV = 8.6% IS-normalized Matrix factor = 1.04±0.05 at 180 pg/mL with %CV = 4.8%	
5% Hemolyzed QC precision (%CV)		4.5 to 6.7	
5% Hemolyzed QC accuracy (%Bias)		-4.4 to 8.0	
Selectivity		The selectivity evaluation met the acceptance criteria: no significant interference (≥ 20% of the lower limit of quantitation, LLOQ for glycopyrrolate or ≥ 5% of the IS peak area of accepted calibration standards and QC samples for the IS) was detected at the retention times of the analyte or the IS in all tested human plasma lots.	
Interference		There was no interference detected from glycopyrrolate to the IS.	
Whole Blood Stability		120 minutes at room temperature and in an ice-water bath (~4 °C) for glycopyrrolate	
Batch size evaluation		135 injections (Run 5)	

[Source: NDA 208437, Module 5.3.1.4, Bioanalytical Report for Determination of Glycopyrrolate in Human Plasma Samples by LC-MS/MS for Sunovion Study Protocol No. SUN101-201: 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)]

Table 14 Method validation report SUN-R4511

Method description		Method BTM-1965-R0 is an LC-MS/MS method for the determination of glycopyrrolate in human plasma using d_3-glycopyrrolate iodide as the internal standard (IS). Glycopyrrolate and IS were extracted using solid phase extraction from human plasma. HPLC separation was achieved with an Agilent Pursuit 5 PFP column (150 x 2.0 mm, 5 micron). MS/MS detection was set at transitions of m/z 318.3→116.1 for glycopyrrolate and 321.3→119.1 for the IS in TIS positive mode.	
Biological matrix		Human plasma (Lithium heparin)	
Sample volume		200 µL	
Regression		Linear regression	
Weighting factor		$1/x^2$	
Calibration curve range		4.00 - 2,000 pg/mL	
QC concentrations		4.00 pg/mL (LLOQ), 12.0 pg/mL (Low), 400 pg/mL (Mid), and 1,600 pg/mL (High), 8,000 pg/mL (Dilution-QC)	
Analyte		Glycopyrrolate	
Internal standard		d_3-glycopyrrolate iodide	
Linearity		$R^2 \geq 0.9960$	
Lower limit of quantitation (LLOQ)		4.00 pg/mL	
Average recovery of the analyte (%)		90.2%	
QC Level		LLOQ	QC (Low, Mid, High)
QC Intra-run precision (%CV)	Run 1	7.5	0.3 to 1.4
	Run 2	6.8	0.5 to 1.4
	Run 3	11.1	0.4 to 4.4
QC Intra-run accuracy (%Bias)	Run 1	2.5	3.3 to 10.3
	Run 2	12.8	0.6 to 6.7
	Run 3	-2.5	3.3 to 6.5
QC Inter-run precision range (%CV)		10.2	3.2 to3.8
QC Inter-run accuracy range (%Bias)		4.3	4.2 to 6.0
QC sample bench-top stability		24.5 hours at room temperature	
Processed sample stability[1]		124 hours at room temperature	
Re-injection reproducibility[1]		93 hours at room temperature	
QC sample freeze/thaw stability		3 freeze (-20 °C)/thaw (RT) cycles 3 freeze (-70 °C)/thaw (RT) cycles	
Long-term stability in matrix		98 days at -20 °C and -70 °C (longer storage stability evaluations are on-going)	
Dilution integrity		5-fold and 20-fold	
Stock solution stability in diluent (ACN/H_2O 50:50)[1]		6 hours under white light at room temperature 92 days at -20 °C	
Spike solution stability in diluent (ACN/H_2O 50:50)[2]		17 hours under white light at room temperature 77 days at -20 °C	
Matrix Effect[2]		IS-normalized Matrix factor = 1.16±0.10 at 1.50 pg/mL with %CV = 8.6% IS-normalized Matrix factor = 1.04±0.05 at 180 pg/mL with %CV = 4.8%	
5% Hemolyzed QC precision (%CV)[2]		4.5 to 6.7	
5% Hemolyzed QC accuracy (%Bias)[2]		-4.4 to 8.0	
Selectivity		The selectivity evaluation met the acceptance criteria: no significant interference (≥ 20% of the lower limit of quantitation, LLOQ for glycopyrrolate or ≥ 5% of the IS peak area of accepted calibration standards and QC samples for the IS) was detected at the retention times of the analyte or the IS in all tested human plasma lots.	
Matrix Lot-to-Lot variation (%CV)		1.2 (n = 5)	
Measured mean in multiple matrix lots (%Bias)		5.8 (n = 5)	
Interference		There was no interference detected from glycopyrrolate to the IS.	
Whole blood processing stability[2]		120 minutes at room temperature and in an ice-water bath (~4 °C) for glycopyrrolate	
Batch size evaluation[2]		135 injections (Run 5)	
Carryover and contamination evaluation		No carryover or contamination	
Interference with potential concomitants		Interference was not detected at the retention time of glycopyrrolate from ipratropium, ethinyl estradiol, fluticasone propionate, salbutamon, budesonide, roflumilast, levonorgestrel, norethindrone acetate, nicotine, prednisone, metoprolol, fexofenadine, atenolol, acetaminophen, ibuprofen, acetylsalicylic acid, salicylic acid, and salbutamol.	
Bridging test for two validated curve ranges		Consistency of the assay performance and study data integrity was demonstrated between method BTM-1765-R0 and BTM-1965-R0.	

[Source: NA 208437, Module 5.3.1.4, Bioanalytical Report for Determination of Glycopyrrolate in Human Plasma Samples by LC-MS/MS for Sunovion Clinical Study Protocol SUN101-105: "A Crossover Clinical Pharmacology Study to Evaluate the Total Systemic Exposure and Lung Bioavailability of SUN-101 and Seebri® Breezhaler® Administered with and without Activated Charcoal in Subjects with Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD) (GOLDEN-7)]

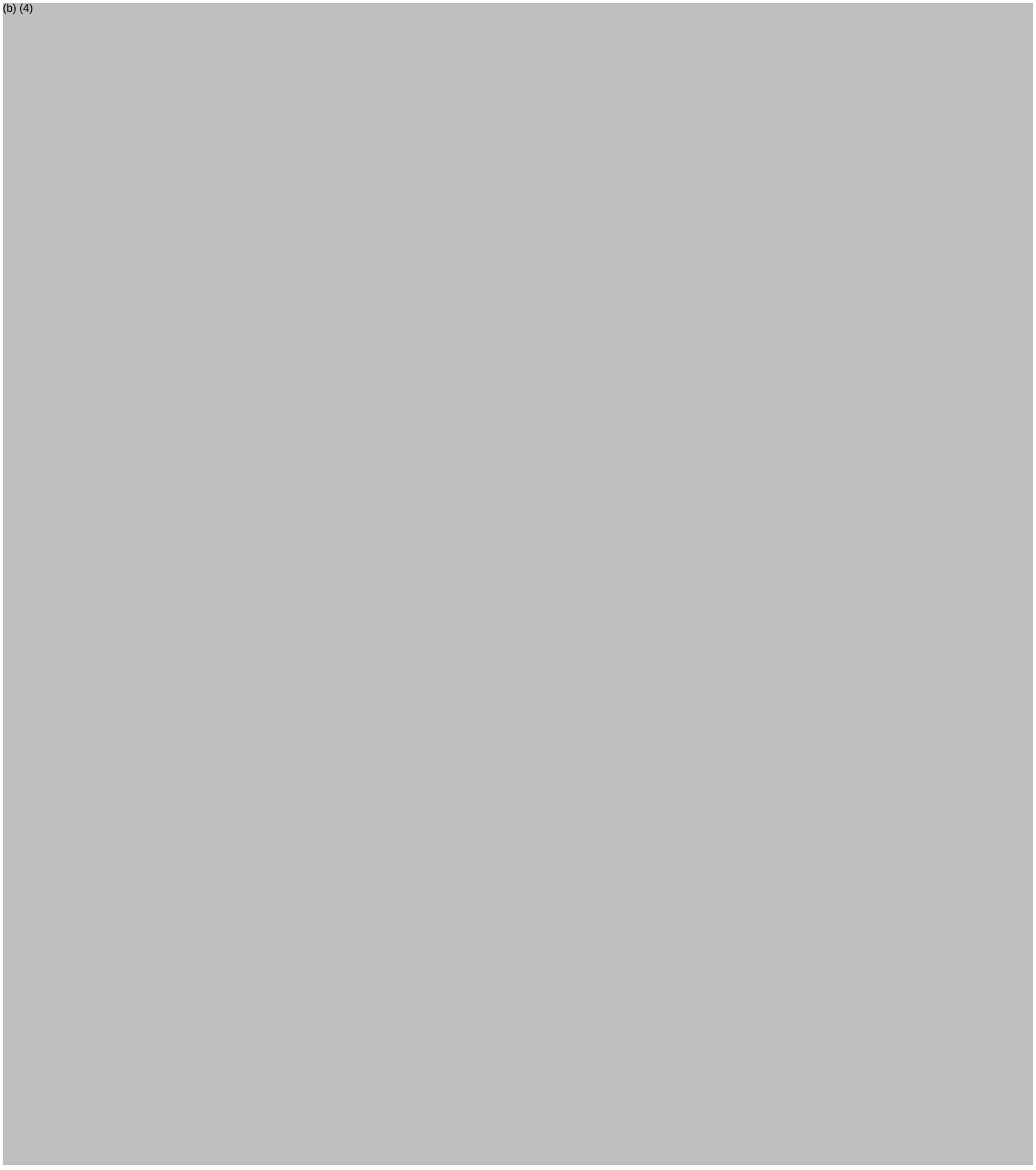
2.10.2. Which metabolites have been selected for analysis and why?

No metabolites were measured in the PK samples. No metabolites were quantified because the metabolites of glycopyrronium are not active and associated with efficacy or safety.

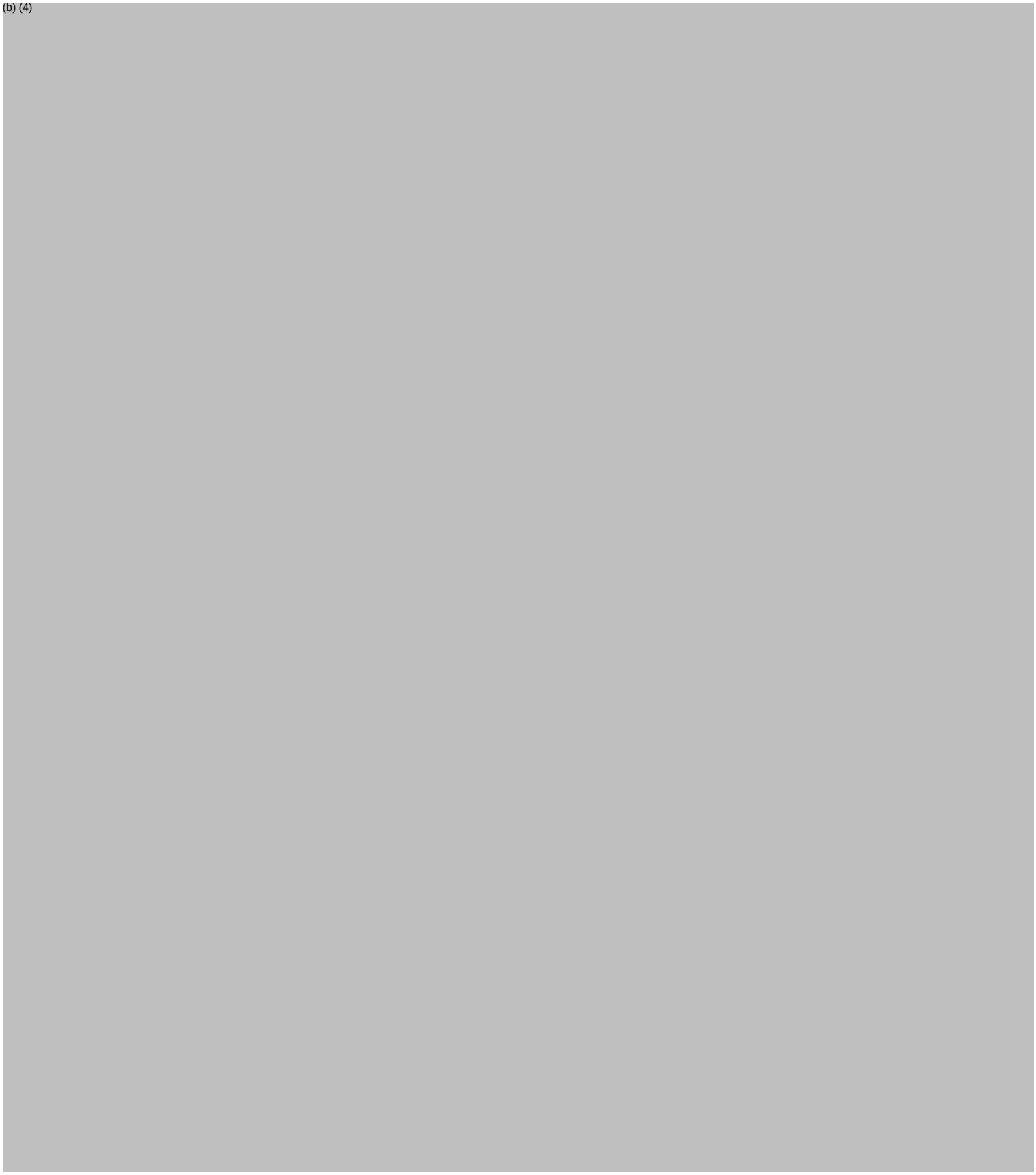
3. Label Recommendations

The revised labeling language based on the preliminary review is as below. Labeling statements to be removed are shown in ~~red strikethrough~~ font.

(b) (4)



(b) (4)



Reviewer's comments –

The text was deleted because the data/language (b) (4) . Additional text was deleted in section 12.3 (absorption and distribution) because the data to support these statements was (b) (4) .

4. Appendix

4.1. Individual Study Synopsis

4.1.1. SUN101-201

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)

Study Phase: Phase 2b, dose-ranging study

Objectives:
Primary: To determine the efficacy and dose-response profile of glycopyrrolate inhalation solution administered twice daily (BID) via CS eFlow® nebulizer following 7 days of treatment in subjects with moderate to severe COPD

Secondary: To assess the safety and tolerability of glycopyrrolate inhalation solution

Other: To assess the PK profile of glycopyrrolate inhalation solution

Study 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

Study Design:
This was a randomized, 6-way crossover, dose-range finding Phase 2 study of glycopyrrolate inhalation solution (GIS) in 96 subjects with moderate to severe COPD. The study was double-blind for GIS and placebo groups, and open-label for the active comparator aclidinium. Each subject received each of the following 6 treatments in a random order, BID:

- Placebo
- GIS 3 mcg via CS eFlow® nebulizer
- GIS 6.25 mcg via CS eFlow® nebulizer
- GIS 12.5 mcg via CS eFlow® nebulizer
- GIS 50 mcg via CS eFlow® nebulizer
- Aclidinium 400 mcg

The duration of study was approximately 14 weeks, consisting of a screening period of up to 2 weeks prior to randomization, 6 treatment periods consisting of 7 days of dosing followed by 5 to 7 days of washout each (for a total of 11 weeks), and a safety follow-up phone call 5 to 7 days following Day 7 of the last treatment period.

PK Assessment:
Blood sampling for pharmacokinetics were collected 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.

Results:
A total of 164 subjects were screened, of which 96 subjects were randomly assigned to a treatment sequence; of these, 88 subjects completed all treatments. The efficacy and safety populations each comprised 96 subjects and the PK population comprised 80 subjects.

PK Results
Plasma concentrations of the drug increased with increasing dose of glycopyrrolate inhalation solution and the highest serum drug concentration occurred 15 minutes to 30 minutes for all treatment groups.

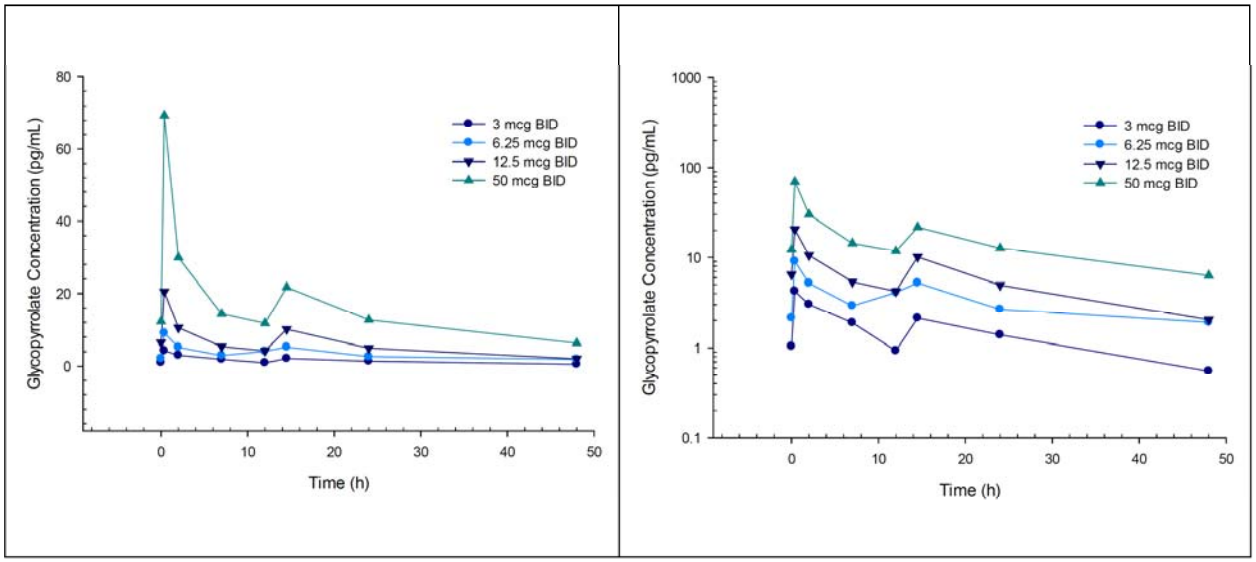


Figure 7 Plasma concentration-time profiles in linear and logarithmic scales on Day 7 after 3 to 50 mcg BID administration of glycopyrrolate inhalation solution (Study SUN101-201)
(Source – NDA 208437, Module 2.7.2, Summary of Clinical Pharmacology Studies), Results reported are for the glycopyrrolate (glycopyrronium bromide)

Table 15 Key drug PK parameters in subjects with moderate to severe COPD on Day 7 following daily administration of 3, 6.25, 12.5 or 50 mcg BID of glycopyrrolate inhalation solution (Study SUN101-201)

Treatment	C_{max} (pg/mL)	$AUC_{(0\text{-}tau)}$ (pg/mL*hr)	$t_{1/2}$ (hr)	Accumulation Index
	Mean (SD)	Mean (SD)	Median	Mean
3 mcg BID	5.623 (3.948)	32.714 (19.131)	5.93	1.385
6.25 mcg BID	9.407 (6.299)	51.314 (39.931)	9.17	1.770
12.5 mcg BID	20.538 (16.486)	88.684 (59.751)	7.75	2.051
50 mcg BID	69.381 (40.343)	255.471 (137.343)	6.25	1.398

(Source – NDA 208437, Module 5.3.3.5, Study 101-900: Pop-PK Report)

Efficacy Summary
Assessments of lung function showed that the 3 mcg BID treatment was not associated with statistically significant improvements in either FEV1 or AUC_{0-12} compared to placebo, and can be described as a "no-effect" treatment level. The 6.25 mcg BID treatment was associated with statistically significant improvements in both trough FEV1 and AUC_{0-12}, however it failed to achieve clinical relevance. The 12.5 mcg BID treatment was statistically superior to placebo in both trough FEV1 and AUC_{0-12} and exceeded the MCID of 100 mL for FEV1. The 50 mcg BID treatment was associated with improvement in trough FEV1 that was both clinically relevant and statistically significant compared to placebo. However, the 50 mcg BID treatment was approximately 20 mL inferior to treatment with aclidinium.

Conclusion:

- There were dose-dependent increases in lung function observed for both primary (trough FEV1) and secondary (AUC_{0-12}) endpoints. All doses produced statistically significant improvement for the primary and secondary endpoints except for the 3 mcg dose, which was not effective in improving trough FEV1.
- Glycopyrrolate reached median T_{max} within 0.5 hour postdose.

4.1.2. SUN101-105

Title: A Crossover Clinical Pharmacology Study to Evaluate the Total Systemic Exposure and Lung Bioavailability of SUN-101 and Seebri® Breezhaler® Administered with and without Activated Charcoal in Subjects with Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD) (GOLDEN-7)

Study Phase: Phase 1, PK

Objectives:
Primary: Determine the extent of pulmonary absorption of glycopyrrolate following dosing via CS eFlow® nebulizer with and without activated charcoal in subjects with moderate to severe COPD

Secondary: Further assess the safety of glycopyrrolate inhalation solution administered by the CS eFlow® nebulizer

Study Population: Subjects 40 to 70 years of age with a diagnosis of moderate to severe COPD

Study Design:
Eligible subjects were randomized to one of 10 treatment sequences. There was a minimum of a 7-day washout period between each treatment visit. At each visit, subjects received one dose of study medication according to the sequence assigned. The respective treatments were:

- 50 mcg of glycopyrrolate inhalation solution via CS eFlow® nebulizer;
- 50 mcg of glycopyrrolate inhalation solution via CS eFlow® nebulizer with administration of activated charcoal 2 minutes pre-dose and 2 minutes and 1, 2, and 3 hours postdose (i.e., following end of inhalation);

Reviewer's Note – *The other three treatment will not be discussed since they are not US FDA approved products.*

PK Assessment:
Pharmacokinetic samples were collected at the following times: within 15 minutes prior to dosing, immediately at the end of inhalation (~ 5 minutes from the start of inhalation) and post-dose at 0.25-0.5 hours, 1.5-2.5 hours, 6-8 hours, 12 hours (± 15 minutes), 13-16 hours, 24 hours (± 15 minutes), and 48 hours (± 15 minutes) on Days 1, 8, 15, 22, and 29.

Results:
Screened: 47; Randomized: 30; Completed: 26

Co-administration of glycopyrrolate inhalation solution via CS eFlow® nebulizer with activated charcoal, given as an oral suspension prior to the inhaled glycopyrrolate, led to a reduction in both C_{max} and AUC_{0-24} of the drug by approximately 6 and 24%, respectively, indicating that systemic exposure for glycopyrrolate occurs primarily from the lung.

Table 16 Summary of drug PK parameters by treatment (Study SUN101-105)

Parameter Statistic	SUN-101 50 mcg N = 29	SUN-101 50 mcg + Charcoal N = 29
C_{max} (pg/mL)		
n	29	29
Mean (SD)	61.46 (39.415)	57.51 (36.322)
CV%	64.136	63.162
t_{max} (h)		
n	29	29
Median	0.317	0.250
$t_{½}$ (h)		
n	13	10
Median	4.658	5.078
AUC_{0-24} (pg/mL*hr)		
n	29	29
Mean (SD)	273.47 (442.436)	208.20 (152.776)
CV%	161.787	73.378
AUC_{0-48} (pg/mL*hr)		
n	29	29
Mean (SD)	314.90 (567.826)	255.48 (223.900)
CV%	180.321	87.638
$AUC_{0-\infty}$ (pg/mL*hr)		
n	8	6
Mean (SD)	292.94 (237.338)	179.56 (75.637)
CV%	81.018	42.123
CL/F (L/hr)		
n	8	6
Mean (SD)	255.12 (147.863)	316.99 (117.644)
CV%	57.957	37.113
Vz/F (L)		
n	8	6
Mean (SD)	1316.34 (395.419)	1690.06 (286.283)
CV%	30.039	16.939

(Source – Adapted from NDA 208437, Module 2.7.2, Summary of Clinical Pharmacology)

Conclusion:
Co-administration of glycopyrrolate inhalation solution via CS eFlow® nebulizer with activated charcoal, given as an oral suspension prior to the inhaled glycopyrrolate, led to a reduction in both C_{max} and $AUC_{0-\infty}$ of glycopyrrolate, as compared with glycopyrrolate inhalation solution administered via eFlow® nebulizer alone. The drug product was generally well tolerated with no new safety concerns.

4.1.3. EP-101-01

Title: Single-dose, dose escalation study to assess the safety, tolerability, pharmacokinetics and bronchodilatory effects of glycopyrrolate inhalation solution using a high efficiency nebulizer in patients with COPD

Study Phase: Phase 2a

Objectives:
Primary: To assess the safety and tolerability of single ascending doses of glycopyrrolate inhalation solution when administered using a high efficiency nebulizer in patients with COPD.

Secondary:
- To assess and to compare the magnitude and duration of bronchodilator response in patients with COPD following single doses of glycopyrrolate inhalation solution when administered using a high efficiency nebulizer and a general purpose nebulizer.
- To assess the pharmacokinetic (PK) profile of glycopyrrolate.

Study Population: Subjects 40 to 75 years of age with a diagnosis of COPD

Study Design:
This two part study was a two-center, single dose, dose-escalation study in patients with COPD of 40-75 years of age. A total of 12 subjects were included in the study.

Part 1 (n=12): Subject was randomly allocated to one of 2 cohorts running in parallel.

Cohort 1 (n=6):
Glycopyrrolate inhalation 25 mcg / 0.5 mL via open system (OS) eFlow® nebulizer
Glycopyrrolate inhalation solution 200 mcg / 0.5 mL via open system (OS) eFlow® nebulizer

Cohort 2 (n=6):
Glycopyrrolate inhalation solution 75 mcg / 0.5 mL via open system (OS) eFlow® nebulizer
Glycopyrrolate inhalation solution 500 mcg / 0.5 mL via open system (OS) eFlow® nebulizer
Glycopyrrolate inhalation solution 1000 mcg / 0.5 mL via open system (OS) eFlow® nebulizer

Part 2 (n=12): All subjects who participated in Part 1 were included.
Glycopyrrolate inhalation solution 200 mcg / 2 mL (6 subjects) or 2 mL Placebo (6 subjects) oral inhalation via general purpose nebulizer

PK Assessment:
Pharmacokinetic samples were collected at the following times: Pre-dose and 5, 15, 30, 45, and 60 minutes and 2, 4, 6, 8 and 12 hours post-dose.

Results:
Number of subjects - 12 male or female patients with COPD.

Administration of 200 mcg, 500 mcg and 1000 mcg glycopyrrolate inhalation suspension via OS eFlow® nebulizer produced dose proportional increases in C_{max} and AUC_{0-t}.

Table 17 Statistical analysis of dose proportionality (Study EP-101-01)

Parameter	GIS 200mcg/0.5mL eFlow	GIS 500mcg/0.5mL eFlow	GIS 1000mcg/0.5mL eFlow	Slope (95% CI)
	Geometric LSmean (95% CI)			
Cmax (pg/ml)	167.05 (117.57 – 237.37)	721.83 (508.01 – 1025.66)	1480.42 (1041.88 – 2103.53)	1.16 (0.94 – 1.39)
AUC_{0-t} (pg/ml.h)	381.71 (251.11 – 580.26)	1938.49 (1275.21 – 2946.76)	4017.31 (2642.73 – 6106.85)	1.17 (0.94 – 1.41)
AUC_{0-inf} (pg/ml.h)	524.93 (377.09 – 730.72)	2403.95 (1726.94 – 3346.37)	5179.31 (3720.68 – 7209.76)	1.25 (1.02 – 1.47)

(Source – NDA 208437, Module 2.7.2, Summary of Clinical Pharmacology)

Conclusion:
Over a dose range of 200-1000 mcg of glycopyrrolate inhalation solution administered via OS eFlow® nebulizer, the increases in C_{max} and AUC_{0-t} were dose proportional.

4.1.4. EP-101-02

Title: Randomized, Placebo-Controlled, Double-Blind, Dose Ranging, Single Dose, 6-Way Crossover Study to Assess the Safety, Efficacy and Pharmacokinetics of EP-101[2] Using eFlow® Nebulizer in Patients with COPD

Study Phase: Phase 2a

Objectives
- To establish the dose-response characteristics of glycopyrrolate inhalation solution as demonstrated by changes in forced expiratory volume in one second (FEV1)
- To assess the pharmacokinetic (PK) profile of glycopyrrolate
- To assess the safety and tolerability of glycopyrrolate

Study Population: Subjects 40 to 75 years of age with COPD

[2] This refers to glycopyrrolate inhalation solution

Study Design:
The study treatments were as follows:

- Glycopyrrolate inhalation solution 12.5 mcg/0.5 mL via OS eFlow® nebulizer
- Glycopyrrolate inhalation solution 50 mcg/0.5 mL via OS eFlow® nebulizer
- Glycopyrrolate inhalation solution 100 mcg/0.5 mL via OS eFlow® nebulizer
- Glycopyrrolate inhalation solution 200 mcg/0.5 mL via OS eFlow® nebulizer
- Glycopyrrolate inhalation solution 400 mcg/0.5 mL via OS eFlow® nebulizer
- Placebo 0.5 mL via OS eFlow® nebulizer

Each completed subject received all 6 study treatments as a single dose oral inhalation in a randomized, blinded manner. Each treatment visit was separated by a washout period of 5-12 days.

PK Assessment:
Pharmacokinetic samples were collected at the following times in a subset of subjects (n=14): Pre-dose (within 30 minutes prior to dose); and 5, 15, 30 and 45 minutes and 1, 2, 4, 6, 8, 12 and 24 hours post-dose.

Results:
42 total subjects with moderate to severe COPD were enrolled into the study, and PK was collected from a subset of patients (n=14).

Following the inhalation of 12.5 mcg, 50 mcg, 100 mcg, 200 mcg and 400 mcg doses of glycopyrrolate inhalation solution in 0.5 mL volumes via the OS eFlow® nebulizer, the drug was rapidly absorbed via the lung, with a median T_{max} ranging from 5 to 15 min.

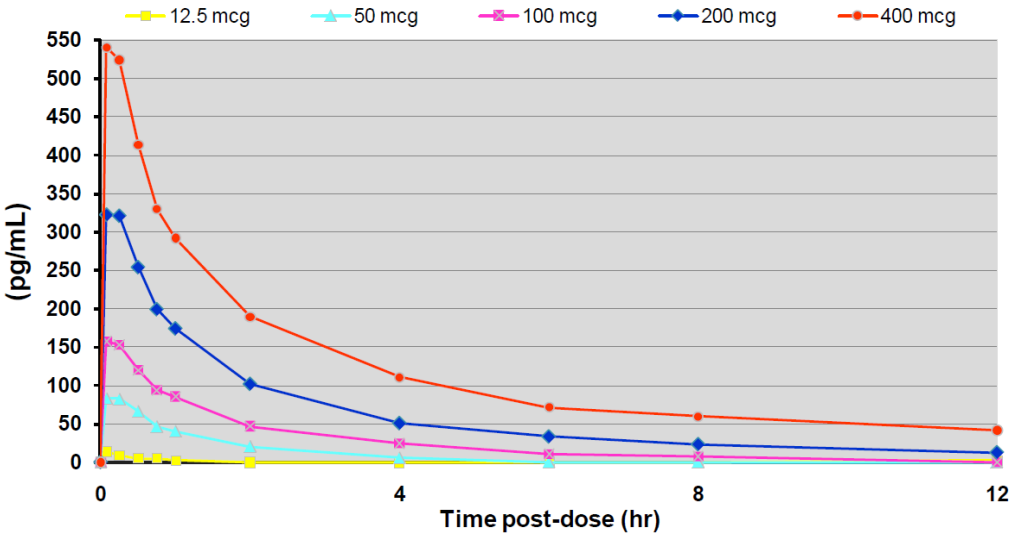


Figure 8 Mean glycopyrrolate concentration-time profiles at single doses of 12.5 to 400 mcg glycopyrrolate administered via OS eFlow® nebulizer (Study EP-101-02)
(Source – NDA 208437, Module 2.7.2, Summary of Clinical Pharmacology)

Table 18 Summary of derived plasma glycopyrrolate pharmacokinetic data (Study EP-101-02)

Dose	Summary Statistic	C_{max} (pg/ml)	t_{max} (hr)	$t_{½}$ (hr)	AUC_{0-t} (pg.h/ml)	$AUC_{0-\infty}$ (pg.h/ml)	AUC_{exp} (%)
SUN-101 12.5 mcg	n	2	2	0	2	0	0
	Mean	66.50	0.165	N/A	197.15	N/A	N/A
	SD	42.71	0.021	N/A	202.02	N/A	N/A
	Min	36.30	0.150	N/A	54.30	N/A	N/A
	Median	66.50	0.165	N/A	197.15	N/A	N/A
	Max	96.70	0.180	N/A	340.00	N/A	N/A
	Geo. Mean	59.25	N/A	N/A	135.87	N/A	N/A
	Geo. CV	78.49	N/A	N/A	209.27	N/A	N/A
SUN-101 50 mcg	n	13	13	2	13	2	2
	Mean	86.75	0.251	0.8950	100.88	255.00	22.00
	SD	51.91	0.087	0.0212	80.88	90.51	0.99
	Min	33.20	0.150	0.8800	7.72	191.00	21.30
	Median	76.60	0.320	0.8950	92.10	255.00	22.00
	Max	213.00	0.350	0.9100	251.00	319.00	22.70
	Geo. Mean	74.48	N/A	0.8949	67.18	246.84	21.99
	Geo. CV	62.24	N/A	2.3707	143.22	37.49	4.50
SUN-101 100 mcg	n	12	12	4	12	4	4
	Mean	161.72	0.243	3.2450	305.68	659.00	20.58
	SD	82.16	0.084	1.2353	194.00	188.41	3.23
	Min	65.10	0.150	1.5000	56.80	390.00	16.60
	Median	149.50	0.260	3.6650	276.50	709.00	20.85
	Max	318.00	0.330	4.1500	644.00	828.00	24.00
	Geo. Mean	144.58	N/A	3.0137	237.80	634.65	20.38
	Geo. CV	52.53	N/A	50.7557	98.45	34.28	16.24

Dose	Summary Statistic	C_{max} (pg/ml)	t_{max} (hr)	$t_{½}$ (hr)	AUC_{0-t} (pg.h/ml)	$AUC_{0-\infty}$ (pg.h/ml)	AUC_{exp} (%)
SUN-101 200 mcg	N	12	12	7	12	7	7
	Mean	346.58	0.254	3.4114	796.83	795.71	19.86
	SD	155.08	0.096	1.3358	505.32	216.63	3.78
	Min	133.00	0.150	1.5000	184.00	529.00	14.60
	Median	323.00	0.275	3.4900	593.50	753.00	20.00
	Max	719.00	0.380	5.3400	2130.00	1210.00	25.00
	Geo. Mean	316.05	N/A	3.1663	677.24	772.59	19.55
	Geo. CV	48.35	N/A	45.4839	66.34	26.30	19.39
SUN-101 400 mcg	n	13	13	6	13	6	6
	Mean	566.31	0.224	4.7683	1804.54	1641.67	15.85
	SD	269.09	0.078	2.9633	1007.58	1077.27	5.12
	Min	175.00	0.150	1.9100	376.00	484.00	11.30
	Median	530.00	0.180	4.0250	1650.00	1465.00	13.60
	Max	1090.00	0.320	10.2000	3340.00	3570.00	22.40
	Geo. Mean	504.93	N/A	4.1238	1481.36	1367.76	15.22
	Geo. CV	55.67	N/A	63.5353	82.17	76.70	31.39

(Source – NDA 208437, Module 2.7.2, Summary of Clinical Pharmacology)

Conclusion:
Single doses of glycopyrrolate inhalation solution (12.5 mcg - 400 mcg), delivered via the OS eFlow® nebulizer, were safe and well tolerated. Glycopyrrolate plasma levels increased in a dose-dependent manner for all doses tested and returned to near baseline by 12 hours post-dose.

4.1.5. EP-101-03

Title: A Randomized, Double-Blind, Placebo-Controlled, Multi-Center, 7-Arm, 4-Period Cross-over, Incomplete Block Design, 7-Day Dosing Study to Assess the Dose-Response, Safety, and Efficacy of EP-101 in Subjects with Moderate-to-Severe COPD

Study Phase: Phase 2b

Objectives:
Primary: To determine the steady-state efficacy and dose-response profile of EP-101 administered once-daily via eFlow® nebulizer following 7 days of treatment in subjects with moderate-to-severe chronic obstructive pulmonary disease (COPD)

Secondary:
- To assess the safety and tolerability of glycopyrrolate
- To assess the pharmacokinetic profile of glycopyrrolate

Study Population: Subjects 40 to 75 years of age with COPD

Study Design:
The study treatments were as follows:
- Glycopyrrolate inhalation solution 25 mcg/0.5 mL via OS eFlow® nebulizer QD
- Glycopyrrolate inhalation solution 50 mcg/0.5 mL via OS eFlow® nebulizer QD
- Glycopyrrolate inhalation solution 100 mcg/0.5 mL via OS eFlow® nebulizer QD
- Glycopyrrolate inhalation solution 200 mcg/0.5 mL via OS eFlow® nebulizer QD
- Placebo 0.5 mL via OS eFlow® nebulizer QD
- Tiotropium bromide 18 mcg QD
- Ipratropium bromide 500 mcg TID

Each subject received four study test treatments, each separated by a washout period of at least 7 days. The total duration of the study was up to 11 weeks for each subject, consisting of a Screening Period and placebo run-in phase of up to 21 days; four 7-day Treatment Periods with a 7-day washout (±2 days) between each Period; and a Final Study Visit 7 days (±2 days) following last study treatment.

PK Assessment:
Pharmacokinetic samples were collected at the following times in a subset of subjects (n=14): Days 1 and 7 of each Treatment Period at the following time points (all time points were relative to the end of study treatment administration): within 30 minutes pre-dose; and 5, 15, 30, and 45 minutes and 1, 2, 4, 6, 8, 12 hours and 23 hours 45 minutes post-dose.

Results:
Following the inhalation of 25 mcg, 50 mcg, 100 mcg, 200 mcg doses of glycopyrrolate inhalation solution via the OS eFlow® nebulizer, the drug was rapidly absorbed via the lung, with a median T_{max}

ranging from 5 to 15 min. Plasma glycopyrrolate concentrations returned to near baseline by 24 hours post-dose.

Table 19 Pharmacokinetic parameters on Day 1 and Day 7 (Study EP-101-03)

Day 1					
Dose	**C_{max} (pg/mL)** Mean (SD), n	**t_{max} (hr)** Median (min-max), n	**$t_{½}$ (h)** Mean (SD), n	**AUC_{0-t} (hr*pg/mL)** Mean (SD), n	**$AUC_{0-\infty}$ (hr*pg/mL)** Mean (SD), n
25 mcg	30 (12), 13	0.08 (0.05-1.04), 13	1.6 (0.8), 7	29.8 (29), 13	52 (21), 7
50 mcg	63 (38), 19	0.23 (0.06-0.76), 19	2.7 (3.2), 17	109 (85), 19	140 (111), 17
100 mcg	116 (86), 18	0.22 (0.05-0.51), 18	6.8 (6.1), 15	286 (194), 18	384 (287), 15
200 mcg	262 (212), 12	0.21 (0.09-0.75), 12	11.7 (8.0), 9	704 (376), 12	793 (352), 9
Day 7					
Dose	**C_{max} (pg/mL)** Mean (SD), n	**t_{max} (hr)** Median (min-max), n	**$t_{½}$ (h)** Mean (SD), n	**AUC_{0-t} (hr*pg/mL)** Mean (SD), n	**AUC_{0-tau} (hr*pg/mL)** Mean (SD), n
25 mcg	36 (9), 11	0.11 (0.06-1.04), 11	3.9 (3.5), 7	73 (51), 11	116 (75), 7
50 mcg	83 (48), 19	0.14 (0.06-0.53), 19	4.6 (4.7), 15	201 (145), 19	217 (147), 15
100 mcg	145 (122), 17	0.22 (0.06-1.01), 17	14 (8.8), 8	534 (315), 17	573 (310), 8
200 mcg	313 (177), 11	0.23 (0.05-0.28), 11	15 (7.9), 9	1116 (514), 11	1143 (560), 9

(Source – NDA 208437, Module 2.7.2, Summary of Clinical Pharmacology)

Conclusion:
Glycopyrrolate inhalation solution delivered via the OS eFlow® nebulizer at doses of 25-200 mcg QD for 7 days was safe and well tolerated. Following inhalation, mean glycopyrrolate concentrations on Day 1 and Day 7 peaked approximately at 5 to 15 minutes post-dose for all dose levels. Systemic exposure to glycopyrrolate increased across the dose range from 25 μg to 200 mg. C_{max} and AUC values increased with increasing doses, approximately 1.15 to 1.36-fold for C_{max} and 1.6 to 1.9-fold for $AUC_{(0-t)}$ following multiple-dose administration for 7 days compared to Day 1.

4.2. PM Review

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

NDA Number	208437
Drug Name	LONHALA MAGNAIR (glycopyrrolate)
Dose Regimen	One vial (25 mcg of glycopyrrolate) vial twice-daily using MAGNAIR.
Indication	The long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD)
Pharmacometrics Reviewer	Chao Liu, Ph.D.
Pharmacometrics Team Leader	Jingyu Yu, Ph.D.
Applicant	Sunovion Pharmaceuticals, Inc.

Table of Contents

1 Summary of Findings

The proposed dose of 25 mg Q2D for glycopyrrolate inhalation solution is acceptable for the proposed indication.

1.1 Key Review Questions

The purpose of this review is to address the following key question:

1.1.1 Is the relevant labeling regarding intrinsic factors (body weight, race) adequately supported by population PK analysis?

Yes. There was no evidence of clinically relevant effect of age or body weight on systemic exposure to glycopyrrolate. In addition, there was no evidence of clinically significant ethnic/race effects. Population PK analysis suggested the apparent glycopyrrolate clearance (CL/F) increases with greater dose levels. In addition, renal function was identified as a significant factor for patient clearance (CL/F). Patients with mild (N=41) and moderate (N=67) renal impairment would have 17.2% and 27.6% greater dose normalized AUC at steady state as compared with patients with normal renal function (N=67). There was a possible study effect on relative bioavailability (F1) with studies S001 and S002 having higher F1 ~85.3% relative to studies S003 and S201.

2 Recommendations

This application is acceptable from pharmacometrics perspective.

3 Results of Sponsor's Analysis

3.1 Population PK Analysis

Sponsor's PPK analysis was based on four phase 2 studies (Studies EP-101-01, EP-101-02, EP-101-03, SUN101-201) in patients with moderate to severe COPD.
The objectives of sponsor's population PK analysis were:

- Develop a population PK model to describe the time-course of SUN101 plasma concentration following inhaled oral administration using a novel inhalation "eFlow®" device.
- Estimate the magnitude of inter-individual and intra-individual variability associated with the PK parameters.
- Evaluate the influence of covariates effects on model parameters using baseline demographic and clinical laboratory values.
- Predict empirical Bayesian post-hoc individual exposure of SUN101 in the plasma of patients following oral inhalation of SUN101 using an eFlow® device.

3.2 Data

The population PK analysis included data obtained from four clinical studies of glycopyrrolate solution for inhalation (**Table 20**):

Table 20: Clinical Studies for Population PK Analysis

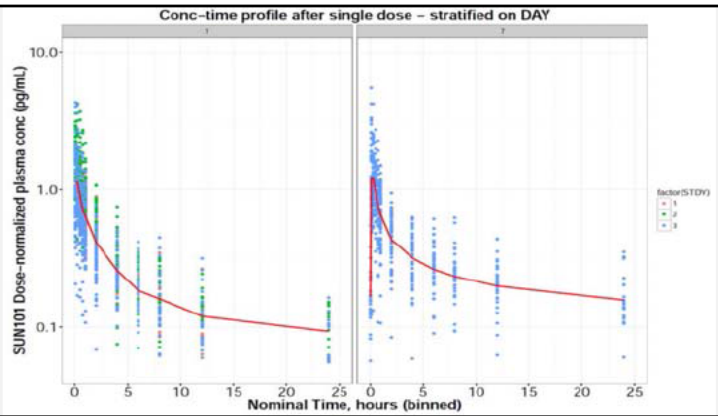
Study /Phase	Dosing Regimen	Pharmacokinetic Sampling Times
S001 Phase 2a	Single dose study Part 1: 25, 75, 200, 500, and 1000 µg inhaled via investigational eFlow® OS nebulizer Part 2: 200 µg inhaled via general purpose nebulizer	Pre-dose and 5, 15, 30, 45, and 60 minutes and 2, 4, 6, 8 and 12 hours post-dose.
S002 Phase 2a	Single dose study 12.5, 50, 100, 200, and 400 µg and placebo inhaled via eFlow® OS nebulizer	Pre-dose (within 30 minutes prior to dose); and 5, 15, 30 and 45 minutes and 1, 2, 4, 6, 8, 12 and 24 hours post-dose.
S003 Phase 2b	Multiple dose study (7 days) 25, 50, 100, and 200 µg, and placebo inhaled once daily for 7 days via eFlow® OS nebulizer	For a subset of subjects on Days 1 and 7 of each treatment period: Pre-dose (within 30 minutes); and 5, 15, 30, and 45 minutes and 1, 2, 4, 6, 8, and 12 hours and 23 hours 45 minutes post-dose.
S201 Phase 2b	Multiple dose study (7 days) Placebo and 3, 6.25, 12.5, and 50 µg bid via eFlow® OS nebulizer and Aclidinium 400 µg bid via TUDORZA PRESSAIR dry-powder inhaler will be administered over 7-day period	Pre-dose, and 0.25-0.5, 1.5-2.5, 6-8, 12, 13-16, and 24h post-dose on Day 7 of the first treatment sequence only (one sample per window). A final blood sample was to be collected between 24-72 hours after the final evening dose on Day 7 of the first treatment period only.

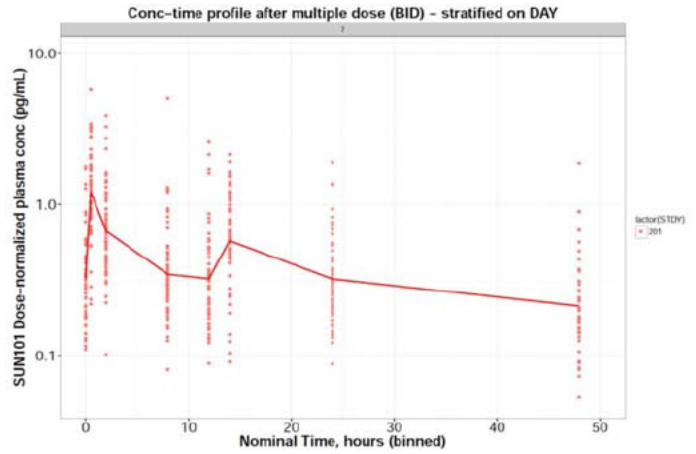
Source: Sponsor's Population PK Analysis Report 101-900, Table 2

3.3 Population PK Model Development

Semilog scatterplots of glycopyrrolate plasma concentrations versus time, stratified by on day 1 or 7, are provided in Figure 9. After oral inhalation, glycopyrrolate plasma concentrations appeared to decline in a poly-phasic manner.

Figure 9 : SUN101 Dose-Normalized Plasma Concentration-Time Profiles Following Single and Multiple Dosing (Semi-Log Scale)





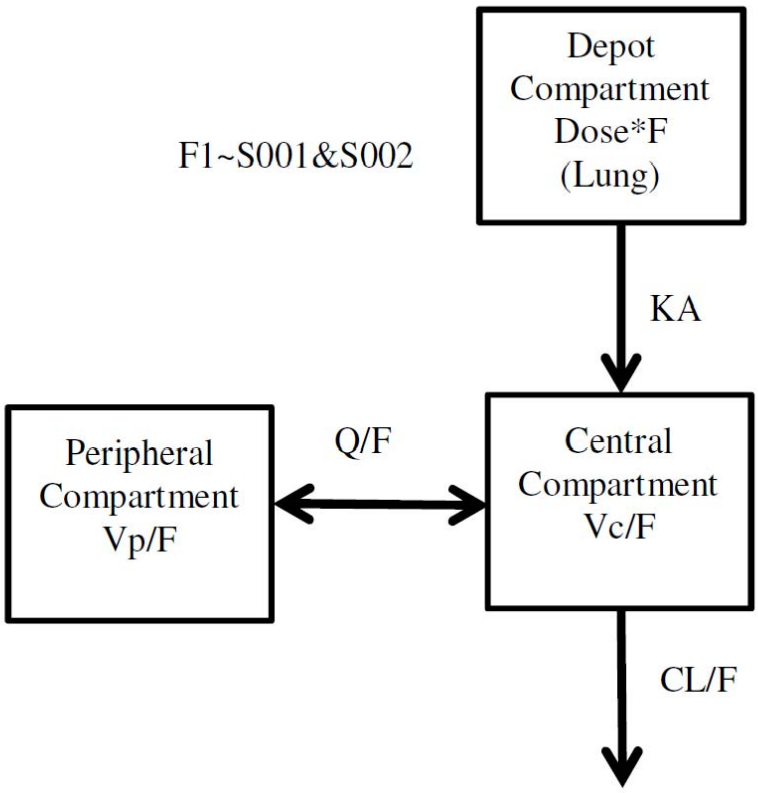
Source: Sponsor's Population PK Analysis Report 101-900, Figure 2

3.3.1 Structural Model

A total of 2597 plasma concentration data were used in the analysis. Based on the graphical exploration of dose normalized plasma glycopyrrolate concentration versus nominal time profile, the applicant explored two- and three- compartment models. However, the 3-compartment model mostly failed to minimize and/or converge successfully. Hence a 2-compartment model was chosen for further exploration as the structural model. Since the number of BQL samples was > 10% (~22%) the Beal-M3 and Laplacian estimation method was used.

The base model consisted of a 2-compartment disposition model with first-order absorption and first-order elimination rate constant. Different omega structures were explored including Omega block and Omega diagonal structures. The base model included a covariate effect of study (S001 & S002) on relative bioavailability (F1) which resulted in a significant drop in OFV (by 16.998 points), and a lower RSE (from 44% CV to 18.6%CV). The effect of study on F1 was modelled as an exponential model.

Figure 10: Two-Compartment Model Schematic



Source: Sponsor's Population PK Analysis Report 101-900, Figure 4

3.3.2 Covariate Model Development

Potential covariate-parameter relationships were explored by inspection of plots of individual random effects for F1, CL/F and V2/F estimated from the base model versus covariates of interest (AGE, SEXF, WTKG, PBFEV1PN, AST, ALT, TBIL, CRCL, SEXF, RACE, ELDERLY, COPDMOD, RFCAT, STUD, DOSFRQ, DAY, DOSE). Covariates were selected based on scientific plausibility and evaluated for significance at p=0.05 (1 df, 3.84) for the forward search and at p=0.001 (1 df, 10.83) for the backward search. No covariate was found to have significant effect on the PK of SUN101, except for studies S001, S002 and S003 which were identified as potential covariates on CL/F and V2/F.

3.3.3 Final Model

Based on the Stepwise covariate model (SCM) building approach as implemented in PsN and described above, STUDY was identified as potential covariate on CL/F (i.e. CLSTUD1, CLSTUD2 & CLSTUD3) and V2/F (i.e. V2STUD1, V2STUD2 & V2STUD3). However, the final covariate model failed to minimize successfully without errors messages, and in addition the covariance step failed to successfully converge. Attempts to reparameterize the model did not resolve the minimization and/or the convergence errors. As a result the covariate model was reduced back to the base model which included an effect of study (S001 & S002) on F1. Therefore, the base model was declared as the final model. The parameter estimates for the base/final model are presented in Table 21.

Table 21: Parameter Estimates of Base/Final Model

Model parameter	Theta	Estimate (SE)	RSE	Bootstrap mean estimate	Bootstrap 5-95% CI	Explanation
Parameter						
Apparent total clearance (CL/F), [L/h]	1	206 (13)	6.3%	206	183-229	
Apparent central volume of distribution (V2/L), [L]	2	1050 (67)	6.4%	1050	928-1166	
Apparent inter-compartmental clearance (Q/L), [L/h]	3	457 (29.5)	6.5%	460	394-519	
Apparent peripheral volume of distribution (V3/F), [L]	4	3220 (213)	6.6%	3258	2735-3704	
Absorption rate constant (KA), [1/h]	5	21.2 (1.98)	9.3%	22.6	13.2-29.2	
Relative Bioavailability (F1)	6	1 (FIXED)	-	-	-	
Effect of S001 & S002 on F1 TVF1= 1*exp(STDY*THETA(12))	12	0.493 (0.124)	25.5%	0.492	0.324-0.663	63.7% higher F1 in S001 & S002 relative to S003 & S201
Absorption lag time (ALAG), [h]	7	0 (FIXED)	-	-	-	
Inter-individual variability						
IIV on CL/F (ETA1)	NA	28.1%CV [0.0791 (0.0309)]	19.5%			An interindividual variability of 28.1%CV was estimated for CL/F
IIV on V2/F (ETA2)	NA	31.8%CV [0.101 (0.0259)]	12.8%	0.104	0.0560-0.147	An interindividual variability of 31.8%CV was estimated for V2/F
IIV on F1 (ETA6)	NA	46.6%CV [0.217 (0.0404)]	9.3%	0.216	0.144-0.289	An interindividual variability of 46.6%CV was estimated for F1
Inter-Occasion variability						
IOV on CL/F	NA	31.6%CV [0.0996 (0.0244)]	12.2%	0.102	0.050-0.149	An interoccasion variability of 31.6%CV was estimated for CL/F
Residual Unexplained Variability (RUV)						
S001 residual error variance	8	0.134 (0.0088)	6.6%	0.133	0.107-0.161	S001 RUV was 36.6%CV
S002 residual error variance	9	0.249 (0.0099)	4.0%	0.248	0.201-0.297	S002 RUV was 49.9%CV
S003 residual error variance	10	0.264 (0.0064)	2.4%	0.261	0.228-0.299	S003 RUV was 51.4%CV
S201 residual error variance	11	0.448 (0.0167)	3.7%	0.447	0.396-0.501	S201 RUV was 66.9%CV
Shrinkage						
Eta_shrinkage on CL/F		38.4%				
Eta_shrinkage on V2/F		34.6%				
Eta_shrinkage on F1		11.0%				
Epsilon_shrinkage		11.0%				
OFV = -2081.776						

SE- standard error. RSE-relative standard error. RUV – residual unexplained variability. IIV – inter-individual variability. IOV – inter-occasion variability. OFV – objective function value.

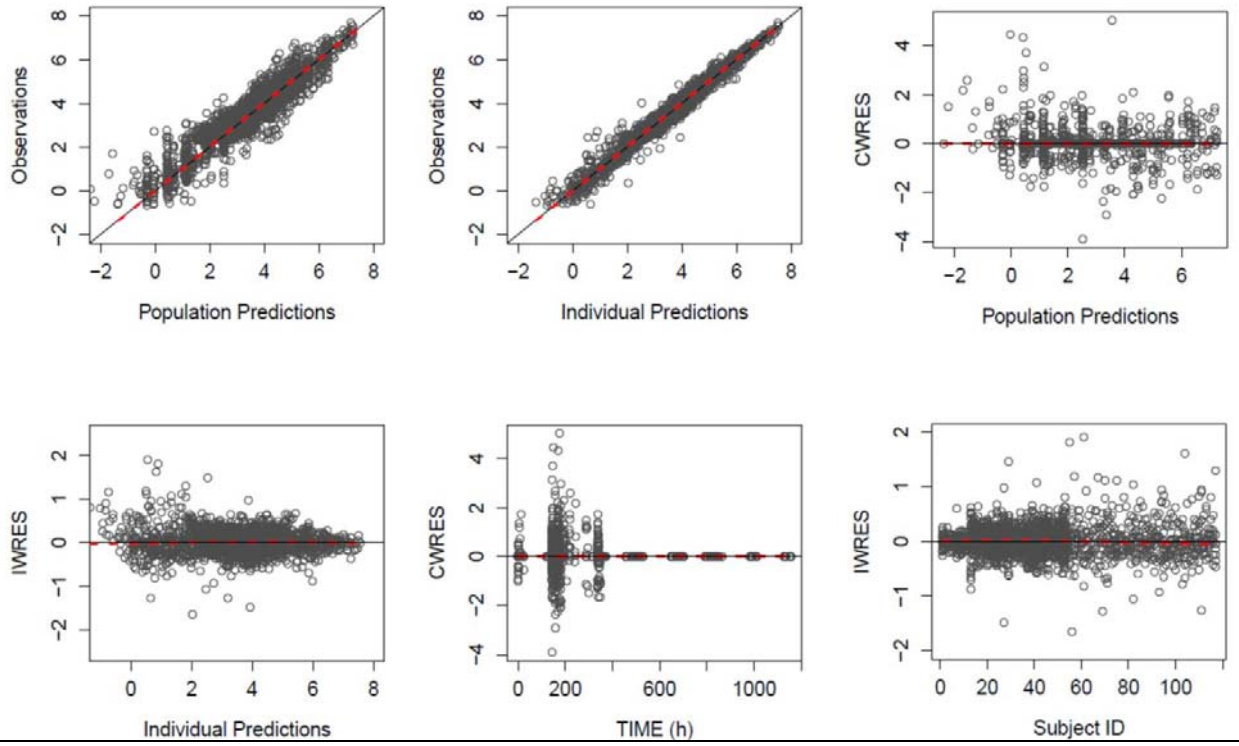
Source: Sponsor's Population PK Analysis Report 101-900, Table 7

Reviewer's Comments: FDA review performed population PK analysis. See Section 4 for details.

3.3.4 Model Evaluation

The primary goodness-of-fit plots for the final population PK model are provided in Figure 11. These plots demonstrate the adequacy of the model fit across dosing regimens and routes of administration.

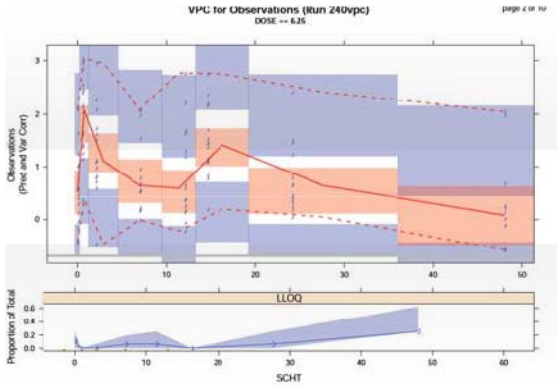
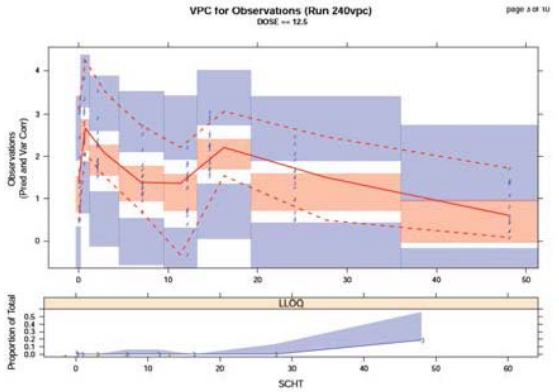
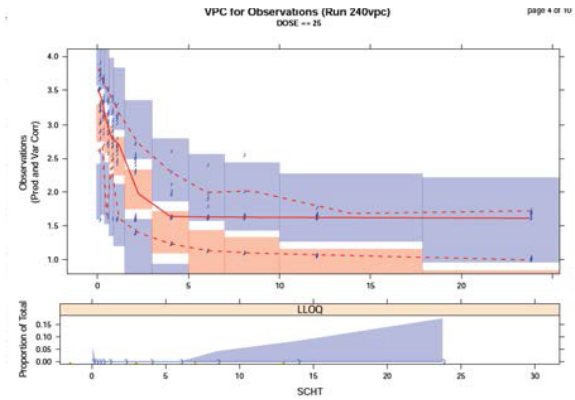
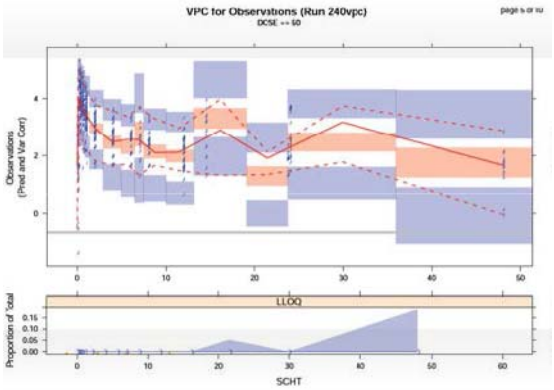
Figure 11: Goodness-of-Fit Plot for Log-Transformed Plasma Concentration from Base/Final Model



Source: Sponsor's Population PK Analysis Report 101-900, Figure 5

Additionally, the adequacy or predictive ability (in terms of general structure and variability components) of the final model was assessed using a simulation-based, visual prediction check (VPC). One thousand (1000) simulation of the model were executed. Figure 12 shows the VPCs stratified dose.

Figure 12: Diagnostic Plots of Prediction/Variance-Corrected Visual Predictive Check Stratified by DOSE (6.25, 12.5, 25, 50 mcg)

6.25 mcg	12.5 mcg
	
25 mcg	**50 mcg**
	

Source: Sponsor's Population PK Analysis Report 101-900, Figure 8

Reviewer's Comments: The sponsor employed stepwise covariate model (SCM) building procedure to select the model covariate. The p=0.001 stay criterial could be too stringent for covariate selection. FDA review performed independent sensitivity analysis for covariate selection. Creatine clearance and dose were identified as statistically significant covariate for the apparent clearance. Based on the sensitivity analysis, patients with mild (N=41) and moderate (N=67) renal impairment would have 17.2% and 27.6% greater dose normalized AUC at steady state as compared with patients with normal renal function (N=67). In addition, the apparent clearance would increase with greater dose levels. The other parameter estimates were consistent with the applicant's results.

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/s/

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04/27/2017

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