CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208294Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	208294
Submission Date	06/25/2015
Proposed Brand Name	Bevespi Aerosphere
Generic Name	Glycopyrrolate/ Formoterol Furoate (GFF) MDI
Clinical Pharmacology Reviewer	Sheetal Agarwal, Ph.D., RAC
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OCP Division	Clinical Pharmacology II
OND Division	Division of Pulmonary, Allergy, and Rheumatology Products
Sponsor/Authorized Applicant	Pearl Therapeutics
Submission Type; Code	505(b)(2) referencing approved NDAs 17558 for glycopyrrolate (Robinul) and 21929 (Symbicort); standard review
Formulation; Strength(s)	GFF MDI 14.4/9.6 µg (ie, 14.4 µg of glycopyrronium)
Indication	COPD
Dosage Regimen	Two inhalations (i.e. 18 µg of glycopyrrolate s[glycopyrronium bromide], equivalent to 14.4 µg of glycopyrronium, and 9.6 µg of formoterol fumarate) twice daily (BID)

1. Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology has reviewed the clinical pharmacology information provided within NDA 208294 and finds the application acceptable.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

1.3.1 Background

In this NDA, the sponsor, Pearl Therapeutics, seeks marketing approval for a fixed-dose combination of glycopyrrolate (G or glycopyrronium bromide) 9 µg and formoterol fumarate (FF) 4.8 µg (GFF MDI) to be administered via oral inhalation. In addition to the GFF MDI combination product, (b) (4) GFF MDI, (b) (4) formulated (b) (4) (b) (4) with micronized glycopyrronium bromide and/or micronized FF cosuspended with a porous particle excipient in a hydrofluoroalkane (HFA) propellant.

GFF MDI is indicated for the long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema at the recommended dose of two inhalations (i.e. 18 µg of glycopyrrolate [glycopyrronium bromide], equivalent to 14.4 µg of glycopyrronium, and 9.6 µg of formoterol fumarate) twice daily (BID). The proposed brand name is Bevespi Aerosphere.

The NDA is a 505(b)(2) NDA referencing approved NDAs 17558 for glycopyrrolate (Robinul) and 21929 (Symbicort) for formoterol furoate for partial nonclinical and partial human PK (for e.g., some ADME and special populations data) information. Most of the PK information included in the product label is with the combination product itself. The sponsor has had several interactions with the Agency before submitting the NDA during which the Agency agreed with the sponsor's choice of the final dose to be carried into Phase 3, i.e., 18/9.6 µg of glycopyrrolate and formoterol fumarate respectively. (b) (4)

The individual components of GFF MDI are available commercially for multiple indications. Glycopyrronium is an anti-cholinergic that exerts its bronchodilatory effect via muscarinic receptors located on smooth muscle cells within the trachea and bronchi. Glycopyrronium is approved in many countries including the US in multiple formulations

for different indications, including for COPD in the EU and Japan; however, it is not currently available as an orally-inhaled product in the US for COPD. Formoterol fumarate is a potent and selective beta agonist approved in many countries worldwide for use in asthma and COPD. It is available in the US as a dry powder inhaler (Foradil Aerolizer inhalation powder) and as an inhalation solution (Perforomist) for the maintenance treatment of bronchoconstriction in patients with COPD. Formoterol fumarate is also available in the US as a combination product, Symbicort Inhalation Aerosol, containing formoterol fumarate dihydrate and budesonide for the treatment of COPD.

1.3.2 Results from Clinical Pharmacology Trials

The following are the major findings of the current review:

1) Pharmacokinetic s (PK): Following oral inhalation, Cmax occurs at 5 minutes for glycopyrronium and at 20-60 minutes for formoterol. Linear increases in systemic exposure is observed with glycopyrronium at doses 18-144 mcg and with formoterol at doses ranging from 2.4 to 12 mcg. Mean half life ranges from 5-10 h for glycopyrronium and about 12 h for formoterol. Steady state is expected to be achieved within 2-3 days of repeated dosing and there is a ~2.3 fold and a ~1.5 fold accumulation for G and FF components respectively. Metabolism plays a minor role in the overall elimination of glycopyrrolate and the primary metabolism of formoterol fumarate is by direct glucuronidation and by O-demethylation followed by conjugation to inactive metabolites.
2) Drug-Drug Interaction: No clinically significant pharmacokinetic drug-drug interaction is observed at steady-state when inhaled formoterol and inhaled glycopyrronium are concomitantly administered in healthy subjects. Therefore, the relevant findings and conclusions for the mono-therapies may be extrapolated to the combination product.
3) Thorough QT Study: This study was reviewed by the QT-IRT team. No significant QTc prolongation effect of GFF MDI (14.4/9.6 µg and GFF MDI 115.2/38.4 µg) was detected in the TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between GFF MDI (14.4/9.6 µg and GFF MDI 115.2/38.4 µg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines.
4) Dose Ranging: The dose ranging performed in the GFF program included full characterization (dose-ranging) of the individual components as well as the combination product, and was adequate for the Phase 3 dose selection.
    a. FF 9.6 mcg was selected to be studied in combination with glycopyrronium as it was found to be non-inferior to Foradil 12 mcg in 2 dose ranging studies and lower doses of FF were not found to be as efficacious as 9.6 mcg
    b. Glycopyrronium 18 mcg was selected to be studied in combination with 9.6 mcg FF as lower doses were less effective and no additional benefit was observed at doses higher than 18 mcg
    c. The BID dosing regimen was selected as FEV1 response over time curve for the glycopyrronium component was consistent with a BID dosing profile

when compared with the known profile of an approved product, Atrovent HFA (ipratropium), which is dosed QID

d. When glycopyrronium 18 mcg was added on top of FF 9.6 mcg, additional efficacy benefit was observed in patients with moderate to severe COPD

5) Population PK analysis (impact of extrinsic and intrinsic factors):
   a. Population pharmacokinetic analyses demonstrated that there was no significant effect of sex, race/ethnicity, or body weight on the pharmacokinetics of both glycopyrrolate and formoterol. The CL/F of a subject 71 years of age is expected to be approximately 31% lower than a subject 50 years of age (reviewer's analysis). This age effect is not expected to have a clinical significant effect. Age did not have significant effect on formoterol clearance.
   b. Population pharmacokinetic analyses of glycopyrrolate estimated that CL/F of a subject with mild (CRCL=75 mL/min) and moderate (CRCL=45 mL/min) renal impairment is expected to be approximately 11% and 31% lower than a subjects with normal renal function (CRCL=94 mL/min), respectively (reviewer's analysis). Population pharmacokinetics analysis of formoterol CL/F of a subject with mild (CRCL=75 mL/min) and moderate (CRCL=45 mL/min) renal impairment is expected to be approximately 11% and 32% lower than a subject with normal renal function (CRCL=94 mL/min), respectively (reviewer's analysis). Based on the effect of renal impairment on CL/F of glycopyrrolate and formoterol, in patients with severe renal impairment (creatinine clearance of <30 mL/min/1.73 m^2) or end-stage renal disease requiring dialysis, BEVESPI AEROSPHERE should be used if the expected benefit outweighs the potential risk.

2. Question Based Review

2.1 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 or BLA

The clinical pharmacology studies/clinical studies are summarized in Table 1 below.

Table 1: Listing of clinical pharmacology/clinical studies.

Study Number	Phase	Primary Objectives	Study Design	Treatment Arms [a]
Phase I/II Single-Dose Clinical Studies in Subjects with COPD				
PT0010801	I/IIa	Efficacy, safety, and PK	MC, R, DB, PC, AC, SD, 4-period, BIBD crossover study in subjects with mild to moderate COPD.	GP MDI 18, 36, 72 , 144 µg, Spiriva Handihaler 18 µg (OL), and Placebo MDI
PT0050801	I/IIa	Efficacy, safety, and PK	MC, R, DB, PC, AC, SD, 5-period crossover study in subjects with moderate to severe COPD.	FF MDI 2.4, 4.8, 9.6 µg, Foradil Aerolizer 12 µg (OL), and Placebo MDI
PT005003	IIb	Efficacy, safety, and PK	MC, R, DB, PC, AC, SD, 6-period crossover study in subjects with moderate to severe COPD.	FF MDI 7.2, 9.6 µg, 19.2 µg, Foradil Aerolizer 12 µg and 24 µg (OL), and Placebo MDI
Phase I Single-Dose Studies in Healthy Subjects				
PT0030901	I	Safety and PK	SC, R, DB, SD, 5-period crossover study in healthy subjects	GFF MDI 72/9.6 µg, GP MDI 72 µg, FF MDI 9.6 µg, GP MDI 72 µg + FF MDI 9.6 µg (loose combination)
PT003009	I	Thorough QT/QTc and PK	SC, R, DB, SD, AC, 4-period crossover TQT study in healthy subjects	GFF MDI 14.4/9.6 µg , GFF MDI 115.2/38.4 µg, GP MDI 115.2 µg, moxifloxacin 400 mg, and Placebo MDI
PT003010	I	Safety and PK (Japanese subjects)	SC, R, DB, SD, 4-period crossover study in healthy Japanese subjects	GFF MDI 28.8/9.6 µg, GFF MDI 14.4/9.6 µg, GP MDI 28.8 µg, and GP MDI 14.4 µg
PT010001	I	Safety and PK	SC, R, DB (within device), SD, 4-period crossover study in healthy subjects	BGF MDI 320/14.4/9.6 µg, 160/14.4/9.6 µg, 80/14.4/9.6 µg, GFF MDI 14.4/9.6 µg, and Symbicort MDI 320/9 µg, 160/9 µg
Phase IIb Chronic Dosing (7- to 14-Day) Clinical Studies in Subjects with COPD				
PT001002	IIb	Efficacy and safety	MC, R, DB, PC, AC, 7-day, 3-period, IBD, crossover study in subjects with moderate to severe COPD	GP MDI 4.6, 9, 18, 36 µg BID, Atrovent 34 µg QID (OL), and Placebo MDI BID
PT001003	IIb	Efficacy and safety	MC, R, DB, PC, AC, 14-day, 4-period, BIBD crossover study in subjects with moderate to severe COPD.	GP MDI 0.6, 1.2, 2.4, 4.6, 9, 18 µg BID, Spiriva Handihaler 18 µg QD (OL), and Placebo MDI BID
PT0031002	IIb	Efficacy, safety, and PK	MC, R, DB, PC, AC, 7-day, 4-period, customized, unbalanced, IBD, crossover study in subjects with moderate to very severe COPD	GFF MDI 36/9.6, 72 /9.6 µg BID, GP MDI 36 µg BID, FF MDI 7.2, 9.6 µg BID, Foradil Aerolizer 12 µg BID (OL), Spiriva Handihaler 18 µg QD (OL), and Placebo MDI BID
PT003003	IIb	Cardiovascular safety including Holter monitoring and efficacy	MC, R, DB, AC, PG 14-day cardiovascular safety study in subjects with moderate to severe COPD	GFF MDI 36/9.6 µg BID, GP MDI 36 µg BID, FF MDI 9.6 µg BID, and Foradil Aerolizer 12 µg BID (OL)
PT003004	IIb	Efficacy and safety	MC, R, DB, 7-day, 2-period, BIBD, crossover study in subjects with moderate to severe COPD	GFF MDI 9/9.6, 18/9.6, 36/7.2, 36 /9.6 µg BID, GP MDI 36 µg BID, and FF MDI 9.6 µg BID
PT003005	IIb	Efficacy and safety	MC, R, DB, AC, 7-day, 4-period, IBD[c] crossover study in subjects with moderate to severe COPD.	GFF MDI 1.2/9.6, 2.4/9.6, 4.6/9.6, 9/9.6, 18/9.6 µg BID, GP MDI 18 µg BID, FF MDI 9.6 µg BID, and Spiriva Handihaler 18 µg QD (OL)
Phase III Clinical Studies in Subjects with COPD				
PT003006	III	Efficacy, safety, and PK	MC, R, DB, PC, AC, PG, 24-week study in subjects with moderate to very severe COPD	GFF MDI 14.4/9.6 µg BID, GP MDI 14.4 µg BID, FF MDI 9.6 µg BID, Spiriva Handihaler 18 µg QD (OL), and Placebo MDI BID
PT003007	III	Efficacy and safety including Holter monitoring	MC, R, DB, PC, PG, 24-week study in subjects with moderate to very severe COPD	GFF MDI 14.4/9.6 µg BID, GP MDI 14.4 µg BID, FF MDI 9.6 µg BID, and Placebo MDI BID
PT003008	III	Long-term safety, tolerability, and efficacy	MC, R, DB, AC, PG, 28-week extension of Studies PT003006 and PT003007	GFF MDI 14.4/9.6 µg BID, GP MDI 14.4 µg BID, FF MDI 9.6 µg BID, and Spiriva Handihaler 18 µg QD (OL)
PT003016	IIIb	Dose indicator and safety	MC, OL, 4-week study in subjects with moderate to very severe COPD	GFF MDI 14.4/9.6 µg BID (OL)

2.2 General Attributes of the Drug

2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Drug Substance

Glycopyrrolate is a quaternary ammonium salt with the following chemical name: 3[(cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethyl pyrrolidinium bromide. Glycopyrrolate is a powder that is freely soluble in water. The molecular formula is C19H28NO3 •Br, and the molecular weight is 398.33 g/mol The structural formula is indicated in Figure 1 below. Glycopyrrolate contains two chiral centers (denoted by * in structure below) and is a racemate of a 1:1 mixture of the R,S and S,R diastereomers. The active moiety, glycopyrronium, is the free base form of glycopyrrolate.

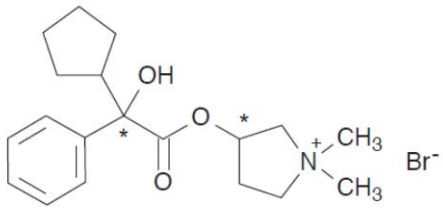


Figure 1: Structural formula for Glycopyrrolate

Formoterol fumarate has the chemical name *N*-[2-Hydroxy-5-[(1RS)-1-hydroxy-2-[[(1RS)-2-(4-methoxyphenyl)-1- methylethyl]-amino] ethyl]phenyl] formamide, (E)-2-butenedioate dihydrate. Formoterol fumarate is a powder that is slightly soluble in water. The molecular formula is $(C_{19}H_{24}N_2O_4)_2.C_4H_4O_4.2H_2O$ and the molecular weight is 840.91 g/mol. The structural formula is indicated in Figure 2 below. Formoterol fumarate contains two chiral centers (denoted by * in structure below), and consists of a single enantiomeric pair (a racemate of R,R and S,S).

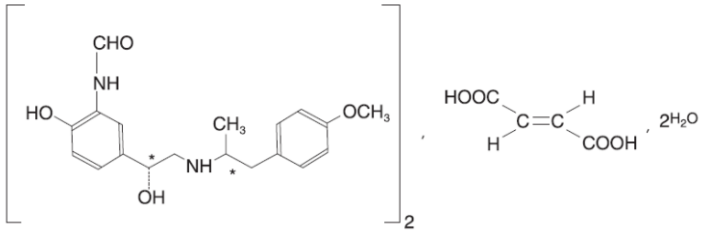


Figure 2: Structural formula for Formoterol Fumarate

Drug Product

BEVESPI AEROSPHERE is a pressurized metered-dose inhaler for delivery of a combination of micronized glycopyrrolate and micronized formoterol fumarate to patients by oral inhalation.

BEVESPI AEROSPHERE is formulated as a hydrofluoroalkane (HFA 134a) propelled pressurized metered dose inhaler containing 120 inhalations with a white plastic actuator body and mouthpiece with an orange dust cap.

After priming each actuation of the inhaler meters 10.4 µg of glycopyrrolate (equivalent to 8.3 µg of glycopyrronium) and 5.5 µg of formoterol fumarate from the valve which delivers 9 µg of glycopyrrolate (equivalent to 7.2 µg of glycopyrronium) and 4.8 µg of formoterol fumarate from the actuator. The actual amount of drug delivered to the lung may depend on patient factors, such as the coordination between actuation of the device and inspiration through the delivery system. BEVESPI AEROSPHERE also contains porous particles that form a cosuspension with the drug crystals. The porous particles are comprised of the phospholipid, 1,2- Distearoyl-sn-Glycero-3-Phosphocholine (DSPC), and calcium chloride. Porous particles and HFA 134a are excipients in the formulation.

Table 2: Composition of GFF MDI, 7.2/4.8 µg per Actuation, 120 Inhalations

Component	Manufacturing Concentration (% w/w)	Quantity per Canister[1]	Metered dose (ex-valve)[2]	Delivered dose (ex-actuator)	Function	Reference to Standard
Glycopyrronium Bromide, micronized		(b) (4)	8.32 µg[3]	7.20 µg[3]	Active Ingredient	Pearl
Formoterol Fumarate, micronized			5.55 µg	4.80 µg	Active Ingredient	Pearl
Porous Particles			(b) (4)		Cosuspending Agent	Pearl
HFA-134a					Propellant	(b) (4)
1		(b) (4)				

2 Formulation overages include drug overages of (b) (4)% to account for losses to the valve and actuator upon actuation. Refer to 3.2.P.2.2.2 Overages for details regarding formulation overages.

3 Metered and delivered dose are expressed as the active moiety (i.e. glycopyrronium).

2.2.2 What are the proposed mechanism of action and therapeutic indications?

GFF MDI, or PT003, is a combination of glycopyrronium, an orally-inhaled long-acting muscarinic antagonist (LAMA), and formoterol fumarate, an orally-inhaled, selective long-acting β2 agonist (LABA), which is being developed for the long-term, maintenance

treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. The individual components, Glycopyrronium Inhalation Aerosol (Glycopyrronium MDI [GP MDI] or PT001) and Formoterol Fumarate Inhalation Aerosol (Formoterol Fumarate MDI [FF MDI] or PT005), are also being developed to fully qualify the monotherapy products to allow appropriate comparisons of the combination product.

2.2.3 What are the proposed dosages and routes of administration?

GFF MDI (glycopyrrolate/formoterol fumarate 9 mcg/4.8 mcg) should be administered as two inhalations taken twice daily in the morning and in the evening by the orally inhaled route only. Do not take more than two inhalations twice daily.

2.2.4 What drugs (substances, products) indicated for the same indication are approved in the US?

The drugs which are approved for treatment of COPD in the United States can be classified into the following classes:

1. *Bronchodilators*

- β2 agonist:
  - long acting: salmeterol, formoterol, arformoterol, indacaterol etc.
  - short acting: salbutamol, albuterol, terbutaline etc.
- Anticholinergics:
  - long acting: tiotropium, aclidinium , umeclidinium
  - short acting: ipratropium
- Methylxanthine: theophylline
- Combination: albuterol+ipratropium (Combivent, Duoneb), umeclidinium +vilanterol (Anoro Ellipta)

2. *Corticosteroids*

- Oral corticosteroids
- ICS
- Combination:
  - salmeterol+fluticasone (Advair)
  - formoterol+budesonide (Symbicort)
  - Vilanterol +fluticasone furoate (Breo)

3. *Other medications*

- Long acting PDE-4 inhibitor: roflumilast (Daliresp)
- Antibiotics

2.3 General Clinical Pharmacology

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

The clinical pharmacology and biopharmaceutics studies supporting this NDA and their design features are listed under section 2.1.

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

Sponsor has selected forced expiratory volume in 1 second area under the curve (FEV1 AUC0-12), relative to baseline as the primary endpoint in FF MDI Phase II dose ranging/regimen selection studies. In GP MDI dose ranging/regimen selection studies, the sponsor has selected peak FEV1 (defined as peak improvement in FEV1 above test day baseline), and FEV1 AUC0-12 relative to baseline as the primary efficacy outcomes. In GFF dose ranging/regimen trials, the sponsor has selected FEV1 AUC0-12 relative to baseline as the primary efficacy outcome.

These endpoints have also been used in the development program of other drugs for COPD.

2.3.3 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 and formoterol concentrations were measured. No metabolites were quantified because the metabolites are not active and are not associated with efficacy or safety.

2.4 Exposure-Response

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

For inhaled GP and FF components, the systemic exposure is not directly related to clinical response (FEV1).

2.4.2 Has the dosing of GFF MDI been adequately explored?

GFF MDI development program includes full characterization (dose-ranging) of the individual components (GP MDI and FF MDI) to establish the appropriate dose for each component, before proceeding to Phase 3 studies with the combination product. One dosing regimen, GFF MDI (glycopyrrolate/formoterol fumarate 18 mcg/9.6 mcg) BID was selected for further evaluation in Phase 3 program. FF 9.6 mcg was selected to be studied in combination with glycopyrronium as it was found to be non-inferior to Foradil 12 mcg in 2 dose ranging studies and lower doses of FF were not found to be as efficacious as 9.6 mcg. Glycopyrronium 18 mcg was selected to be studied in combination with 9.6 mcg FF as lower doses were less effective and no additional benefit was observed at doses higher than 18 mcg. The BID dosing regimen was selected as FEV1 response over time curve for the glycopyrronium component was consistent with a BID dosing profile when compared with the known profile of an approved product, Atrovent HFA (ipratropium), which is dosed QID.

GP MDI and GFF MDI were evaluated in 7 studies in the Phase I/II program.

Study PT0010801: For the primary efficacy endpoint, peak improvement in FEV1 relative to test day baseline, each dose of GP MDI (144, 72, 36 and 18 mcg) showed statistically significantly and clinically relevant superior efficacy compared to Placebo MDI ($p < 0.001$ for all 4 dose levels) with a clear dose-response relationship. Although both GP MDI 36 µg and 18 µg demonstrated clinically relevant and statistically significantly greater improvements in FEV1 than Placebo MDI, the magnitude of these improvements were lower than observed with tiotropium 18 µg. Based on the results of this study, the candidate doses of GP MDI for further study were considered to be 144 µg, 72 µg and 36 µg for once daily dosing, with these doses divided in half for twice daily dosing.

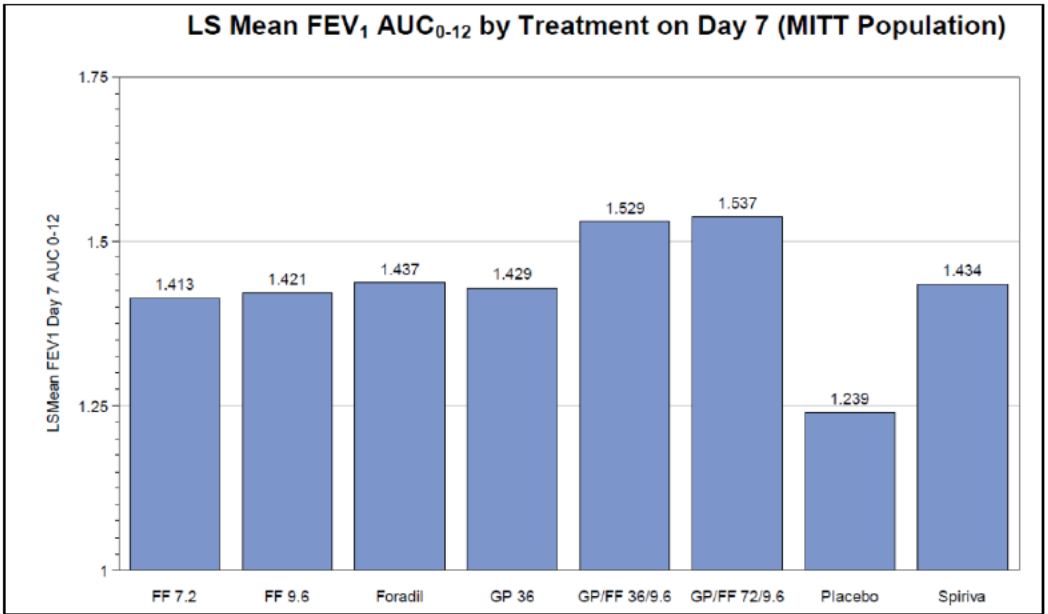
Table 3: Peak Change from Test Day Baseline FEV1 (L) by Treatment (Study PT0010801)

Peak Change from Test Day Baseline FEV_1 (L) by Treatment
mITT Sample

Treatment	N	Mean	SD	Median	Min	Max	Diff From Placebo
Placebo	20	0.19	0.15	0.18	0.01	0.58	
Glycopyrrolate 144 µg	20	0.43	0.16	0.45	0.11	0.69	0.24
Glycopyrrolate 72 µg	20	0.33	0.15	0.27	0.15	0.59	0.14
Glycopyrrolate 36 µg	20	0.37	0.19	0.37	0.08	0.72	0.18
Glycopyrrolate 18 µg	20	0.32	0.18	0.27	0.09	0.77	0.13
Tiotropium 18 µg	20	0.36	0.18	0.35	0.06	0.72	0.17

Source: Page 106/442 in study report for PT0010801

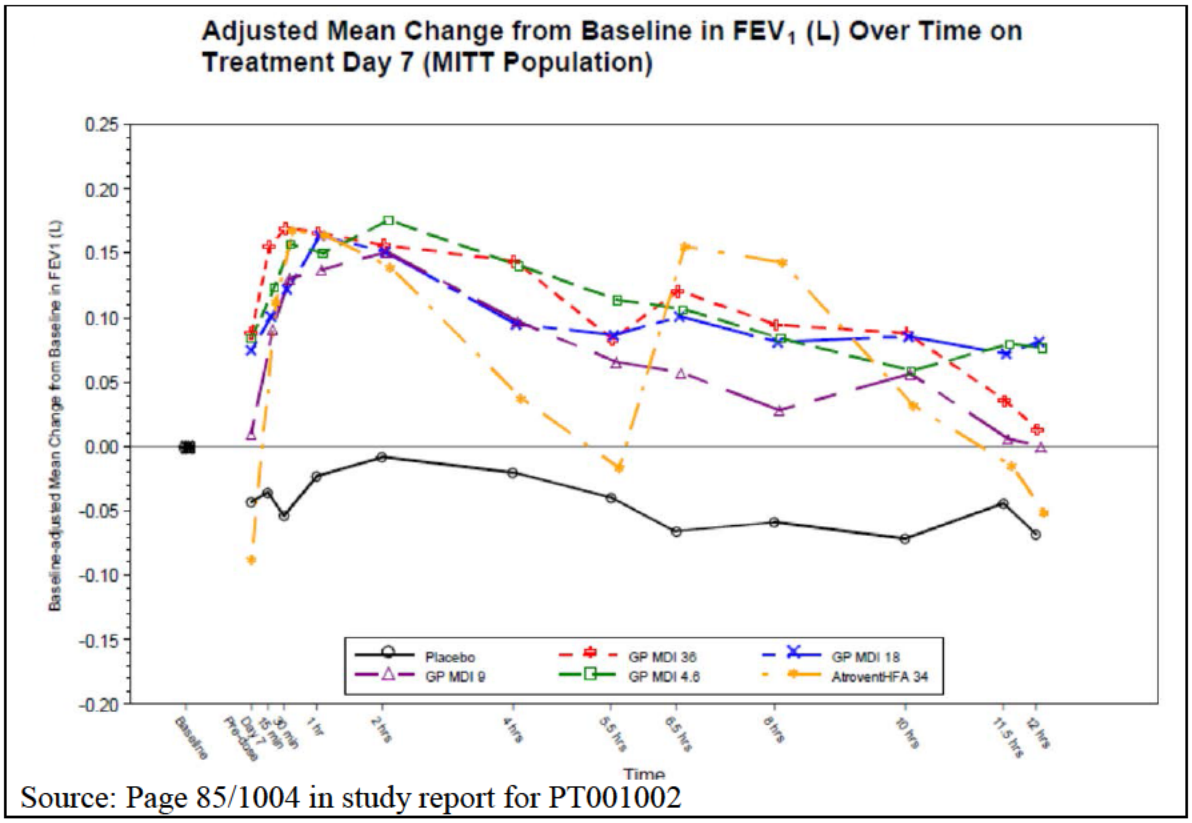
Study PT0031002: This was an initial dose ranging study with GFF MDI to evaluate efficacy with the combination product as compared to the mono components. For the primary efficacy endpoint, FEV1 AUC0-12 on Day 7 relative to test day baseline, combination treatments GFF MDI 72/9.6 µg and GFF MDI 36/9.6 µg showed statistically significant and clinically relevant superior efficacy to each of their components, and to the active open-label comparators Spiriva and Foradil ($p \leq 0.0002$). All active treatments demonstrated superiority to placebo ($p<0.0001$) and non-inferiority was confirmed between GFF MDI doses. Additionally, a similar efficacy response was demonstrated between GFF MDI 72/9.6 and 36/9.6 µg BID doses, indicating that there was no clinically meaningful incremental benefit at BID doses above 36 µg of GP MDI.



Source: Page 103/1980 in study report for PT0031002

Figure 3: LS Mean FEV1 AUC0-12 by Treatment on Day 7 (MITT Population) in Study PT0031002

Study PT001002: In this study, 7-day treatment with GP MDI was evaluated using a range of doses (36, 18, 9, and 4.6 µg) administered BID and compared with placebo MDI administered BID and the active comparator Atrovent HFA 34 µg administered QID. All doses of GP MDI (36, 18, 9, and 4.6 µg) demonstrated statistically significant and clinically relevant increases in FEV1 AUC0-12 compared to placebo following 7-day treatment. In the MITT population, the LSMs for the difference vs placebo were 155, 174, 121, and 191 mL for GP MDI 36, 18, 9, and 4.6 µg, respectively, and 142 mL for Atrovent HFA ($p<0.0001$ for all treatments). Efficacy response was comparable for GP MDI 36 and 18 µg BID. Further evaluation of GP MDI 36 µg BID was therefore not warranted, and the optimal dose of GP MDI was found to be 18 µg BID or lower. The FEV1 response over time curve for GP MDI was consistent with a BID dosing profile when compared with the known profile of Atrovent HFA, a well-established QID product, as such, a BID dosing regimen was selected.



Source: Page 85/1004 in study report for PT001002

Figure 4: Adjusted Mean Change from Baseline in FEV1 (L) Over Time on Treatment Day 7 (MITT Population) in Study PT001002

Study PT003004: In this study, 7-day treatment with GFF MDI was evaluated using a range of doses (36/9.6, 36/7.2, 18/9.6, and 9/9.6 µg as glycopyrrolate/formoterol fumarate) administered BID and compared with the components GP MDI 36 µg and FF MDI 9.6 µg administered BID. All doses of GFF MDI demonstrated statistically significant and increases in FEV1 AUC0-12 compared with GP MDI 36 µg following 7-day treatment (the primary efficacy endpoint). The first comparison in the hierarchical analysis vs FF MDI 9.6 µg was not significant; thus, no claims of superiority can be made for the GFF MDI combinations vs FF MDI 9.6 µg. This finding did not corroborate with the findings in study PT0031002 where the combination product demonstrated more efficacy than both the individual components. The sponsor concluded that additional dose-ranging studies with GFF MDI, including exploring lower doses of GP, are needed.

Table 4: FEV1 AUC0-12 (L) with Pairwise Treatment Comparisons on Treatment Day 7 (MITT Population) in Study PT003004

FEV_1 AUC_{0-12} (L) with Pairwise Treatment Comparisons on Treatment Day 7 (MITT Population)

	GP MDI 36 µg (N=51)	GFF MDI 36/7.2 µg (N=50)	GFF MDI 36/9.6 µg (N=43)	GFF MDI 18/9.6 µg (N=45)	GFF MDI 9/9.6 µg (N=52)	FF MDI 9.6 µg (N=51)
FEV_1 AUC_{0-12} (L)						
LSM	1.399	1.467	1.462	1.493	1.499	1.465
(SE)	(0.0209)	(0.0220)	(0.0229)	(0.0231)	(0.0226)	(0.0219)
95% CI	1.358, 1.441	1.424, 1.511	1.418, 1.508	1.448, 1.539	1.455, 1.544	1.423, 1.509
Comparison vs GP MDI 36 µg						
GMR	NA	1.049	1.045	1.067	1.072	0.955
95% CI		1.013, 1.086	1.009, 1.083	1.031, 1.105	1.036, 1.109	0.923, 0.987
P-value[1]		0.0079	0.0137	0.0003	<0.0001	0.0067
Comparison vs FF MDI 9.6 µg						
GMR	see above	1.001	0.998	1.019	1.023	NA
95% CI		0.968, 1.035	0.962, 1.035	0.984, 1.055	0.988, 1.059	
P-value[1]		0.9510	0.9112	0.2931	0.1925	

Source: Page 89/1166 in study report for PT003004

Study PT001003: In this study, 14-day treatment with GP MDI was evaluated using a range of doses (18, 9, 4.6, 2.4, 1.2, and 0.6 µg) administered BID and compared with placebo MDI administered BID and the active comparator Spiriva 18 µg administered QD. GP MDI 18, 9, 4.6, and 2.4 µg demonstrated statistically significant and clinically relevant increases in FEV1 AUC0-12 compared to placebo following 14-day treatment. GP MDI 1.2 and 0.6 µg demonstrated statistically significant increases that were less than 100 mL. The results indicated that GP MDI 2.4 µg BID may be the minimum effective dose and that GP MDI 18 µg BID was the most effective dose. As such, this study supported 18 µg BID as the most appropriate dose to progress into Phase III studies.

Table 5: FEV1 AUC0-12 (mL) on Treatment Day 14 (MITT Population) in Study PT001003

FEV_1 AUC_{0-12} (mL) on Treatment Day 14 (MITT Population)

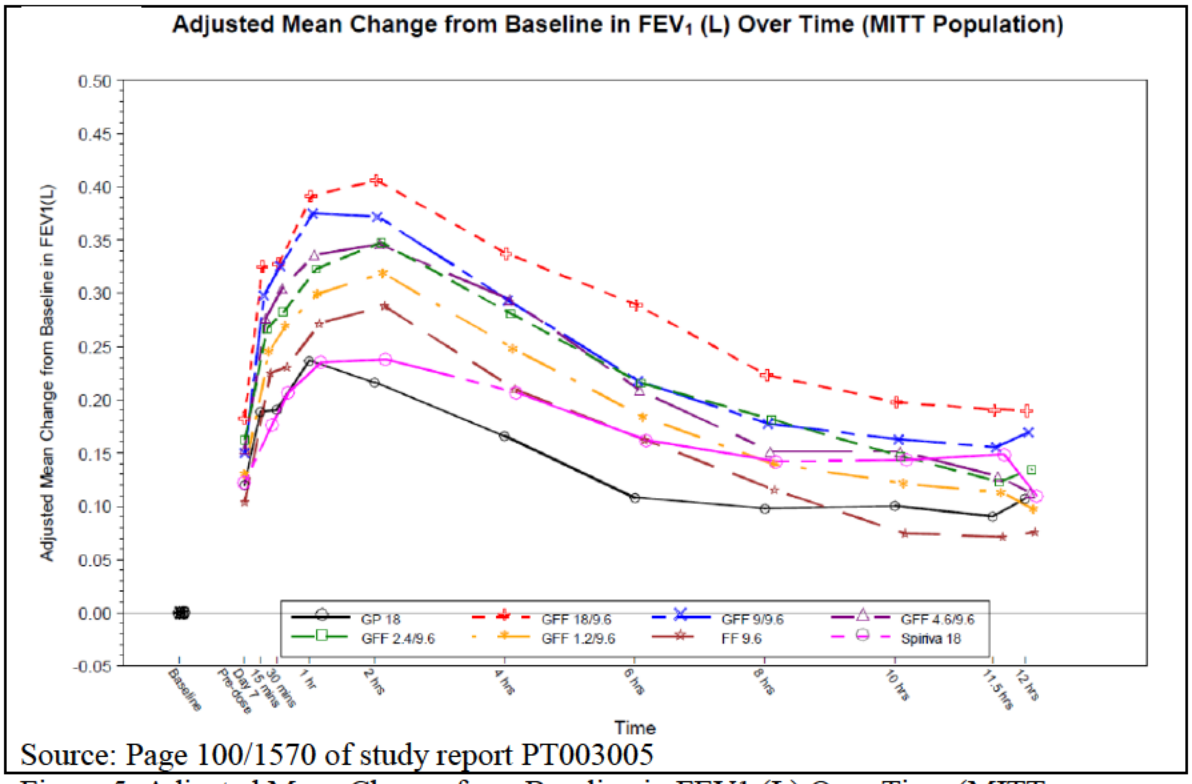
	Placebo MDI BID (N=52)	GP MDI 18 µg BID (N=58)	GP MDI 9 µg BID (N=59)	GP MDI 4.6 µg BID (N=59)	GP MDI 2.4 µg BID (N=60)	GP MDI 1.2 µg BID (N=53)	GP MDI 0.6 µg BID (N=54)	Spiriva 18 µg QD (N=55)
FEV_1AUC_{0-12} (mL)								
LSM	1290	1448	1416	1432	1416	1386	1353	1514
95% CI	(1246, 1335)	(1405, 1491)	(1374, 1459)	(1389, 1474)	(1374, 1458)	(1342, 1430)	(1309, 1397)	(1471, 1558)
Adjusted Difference vs placebo MDI (mL)[1]								
LSM		158	126	141	126	95	63	224
95% CI		(107, 208)	(75, 177)	(91, 191)	(76, 176)	(45 146)	(12 114)	(173, 275)
p-value		<0.0001	<0.0001	<0.0001	<0.0001	0.0003	160	<0.0001
Adjusted Difference vs Spiriva (mL)[2]								
LSM		-66	-98	-83	-98	-129	-161	
95% CI		(-116, -17)	(-148, -48)	(-132, -34)	(-147, -50)	(-179, -78)	(-212, -110)	

Source: Page 103/1819 of study report for PT001003

Study PT003005: In this study, 7-day treatment with GFF MDI was evaluated using a range of doses (18/9.6, 9/9.6, 4.6/9.6, 2.4/9.6, and 1.2/9.6 µg as glycopyrrolate/formoterol fumarate) administered BID and compared with the components GP MDI 18 µg and FF MDI 9.6 µg administered BID as well as the active comparator Spiriva 18 µg administered QD.

For the primary efficacy endpoint, GFF MDI 18/9.6 µg demonstrated statistically significant and clinically relevant (>100 mL) increases in FEV1 AUC0-12 compared with both GP MDI 18 µg and FF MDI 9.6 µg following 7-day treatment ($p<0.0001$), based on LSM differences of 139 and 124 mL, respectively ($p<0.0001$). GFF MDI 9/9.6, 4.6/9.6, and 2.4/9.6 µg demonstrated statistically significant increases compared with GP MDI 18 µg, with LSM differences of 95, 87, and 87 mL, respectively ($p<0.0001$), and compared with FF MDI 9.6 µg, with LSM differences of 79, 71, and 71 mL, respectively ($p\leq0.0011$). For comparisons to Spiriva, all GFF MDI doses except 1.2/9.6 µg were nominally different ($p<0.05$), but only GFF MDI 18/9.6 µg demonstrated an increase in FEV1 AUC0-12 that exceeded 100 mL.

This study demonstrated that the proposed dose of GP MDI to be evaluated alone was the appropriate dose of glycopyrrolate to use in the combination product as it provides meaningful benefit when added to FF MDI 9.6 µg (GFF MDI 18/9.6 µg), with a safety profile that was similar to the individual agents.



Source: Page 100/1570 of study report PT003005

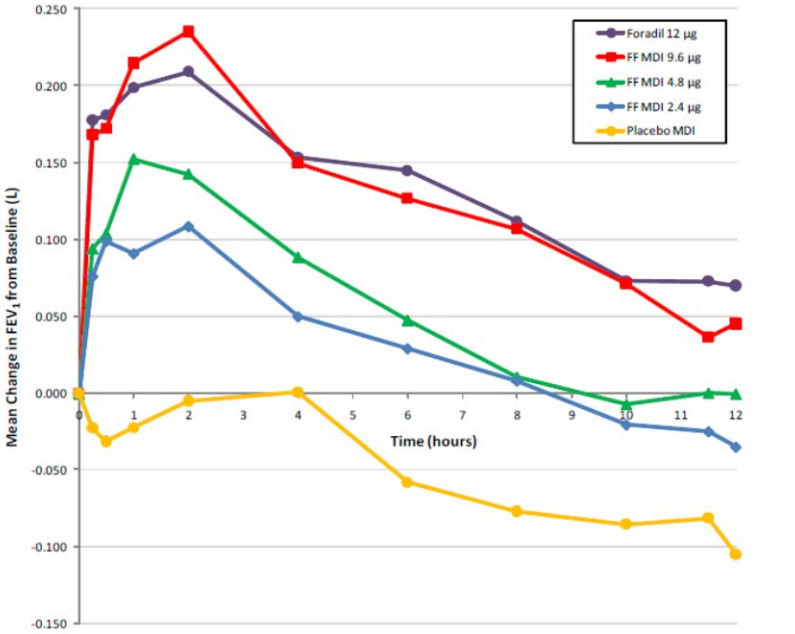
Figure 5: Adjusted Mean Change from Baseline in FEV1 (L) Over Time (MITT Population) in study PT003005

Study PT003003: This was a cardiovascular safety study. The sponsor indicates that there were no clinically relevant changes from baseline in 24-hour Holter monitoring and no untoward safety findings at GP MDI 36 µg BID and GFF MDI 36/9.6 µg BID dosing regimens.

FF MDI

Three clinical studies have been conducted to evaluate the PK and/or PD characteristics of FF MDI and Foradil. Based on the data, FF MDI 9.6 µg was carried forward to evaluation in Phase 3 in combination with GP component.

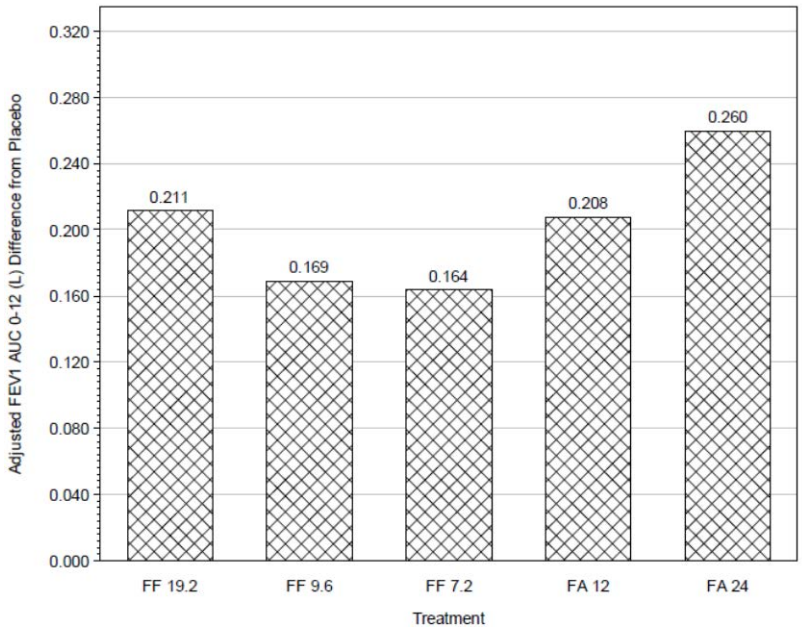
Study PT0050801: FF MDI 2.4 and 4.8 µg were not as efficacious as FF MDI 9.6 µg. FF MDI 9.6 µg was found to be non-inferior to Foradil 12 µg (lower bound of 95% CI was within 50 mL). The FEV1 for FF MDI 9.6 µg was consistent overall with the effects of Foradil 12 µg at all timepoints. Systemic exposure was numerically lower for FF MDI 9.6 µg compared with Foradil 12 µg at all timepoints. Of note, this study was conducted with an (b) (4) formulation and 4 puffs of FF MDI 2.4 µg were administered to provide the 9.6 µg dose. The later studies were conducted using the (b) (4) formulation intended for marketing, and all doses were administered as 2 puffs from the MDI.



Source: Page 45/305 of study report for study PT0050801

Figure 6: Mean Change from Baseline in FEV1 Over Time (MITT Efficacy Population) in study PT0050801

In Studies PT0031002 (described earlier under GP dose ranging) and PT005003, the improvement in FEV1 with FF MDI 9.6 µg was non-inferior and numerically lower than Foradil 12 µg at most of the timepoints (see Figures 3 and 7). In order to determine whether a lower dose of FF MDI could provide comparable efficacy to FF MDI 9.6 µg, an FF MDI 7.2 µg comparator was included in both of these studies. Although FF MDI 7.2 µg provided a reasonable response on lung function, the response was generally numerically lower than with FF MDI 9.6 µg. The safety profiles of FF MDI 9.6 and 7.2 µg were comparable to Foradil 12 µg.



Source: Page 86/545 of study report for study PT005003

Figure 7: Adjusted Mean FEV1 AUC0-12 (L): Difference from Placebo by Treatment (MITT Population) in study PT005003

2.4.3 What are the characteristics of the exposure-response relationships for safety?

The exposure-response relationships for QT-interval and heart rate (HR) were investigated in Study PT003009, a thorough QT study, and Study PT003003, a cardiac safety study.

In Study PT003009, no significant QT prolongation effect glycopyrrolate at the supratherapeutic dose of 400 µg (with mean Cmax of 1495 pg/mL) was detected in the TQT study. No evident relationship between glycopyrrolate plasma concentration and ΔΔQTcF was observed.

A significant relationship between FF concentrations and ΔΔQTcI was observed. The supratherapeutic dose of GFF (115.2/38.4 µg) produced a 2.6-fold margin compared to the therapeutic exposure. Exposure data in patients with hepatic or renal impairment are not available. However, since FF is predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of FF in plasma. Therefore, a marginal QT prolongation might be expected at the GFF dose of 14.4/9.6 µg in some hepatic impairment patients.

In Study PT003003, at the doses evaluated in Study PT003003 for GFF MDI 36/9.6 µg and its components, GP 36 µg MDI and FF MDI 9.6 µg, the known potential class effects

on cardiovascular safety were not observed and the safety profile was similar to Foradil 12 μg.

2.4.4 Does this drug prolong QT/QTc Interval?

No significant QTc prolongation effect of glycopyrronium/formoterol (GFF MDI 14.4/9.6 μg and GFF MDI 115.2/38.4 μg) was detected in the TQT study PT003009. However, a significant relationship between FF concentrations and ΔΔQTcI was observed. The supratherapeutic dose of GFF (115.2/38.4 μg) produced a 2.6-fold margin compared to the therapeutic exposure. Exposure data in patients with hepatic or renal impairment are not available. However, since FF is predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of FF in plasma. Therefore, a marginal QT prolongation might be expected at the GFF dose of 14.4/9.6 μg in some hepatic impairment patients.

For further details refer to QT/IRT review for NDA208294.

2.5 What are the PK characteristics of the drug?

Linear pharmacokinetics were observed for glycopyrrolate (dose range: 18 to 144 mcg) and formoterol fumarate (dose range: 2.4 to 19.2 mcg) after oral inhalation. The PK information listed below was partially generated by the sponsor with the mono and the combination products and is partially borrowed from the reference products' labels.

Absorption
Glycopyrrolate: Following inhaled administration of BEVESPI AEROSPHERE in subjects with COPD, Cmax occurred at 5 minutes. Steady state is expected to be achieved within 2-3 days of repeated dosing of BEVESPI AEROSPHERE and the extent of exposure is approximately 2.3 times higher than after the first dose.
Formoterol Fumarate: Following inhaled administration of BEVESPI AEROSPHERE in subjects with COPD, Cmax occurred within 20 to 60 minutes. Steady state is expected to be achieved within 2-3 days of repeated dosing with BEVESPI AEROSPHERE and the extent of exposure is approximately 1.5 times higher than after the first dose.

Distribution
Glycopyrrolate: The estimated Vc/F (volume of the central compartment), and V2/F (volume of the peripheral compartment) are 951 L, and 2019 L, respectively, via population pharmacokinetic analysis.
Formoterol Fumarate: The estimated Vc/F (volume of the central compartment), and V2/F (volume of the peripheral compartment) are 948 L, and 434 L, respectively, via population pharmacokinetic analysis. Over the concentration range of 10-500 nmol/L, plasma protein binding of formoterol ranged from 46% to 58%. The concentrations of formoterol used to assess the plasma protein binding were higher than those achieved in plasma following inhalation of a single 54 mcg dose.

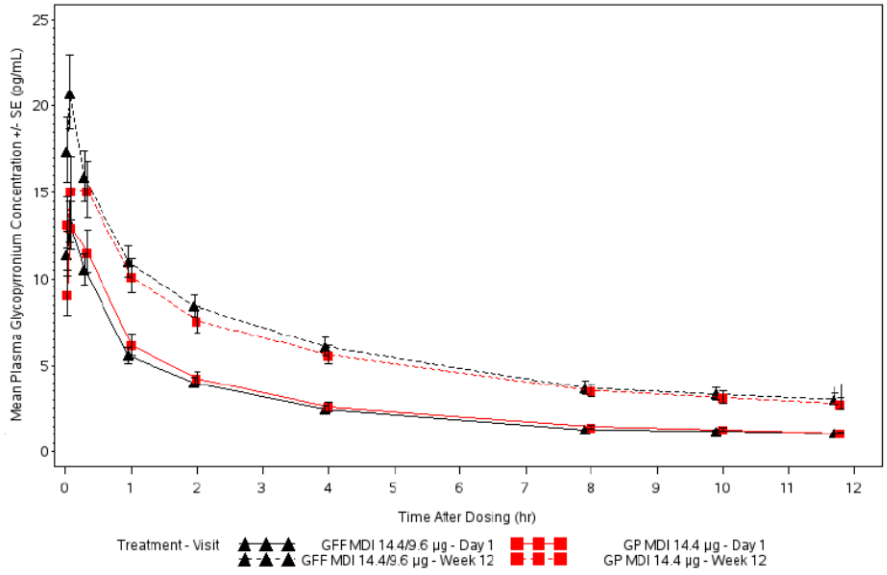
Metabolism
Glycopyrrolate: Based on information from the published literature, metabolism plays a

minor role in the overall elimination of glycopyrrolate.
Formoterol Fumarate: The primary metabolism of formoterol is by direct glucuronidation and by O-demethylation followed by conjugation to inactive metabolites. Secondary metabolic pathways include deformylation and sulfate conjugation. CYP2D6 and CYP2C9 have been identified as being primarily responsible for O-demethylation.

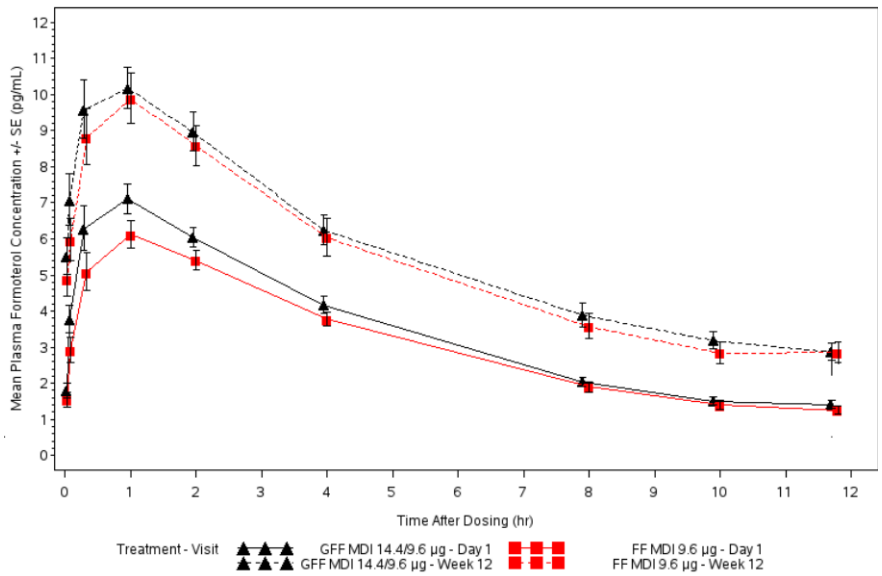
Elimination
Glycopyrrolate: After IV administration of a 0.2 mg radiolabeled glycopyrrolate, 85% of dose recovered was recovered in urine 48 hours post dose and some of radioactivity was also recovered in bile. The terminal elimination half-life derived via population pharmacokinetics analysis was 11.8 hours.
Formoterol Fumarate: The excretion of formoterol was studied in four healthy subjects following simultaneous administration of radiolabeled formoterol via the oral and IV routes. In that study, 62% of the radiolabeled formoterol was excreted in the urine while 24% was eliminated in the feces. The terminal elimination half-life derived via population pharmacokinetics analysis was 11.8 hours.

2.5.1 What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?

The plasma concentration-time profiles for glycopyrronium and formoterol after single- and multiple-dose administration of GFF MDI 14.4/9.6 µg (i.e., 14.4 µg glycopyrronium, equivalent to 18 µg glycopyrrolate and 9.6 µg formoterol), GP MDI 14.4 µg (i.e., 14.4 µg glycopyrronium, equivalent to 18 µg glycopyrrolate) and/or FF MDI 9.6 µg to subjects with COPD (Study PT003006) are presented below in Figures 8 and 9.



Source: Page 39/90 of summary of clinical pharmacology
Figure 8: Geometric Mean (±SE) Plasma Concentration-Time Profile of Glycopyrronium (Linear Scale)



Source: Page 40/90 of summary of clinical pharmacology

Figure 9: Geometric Mean (± SE) Plasma Concentration-Time Profile of Formoterol (Linear Scale)

The glycopyrronium accumulation ratios of Week 12 to dose Day 1 for AUC0-12 and Cmax were 2.3 and 1.4, respectively, following administration of GFF MDI 18/9.6 µg (i.e., 18 µg glycopyrrolate, equivalent to 14.4 glycopyrronium, and 9.6 µg of formoterol fumarate) in a Phase III study (Study PT003006 [PK sub-study]). Based on the terminal elimination half-life of glycopyrronium derived with the population PK model, steady state levels are achieved within 2-3 days of repeated BID dosing.

The formoterol accumulation ratios of Week 12 to Day 1 for AUC0-12 and Cmax were 1.5 and 1.3, respectively, following administration of GFF MDI 18/9.6 µg in a Phase III study (Study PT003006 [PK sub-study]) and suggested weak formoterol accumulation (up to 1.5-fold mean increase) following chronic dosing. Based on the population PK model, steady state levels of formoterol are achieved within 2-3 days of repeated dosing.

2.5.2 How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?

The systemic exposure was slightly higher for patients with COPD compared to healthy subjects. In healthy subjects, single dose GFF MDI 14.4/9.6 µg mean AUC0-12 ranged from 18.2 to 29.9 pg.h/mL; single dose GFF MDI 115.2/38.4 µg and GP MDI 115.2 µg mean AUC0-12 were 179 and 220 pg.h/mL, respectively. In patients with COPD, single dose GFF MDI 14.4/9.6 µg and GP MDI 14.4 µg mean AUC0-12 ranged from 31.6 pg.h/mL to 47.3 pg.h/mL; single dose GP MDI 115.2 µg mean AUC0-12 was 398 pg.h/mL.

Systemic exposure to formoterol was generally comparable between healthy subjects

and subjects with COPD. In healthy subjects, single dose GFF MDI 14.4/9.6 µg and FF MDI 9.6 µg mean AUC0-12 ranged from 40.7 to 55.6 pg.h/mL. In patients with COPD, mean AUC0-12 ranged from 45.8 to 57.2 pg.h/mL.

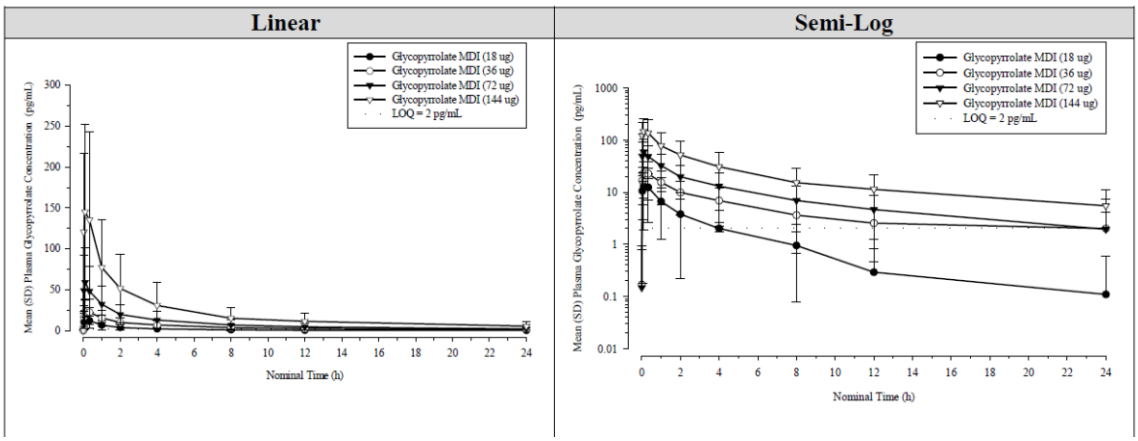
2.5.3 What are the characteristics of drug absorption?

No absolute bioavailability assessment has been performed with GFF MDI.

2.5.4 Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?

GP component:

Study PT0010801 assessed the dose proportionality of glycopyrronium exposure from GP MDI over the 18 to 144 µg (i.e., 18 to 144 µg glycopyrrolate, equivalent to 14.4 to 115.2 µg glycopyrrolate) single dose range in adults with mild to moderate COPD. For each successive increase of 2-,4-, and 8-fold in dose, AUC0-12h increased by 2.8-, 5.1-, and 12.5-fold respectively (see Figure 10 below). Slope estimates of AUC_{0-12} and C_{max} for glycopyrrolate were 1.231 and 1.096, respectively.

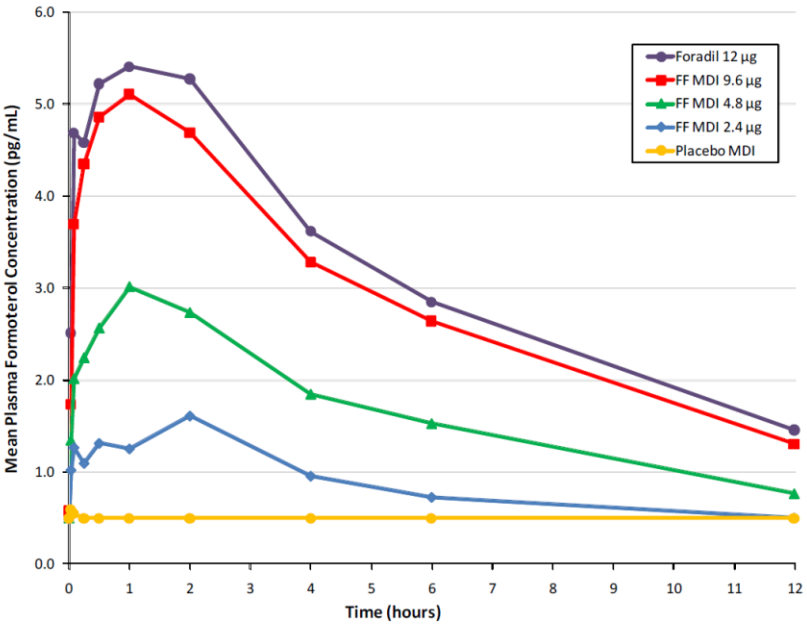


Source: Page 70/442 of study report for study PT0010801

Figure 10: Mean (± SD) Plasma Concentration Profiles of Glycopyrrolate (Study PT0010801)

FF component:

Study PT0050801 assessed the bioavailability for each dose of FF MDI (2.4, 4.8, and 9.6 µg) relative to Foradil Aerolizer 12 µg in subjects with moderate to severe COPD and explored the dose proportionality of formoterol over the 2.4 to 9.6 µg single dose range in subjects with COPD. For each successive increase of 2-, and 4-fold in dose, AUC0-12h increased by 0.68 and 0.89-fold respectively, i.e., less than dose proportionally (see Figure 11 below).



Source: Page 52/305 of study report for study PT0050801

Figure 11: Concentration-Time Plots for Formoterol by Treatment (MITT PK Population) in Study PT0050801

2.5.5 How do the PK parameters change with time following chronic dosing?

As indicated in section 2.5.1, glycopyrronium accumulation ratios of Week 12 to dose Day 1 for AUC0-12 and Cmax were 2.3 and 1.4, respectively, and formoterol accumulation ratios of Week 12 to Day 1 for AUC0-12 and Cmax were 1.5 and 1.3, respectively, following administration of GFF MDI 18/9.6 µg in a Phase III study (Study PT003006 [PK sub-study]).

2.6 Intrinsic Factors

2.6.1 What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, Cmax, Cmin) in patients with the target disease and how much of the variability is explained by the identified covariates?

No formal PK studies were conducted to evaluate the effect of intrinsic factors such as age, sex, race, renal impairment or hepatic impairment on the PK of glycopyrronium or formoterol given as GFF MDI. The effects of intrinsic factors were evaluated using a population PK analysis methodology conducted on data from GFF MDI and/or the monoproducts from 5 studies in adults with COPD.

Population PK models were developed to describe formoterol and glycopyrronium systemic exposure in patients with COPD.

- Baseline creatinine clearance and age were identified as significant intrinsic

covariates for glycopyrrolate CL/F.

- Glycopyrrolate CL/F of a subject 71 years of age is expected to be approximately 31% lower than a subject 50 years of age (reviewer's analysis).
- Glycopyrrolate CL/F of a subject with mild (CRCL=75 mL/min) and moderate (CRCL=45 mL/min) renal impairment is expected to be approximately 11% and 31% lower than a subjects with normal renal function (CRCL=94 mL/min), respectively (reviewer's analysis).

- Baseline creatinine clearance was identified as significant intrinsic covariate for formoterol CL/F. Formoterol CL/F of a subject with mild (CRCL=75 mL/min) and moderate (CRCL=45 mL/min) renal impairment is expected to be approximately 11% and 32% lower than a subject with normal renal function (CRCL=94 mL/min), respectively (reviewer's analysis).

The reduction of inter-subject variability was limited (<2% CV) upon introducing the above covariates. Please see Pharmacometrics Review in Appendix 4.1 for additional details.

2.6.2 Based upon effects of intrinsic factors on pharmacokinetics, what dosage regimen adjustments are recommended for each group?

No dose adjustment is required for elderly patients.
No dose adjustment is required for patients with mild and moderate renal impairment. However, to be consistent with the approved label of other glycopyrrolate products, BEVESPI AEROSPHERE should be used if the expected benefit outweighs the potential risk in patients with severe renal impairment.

2.6.2.1 Severity of Disease State

Not assessed.

2.6.2.2 Body Weight

As stated in section 2.6.1.

2.6.2.3 Elderly

As stated in section 2.6.1.

2.6.2.4 Pediatric Patients

Inhaled GFF MDI is indicated for the treatment of adult COPD patients only. Pharmacokinetic studies with inhaled GFF MDI were not conducted in children (<18 years old).

2.6.2.5 Race/Ethnicity

2.6.2.6 Renal Impairment

As stated in section 2.6.1.

2.6.2.7 Hepatic Impairment

As stated in section 2.6.1.

2.6.3 Does genetic variation impact exposure and/or response?

No pharmacogenetic impact was assessed in this NDA.

2.7 Extrinsic Factors

No formal PK studies were conducted to evaluate the effect of extrinsic factors on the PK of glycopyrronium or formoterol given as GFF MDI. The effect of extrinsic factors of smoking status and inhaled corticosteroid use were evaluated using a population PK analysis methodology conducted on data from GFF MDI and/or the monoproducts from 5 studies in adults with COPD.

2.7.7 What are the drug-drug interactions?

The PK interaction between glycopyrronium and formoterol was assessed in Study QVA149A2107. Following multiple BID administration of QVA149 27.5/12.5 mcg (x 2), indacaterol 27.5 mcg (x 2) alone, and glycopyrronium 12.5 mcg (x 2) alone, the steady-state systemic exposure (AUC0-12h,ss; Cmax,ss) to indacaterol and glycopyrronium was similar between the combination product and monotherapies, suggesting there is no PK interaction between the two components (Table 15).

Table 6: Comparison of Glycopyrrolate and Indacaterol PK Parameters Following BID Administration of QVA149 and Each Drug Inhaled Alone

Compound	Parameter	GMR (90% CI)
Glycopyrrolate	Cmax,ss	1.07 (0.97, 1.18)
	AUC0-12h,ss	1.09 (1.05, 1.13)
Indacaterol	Cmax,ss	0.97 (0.93, 1.02)
	AUC0-12h,ss	0.95 (0.91, 0.99)

(Source: adapted from Tables 11-5 and 11-6, Study QVA149A2107 report)

2.7.8 Does the label specify co-administration of another drug?

The proposed label does not mention specific co-administration with other drugs.

2.7.9 What other co-medications are likely to be administered to the target population?

All COPD patients are likely to take other medications for treatment of COPD as listed under 2.2.4.

2.7.10 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?

Formoterol is a LABA. Co-administration with additional adrenergic drugs may potentiate the effect of formoterol. Co-administration with xanthine derivatives, steroids,

or diuretics may potentiate any hypokalemic effect of formoterol. Co-administration of LABA and diuretics may worsen the hypokalemia and electrocardiographic changes. Co-administration of beta-blockers may block the bronchodilatory effect and produce severe bronchospasm. Monoamine oxidase inhibitors, tricyclic antidepressants, and other known QTc prolonging drugs may potentiate effect of formoterol on cardiovascular system.

Glycopyrolate is a LAMA. Co-administration of anticholinergics may lead to an increase in anticholinergic adverse effects.

2.8 General Biopharmaceutics

2.8.1 Based on the biopharmaceutic classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

The sponsor did not provide BCS classification information for glycopyrronium and formoterol in this submission.

2.8.2 How is the proposed to-be-marketed formulation linked to the clinical service formulation?

GFF MDI is a fixed dose combination product containing glycopyrronium (GP) and

formoterol fumarate (FF). Several product strengths have been developed and evaluated in clinical studies (as indicated below in Table 7); however, marketing approval is being sought for only the 7.2/4.8 µg/actuation strength. It should be noted that 7.2 µg ex-actuator of glycopyrronium base is equivalent to 9.0 µg exactuator glycopyrrolate (i.e., glycopyrronium bromide). It should also be noted that 4.8 µg ex-actuator of formoterol fumarate is equivalent to (b) (4)

Table 7: Composition of GFF MDI Used for Biopharmaceutical Studies

	Product Strength[1], µg/actuation (clinical study)						
	Phase I				**Phase II**		**Phase III**
Component	**14.4/2.4** (Study PT0030901)	**7.2/4.8** (Studies PT003009 and PT003010)	**14.4/4.8** (Study PT003010)	**57.6/19.2** (Study PT003009)	**14.4/4.8** (Study PT0031002)	**28.8/4.8** (Study PT0031002)	**7.2/4.8** (Study PT003006)
Glycopyrronium Bromide (% w/w)	(b) (4)						
Formoterol Fumarate (% w/w)							
Porous Particles (% w/w)							
HFA-134a (% w/w)							

[1] For consistency, all product strengths are listed as the amount of glycopyrronium per actuation

Source: Page 10/69 of Summary of Biopharmaceutics

The first Phase 1 clinical study (e.g. Study PT0030901) used product formulated with (b) (4) FF cosuspended with micronized GP. All subsequent development and clinical studies used product formulated with (b) (4)

porous particles cosuspended with micronized GP and micronized FF. [redacted] (b) (4) . As this change did not impact the in vitro pharmaceutical performance of the product, an in vivo BA/BE study was not needed.

2.8.3 What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?

The effect of food on the PK of GFF MDI was not assessed. Since GFF MDI is an inhaled drug product, food is not expected to have an impact on its lung deposition.

2.8.4 Was the bioequivalence of the different strengths of the to-be-marketed formulation tested? If so, were they bioequivalent or not?

Only one GFF MDI strength, 7.2/4.8 µg/actuation strength is proposed as the to-be-marketed product.

2.9 Analytical Section

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

Determinations of glycopyrronium and formoterol in plasma were performed by using ultra-high performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS).

The bioanalytical methodology was [redacted] (b) (4) developed and validated for Pearl by [redacted] (b) (4) In general, a 500 µL aliquot of plasma was processed by mixed-mode reversed-phase weak-cation exchange solid-phase extraction followed by analysis using reversed-phase UPLC positive electrospray ionization (+ESI) MS/MS detection and internal standardization with d6-formoterol and d3-glycopyrrolate. Quantitation was performed using analyte to internal standard (IS) peak area ratios and calibration curves constructed using 1/x or 1/x2 weighted least-squares linear regression analysis. During analysis of samples duplicate 8 point calibration curves with concentrations ranging from 1.0 pg/mL to 50.0 pg/mL and 2.0 pg/mL to 100.0 pg/mL for formoterol and glycopyrrolate, respectively, were included in each analytical run. The glycopyrrolate Lower Limit of Quantitation (LLOQ) and the Upper Limit of Quantitation (ULOQ) of both analytes was recently revalidated at 1.0 pg/mL and 200.0 pg/mL, respectively.

All submitted validation reports of analytical methods that were used for the determination of different analytes in human plasma and urine are listed below in Table 8.

Table 8: Validation Reports of Analytical Methods used in GFF Clinical Trials

Protocol No./ CSR No.	Analytical Site/ Study No.	Biomatrix (Anticoagulant)	Specificity/ Sensitivity (Analyte)	Method ID No.	Validation Report No.	Bioanalytical Report No
Study PT0050801	(b) (4)	Plasma (K3EDTA)	Parent/ 1.0 pg/mL (FOR)	(b) (4) SOP-200 REV1	VAL-RPT-1008	NA
Study PT0030901		Plasma (K3EDTA)	Parent/ 1.0 pg/mL (FOR) 2.0 pg/mL (GLY)	(b) (4) SOP-267 REV0	VAL-RPT-1116	NA
Study PT0010801		Plasma (K3EDTA)	Parent/ 1.0 pg/mL (FOR) 2.0 pg/mL (GLY)	(b) (4) SOP-267 REV0	VAL-RPT-1116	NA
Study PT005003		Plasma (K3EDTA)	Parent/ 1.0 pg/mL (FOR) 2.0 pg/mL (GLY)	(b) (4) SOP-267 REV1&2	VAL-RPT-1116 VAL-RPT-1252	BR1131
Study PT0031002		Plasma (K3EDTA)	Parent/ 1.0 pg/mL (FOR) 2.0 pg/mL (GLY)	(b) (4) SOP-267 REV1	VAL-RPT-1116 VAL-RPT-1252	BR1002
Study PT003009		Plasma (K3EDTA)	Parent/ 1.0 pg/mL (FOR) 2.0 pg/mL (GLY)	(b) (4) 3059	(b) (4) 3-059	(b) (4) 13-147
Study PT003006		Plasma (K3EDTA)	Parent/ 1.0 pg/mL (FOR) 2.0 pg/mL (GLY)	(b) (4) 13059	(b) (4) 13-059	(b) (4) 13-045
Study PT003010		Plasma (K3EDTA)	Parent/ 1.0 pg/mL (FOR) 1.0 pg/mL (GLY)	(b) (4) 4053	(b) (4) 14-053	(b) (4) 14-158
Study PT010001		Plasma (K3EDTA)	Parent/ 1.0 pg/mL (FOR) 2.0 pg/mL (GLY)	(b) (4) 13059	(b) (4) 13-059	(b) (4) 13-226

Source: Pages 58,59/69 of summary of biopharmaceutics

Since multiple reports are submitted, important validation parameters for each of the methods used are summarized in Tables 9-12 below:

Table 9: Calibration Curve: Analyte Concentrations for Glycopyrrolate and Formoterol and Minimum and Maximum Accuracy (%bias) and Precision (%CV) for Mean Back Calculated Standard Concentration Values

Lab/Report No.	Glycopyrrolate (pg/mL) Calibration Standards	Formoterol (pg/mL) Calibration Standards
(b) (4) VAL-RPT-1008	NA	1.00, 2.00, 4.00, 5.00, 10.00, 20.00, 40.00, 50.00
(b) (4) VAL-RPT-1116	2.00, 4.00, 7.00, 10.00, 20.00, 40.00, 70.00, 100.00	1.00, 2.00, 3.50, 5.00, 10.00, 20.00, 35.00, 50.00
(b) (4) VAL-RPT-1252	2.00, 4.00, 7.00, 10.00, 20.00, 40.00, 70.00, 100.00	1.00, 2.00, 3.50, 5.00, 10.00, 20.00, 35.00, 50.00
(b) (4) (b) (4) 13059	2.00, 4.00, 8.00, 16.00, 32.00, 64.00, 90.00, 100.00	1.00, 2.00, 4.00, 8.00, 16.00, 32.00, 45.00, 50.00
(b) (4) (b) (4) 14053	1.00, 2.00, 5.00, 10.0, 60.0, 120, 180, 200	1.00, 2.00, 5.00, 10.0, 60.0, 120, 180, 200

NA: not applicable

Lab/ Report No.	Glycopyrrolate				Formoterol			
	% bias		%CV		% bias		%CV	
	Min	Max	Min	Max	Min	Max	Min	Max
(b) (4) VAL-RPT-1008	NA	NA	NA	NA	-5.1	+9.8	2.6	8.4
(b) (4) VAL-RPT-1116	-0.05	+2.5	4.0	14.1	-4.5	+2.0	4.7	9.9
(b) (4) VAL-RPT-1252	-3.2	+4.1	1.6	5.6	-5.2	+18.0	4.3	39.0
(b) (4) (b) (4) 3059	-1.8	+5.0	ISD	ISD	-0.6	+3.6	ISD	ISD
(b) (4) (b) (4) 4053	-2.6	+2.0	1.3	6.1	-1.6	+3.0	1.7	12.0

ISD: insufficient data; Max: maximum; Min: minimum; NA: not applicable

Source: Pages 22 and 23 of summary of biopharm

Table 10: LLOQ: Intra- and Inter-assay Accuracy (%theoretical) and Precision (%CV) Results for Glycopyrrolate and/or Formoterol in Human Plasma

Lab/ Report No.	Glycopyrrolate		Formoterol	
	%Theoretical	%CV	%Theoretical	%CV
(b) (4) VAL-RPT-1008	NA	NA	ND	ND
(b) (4) VAL-RPT-1116	ND	ND	ND	ND
(b) (4) VAL-RPT-1252	ND	ND	ND	ND
(b) (4) (b) (4) 3059	94.5	2.6	104.0	6.1
(b) (4) (b) (4) 4053	Range[1] 94.4 – 97.0	Range[1] +5.2 - +9.9	Range[1] 93.9 – 97.0	Range[1] +1.5 - +9.1

NA: not applicable; ND: no data

[1] n=6/run, 3 runs

Lab/ Report No.	Glycopyrrolate		Formoterol	
	%Theoretical	%CV	%Theoretical	%CV
(b) (4) VAL-RPT-1008	NA	NA	98.0	10.2
(b) (4) VAL-RPT-1116	96.5	10.4	102.0	12.7
(b) (4) VAL-RPT-1252	102.9	8.7	104.0	9.2
(b) (4) (b) (4) 3059	NA	NA	NA	NA
(b) (4) (b) (4) 4053	ND	ND	ND	ND

NA: not applicable; ND: no data

Source: Page 24 of summary of biopharm

Table 11: QC Sample Concentrations for Each Validation Study

Lab/ Report No.	Glycopyrrolate (pg/mL) QC Levels	Formoterol (pg/mL) QC Levels
(b) (4) VAL-RPT-1008	NA	1.00 (LLOQ), 3.00, 16.00, 40.00
(b) (4) VAL-RPT-1116	2.00 (LLOQ), 6.00, 24.00, 80.00	1.00 (LLOQ), 3.00, 12.00, 40.00
(b) (4) VAL-RPT-1252	2.00 (LLOQ), 6.00, 24.00, 80.00	1.00 (LLOQ), 3.00, 12.00, 40.00
(b) (4) (b) (4) 13059	2.00 (LLOQ), 6.00, 40.0, 80.0	1.00 (LLOQ), 3.00, 20.0, 40.0
(b) (4) (b) (4) 14053	1.00 (LLOQ), 3.00, 15.0, 80.0, 160	1.00 (LLOQ), 3.00, 15.0, 80.0, 160

NA: not applicable; QC: quality control

Source: Page 25 of summary of biopharm

Table 12: Recovery: Efficiency of Extraction (%Recovery) of Glycopyrrolate, Glycopyrrolate-d_3, Formoterol and Formoterol- d_6 in Human Plasma

Lab/ Report No.	Glycopyrrolate				Formoterol			
	Low[1]	Med[1]	High[1]	IS	Low[1]	Med[1]	High[1]	IS
(b) (4) VAL-RPT-1008	NA	NA	NA	NA	46.3	48.3	48.0	53.2
(b) (4) VAL-RPT-1116	104.4	87.0	78.7	78.4	49.4	44.5	36.3	36.2
(b) (4) VAL-RPT-1252	NA	NA	NA	NA	NA	NA	NA	NA
(b) (4) (b) (4) 13059	84.1	83.6	82.7	84.9	85.9	101.2	99.6	80.5
(b) (4) (b) (4) 14053	83.7	82.6	80.4	82.3	77.7	78.0	77.3	79.4

IS: internal standard; Med: medium; NA: not applicable

[1] Quality Control Level

Source: Page 29 of summary of biopharm

2.9.2 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 GP and FF are not active and associated with efficacy or safety.

2.9.3 For all moieties measured, is free, bound, or total measured?

Total (bound + unbound) concentrations were measured in plasma PK samples.

3. Detailed Labeling Recommendations

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

Highlights:

USE IN SPECIFIC POPULATIONS
• Use in patients with severe renal impairment should be considered if the potential benefit of the treatment outweighs the risk. (8.7 (b) (4)

(b) (4)

Section 7, Drug Interactions:

No formal drug interaction studies have been performed with (b) (4) -BEVESPI AEROSPHERE.

7.1. Adrenergic Drugs
If additional adrenergic drugs are to be administered by any route, they should be used with caution because the sympathetic effects of formoterol, a component of BEVESPI AEROSPHERE, may be potentiated.

7.2. Xanthine Derivatives, Steroids, or Diuretics
Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of beta2 adrenergic agonists such as formoterol, a component of

BEVESPI AEROSPHERE.

7.5. Beta-Blockers
Beta-adrenergic receptor antagonists (beta-blockers) and BEVESPI AEROSPHERE may interfere with the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of beta2-agonists, but may produce severe bronchospasm in COPD patients. Therefore, patients with COPD should not normally be treated with betablockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution. (b) (4)

Section 8, Special Populations

8.6. Hepatic Impairment
Formal pharmacokinetic studies using BEVESPI AEROSPHERE have not been conducted in patients with hepatic impairment. However, since formoterol fumarate is predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of formoterol fumarate in plasma. Therefore, patients with hepatic disease should be closely monitored. (b) (4)

8.7. Renal Impairment
Formal pharmacokinetic studies using BEVESPI AEROSPHERE have not been conducted in patients with renal impairment. In patients with (b) (4) severe renal impairment (creatinine clearance of ≤ (b) (4) 30 mL/min/1.73 m2) or end-stage renal disease requiring dialysis, (b) (4) BEVESPI AEROSPHERE should be used if the expected benefit outweighs the potential risk [see Clinical Pharmacology (12.3)] (b) (4)

Section 12, Clinical Pharmacology

12.2. Pharmacodynamics
Cardiovascular effects: Healthy Subjects

The potential for QTc interval prolongation was assessed in a double-blind, single-dose, placebo- and positive-controlled crossover trial in 69 healthy subjects. The largest mean (90% upper confidence bound) differences from placebo in baseline-corrected QTcI for 2 inhalations of BEVESPI AEROSPHERE and glycopyrrolate/formoterol fumarate 72/19.2

mcg, were 3.1 (4.7) ms and 7.6 (9.2) ms, respectively, and excluded the clinically relevant threshold of 10 ms. (b) (4)

A dose-dependent increase in heart rate was also observed. The largest mean (90% upper confidence bound) differences from placebo in baseline-corrected heart rate were 3.3 (4.9) beats/min and 7.6 (9.5) beats/min seen within 10 minutes of dosing with 2 inhalations of BEVESPI AEROSPHERE and glycopyrrolate/formoterol fumarate 72/19.2 mcg, respectively. (b) (4)

Special Populations
Effect of age, sex, race/ethnicity, or body weight:
(b) (4) Population pharmacokinetic analysis showed no evidence of a clinically significant effect of age, sex, race/ethnicity, or body weight on the pharmacokinetics of glycopyrrolate and formoterol. (b) (4)
(b) (4)

Hepatic Impairment: Dedicated studies evaluating effect of hepatic impairment on the pharmacokinetics of glycopyrrolate and formoterol were not conducted.

Renal Impairment: Dedicated studies evaluating effect of renal impairment on the pharmacokinetics of glycopyrrolate and formoterol were not conducted. When glycopyrrolate was administered IV in uremic patients undergoing renal transplantation, mean elimination half-life was significantly longer (46.8 minutes) than in healthy patients (18.6 minutes). The mean AUC (10.6 hr-µg/L), mean plasma clearance (0.43 L/hr/kg), and mean 3-hour urine excretion (0.7%) for glycopyrrolate were also significantly different than those of controls (3.73 hr-µg/L, 1.14 L/hr/kg, and 50%, respectively). A population pharmacokinetic analysis using BEVESPI AEROSPHERE showed that formoterol systemic exposure (AUC0-12) in subjects with COPD with moderate renal impairment (45 mL/min creatinine clearance) is expected to be approximately 45% higher compared to subjects with COPD with normal renal function (94 mL/min creatinine clearance).

4. Appendix

4.1 Appendix –PM Review

1. SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Are the PK parameters reported in the label supported by the population PK analysis submitted by the sponsor?

Yes, the PK parameters reported in the label are supported by the population PK (popPK) analysis submitted by the sponsor. The popPK analysis was performed using Phoenix® NLMETM Version 1.3.

Concentration-time data of glycopyrrolate (GP) following administration of either GP metered dose inhaler (MDI) as monotherapy (Studies PT0050801, PT0031002, and PT003006) or GP-formoterol fumarate (FF) MDI as combination therapy (Studies PT0031002 and PT003006) were used to develop the GP population PK model. The dosing regimens of GP from those studies were listed in Table 1. In total 239 subjects with 3471 concentrations were included in the final dataset for GP popPK analysis.

Table 1 Dosing Regimens of Glycopyrrolate Included for Population PK Analysis

Study	Study Design	Dosing Regimen	Dose
PT0010801	Cross-over	Single Dose	GP: 18, 36, 72, or 144 µg
PT0031002	Cross-over	BID for 7 Days	GP: 36 µg GP-FF: 36/9.6 µg or 72/9.6 µg
PT003006	Parallel	BID for 24 Weeks	GP: 14.4 µg GP-FF: 14.4/9.6 µg

Source: Adapted from section 5.3.3.5, pop-pk-analysis.pdf, Table 3.1, Page 10-13

Similarly, concentration-time data of formoterol following administration of either FF MDI as monotherapy (Studies PT0050801, PT005003, PT0031002 and PT003006) or GP-FF MDI as combination therapy (Studies PT0031002 and PT003006) were used to develop the formoterol population PK model. The dosing regimens of FF from those studies were listed in Table 2. In total 304 subjects with 4751 concentrations were included in the final dataset for formoterol popPK analysis.

Table 2 Dosing Regimens of Formoterol Fumarate Included for Population PK Analysis

Study	Dosing Regimen	Dose
PT0050801	Single Dose	FF: 2.4, 4.8, or 9.6 µg
PT005003	Single Dose	FF: 7.2, 9.6, or 19.2 µg
PT0031002	BID for 7 Days	FF: 7.2 or 9.6 µg GP-FF: 36/9.6 µg or 72/9.6 µg
PT003006	BID for 24 Weeks	FF: 9.6 µg GP-FF: 14.4/9.6 µg

Source: Adapted from section 5.3.3.5, pop-pk-analysis.pdf, Table 3.1, Page 10-13

Plasma concentrations of GP and formoterol below the limit of quantification (BLQ) of the assay were flagged and set to missing for the population PK analysis.

The final PK model following GP inhalation was characterized by a 2-compartment model with first-order absorption and linear elimination. The PK parameters of GP derived from the final model were listed in Table 3:

Table 3 Glycopyrrolate PK Parameter Estimates from final PopPK Model

Parameter	Typical Value[1]	Inter-individual Variability[2]
Ka (/hr)	45.2 (8.8%)	56.5%
CL/F (L/hr)	217 (5.7%)	71.2%
Vc/F (L)	951 (8.3%)	82.5%
Q/F (L/hr)	456 (8.3%)	78.1%
V2/F (L)	2019 (8.0%)	N/A

[1] Typical value (RSE%)
[2] Coefficient of variance (%CV)
Source: Adapted from pop-pk-analysis.pdf, Page 28, Table 6.4:1

The final PK model following FF inhalation was characterized by a 2-compartment model with first-order absorption and linear elimination. The PK parameters of GP derived from the final model were listed in Table 4:

Table 4 Formoterol Fumarate PK Parameter Estimates from final PopPK Model

Parameter	Typical Value[1]	Inter-individual Variability[2]
Ka (/hr)	10.9 (9.8%)	93.2%
CL/F (L/hr)	102 (3.6%)	57.3%
Vc/F (L)	948 (5.9%)	66.7%
Q/F (L/hr)	56.9 (9.0%)	N/A
V2/F (L)	434 (9.1%)	N/A

[1] Typical value (RSE%)
[2] Coefficient of variance (CV%)
Source: Adapted from pop-pk-analysis.pdf, Page 35, Table 7.4:1

1.1.2 What are the effects of intrinsic factors and extrinsic factors on the PK of GP and formoterol?

- GP:
  - Ka (Absorption rate): According to sponsor's model, age was identified as a significant covariate of GP Ka, whereby older patients displayed slower absorption rate than younger subjects. The power function of the effect of age on Ka was -2.44 $[(Age/62)^{-2.44}]$. Based on this model, the Ka of GP in a 79-year old subject would be ~45% lower than in a typical 62 year old subject.

  - CL/F: According to sponsor's model, baseline creatinine clearance (BCRCL), age, co-administration of FF, and dosing level were identified as significant covariates of CL/F.
    - Baseline creatinine clearance: The power function of baseline creatinine clearance on CL/F was 0.250 $[(CRCLBSLC/94.2)^{0.250}]$. The typical CL/F of GP in patients with moderate renal impairment (45 mL/min) is expected to be approximately 17% lower than subjects with normal renal function (94.2 mL/min, the median value of creatinine clearance in popPK dataset).

    - Age: The power function of age on CL/F was -1.33 $[(Age/62)^{-1.33}]$. Based on this model, the CL/F would decrease in older subjects. GP CL/F of a 40- and a 79-year old subject would be expected to be approximately 79% higher and 28% lower relative to a typical 62-year old subject, respectively.

    - Co-administration of FF: The GP CL/F following administration of GP MDI (monotherapy) was approximately 15% (RSE of 4.0%) lower than that following administration of GP-FF MDI (combination therapy).

    - Dosing level: There was a slight departure from dose linearity at the highest dose level of 144 µg GP. Typical values of CL/F at 144 µg were approximately 35% lower than that of 14.4 µg dose. The differences of CL/F at other dosing levels were less than 20% comparing to the typical value at 14.4 µg.

  Reviewer's comments:
    - *Effects of creatinine clearance and age on CL/F: Keeping both age and creatinine clearance as the final parameters for a primarily renal-cleared drug is unusual, as these two factors are confounded. The reviewer evaluated these two factors in an independent analysis by using NONMEM Version 7.3. It appeared that age did have an extra effect on CL/F after the adjustment of baseline creatinine clearance (section 3.4). The estimated power*

function of baseline creatinine clearance and age on CL/F was 0.502 and -1.06, respectively. Therefore, the effect of creatinine clearance on CL/F could be greater than what sponsor proposed; and the effect of age on CL/F could be smaller than what sponsor proposed.

Sponsor estimated that subjects with moderate renal impairment (45 mL/min) had about 17% lower CL/F than subjects with normal renal function (94 mL/min). Reviewer estimated that subjects with moderate renal impairment (45 mL/min) had about 31% lower CL/F than subjects with normal renal function (94 mL/min). Reviewer's estimation is consistent with the results from renal impairment study described in the product label of a previously approved GP product (NDA 207923 Seebri Neohaler GP inhalation powder): moderate mean increase in total systemic exposure (AUC_{last}) 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/1.73m^2]

- *Effects of dosing level on CL/F: Sponsor not only imposed the dose effect on CL/F, but also on Vc/F and Q/F with the same estimation. This is equivalent to introduction of a bioavailability factor on different dosing levels, rather than a CL/F-specific covariate. In the single-dose ascending crossover Study PT005801, the GP C_{max} and AUCs generally increase in a dose-proportional manner by non-compartmental analysis (Table 16). Therefore, the dosing level effect may not necessarily be assessed in the population PK model (reviewer did not evaluate the bioavailability from different dosing levels as a covariate in reviewer's model).*

- Vc/F: Baseline body weight, co-administration of inhaled corticosteroid (ICS), and dosing level were identified as a significant covariate of Vc/F.

  - The power function of the effect of body weight on Vc/F was 0.480 [WTSCR/83.3)$^{0.480}$]. Based on this model, the Vc/F would increase with body weight increase. GP Vc/F of a 43 kg and 158 kg subjects would be ~27% lower and ~36% higher than in a typical 83.3-kg subject, respectively.

- The power function of the effect of body weight on Vc/F was 0.480 [WTSCR/83.3)$^{0.480}$]. Based on this model, the Vc/F would increase with body weight increase. GP Vc/F of a 43 kg and 158 kg subjects would be ~27% lower and ~36% higher than in a typical 83.3-kg subject, respectively.

- The typical Vc/F of GP in subjects taking ICS at baseline was 31% greater than subjects who did not take ICS.

- Dosing level: The same dosing level covariates for CL/F were applied to Vc/F (Table 5). Therefore, typical value of Vc/F decreases with dose increases.

Reviewer's comments:
See reviewer's discussion on effect of dosing level on Vc/F under comments on CL/F

- Formoterol:
  - Absorption: COPD severity was identified as a significant covariate of formoterol Ka, whereby severe and very severe COPD subjects would display slower absorption than moderate COPD subjects. Based on this model, the typical value of Ka in subjects having severe or very severe COPD would be ~37% lower than that in subjects with moderate COPD.

  - CL/F:BCRCL and post-Ventolin FEV1 (PVFEV1) were identified as significant covariates of CL/F.
    - BCRCL: The power function of BCRCL on CL/F was 0.502 [(CRCLBSLC/94.1)$^{0.502}$]. The typical CL/F of formoterol in patients with moderate renal impairment (45 mL/min) is expected to be approximately 31% lower than subjects with normal renal function (94.2 mL/min, the median value of creatinine clearance in popPK dataset).

    - PVFEV1: The power function of PVFEV1 on CL/F was 0.303 [(PVFEV1/1.52)$^{0.303}$]. PVFEV1 values reflected COPD patients' response to albuterol, a short-acting β-adrenergic agonist.

Reviewer's comments:
The clinical meaning and the mechanism of effect of PVFEV1 on CL/F is not clear. Therefore, the effect of PVFEV1 may not necessarily be assessed in the population PK model

  - Vc/F: Baseline body weight and co-administration of inhaled corticosteroid (ICS) were identified as a significant covariate of Vc/F.
    - The power function of the effect of body weight on Vc/F was 0.428 [WTSCR/81.5)$^{0.428}$]. Based on this model, the Vc/F would increase with body weight increase. Formoterol Vc/F of a 36.3 kg

and 167 kg subjects would be ~29% lower and ~36% higher than in a typical 81.5-kg subject, respectively.

- The typical Vc/F of GP in subjects taking ICS at baseline was 32% larger than subjects who did not take ICS.

1.1.2 What is the characteristic of dose -response relationship for efficacy? Does it support the proposed dose regimen?

The dose-response relationship of GP was established. A statistically significant effect of GP dose on ΔFEV1 AUC_{0-12} and AUC_{0-24} was observed.

Dose-response analyses was performed using efficacy (FEV1 AUC_{0-12} or AUC_{0-24} change from baseline) and PK data from Study PT0010801 to guide the selection of candidate dosing of GP as a combination product with FF. Study PT0010801 was a randomized, double-blind, placebo-controlled, active-controlled, single dose, 6-treatment, 4-period, partial crossover study. In total 33 patients with mild to moderate COPD were randomized. The six single-dose treatments were: placebo, 18 µg tiotropium via Spiriva Handihaler®, and 18, 36, 72, and 144 µg GP via MDI.

An E_{max} model [$E= E_{max} \times Dose / (Dose + ED_{50})$] provided the best quality of fit for the dose-response analysis of ΔFEV1 AUC_{0-12} (Table 5) and AUC_{0-24} (Table 6) change from baseline. The estimated ED_{50} for ΔFEV1 AUC_{0-12} and AUC_{0-24} was 15.7 µg and 19.0 µg, respectively.

Table 5 Dose-Response Parameters for ΔFEV1 AUC_{0-12} Estimated by E_{max} Model

PD Parameters	△ FEV_1 AUC_{0-12} vs Glycopyrrolate MDI Dose			
	Estimate	BSV%	CV %	95% CI
E_{max}(L.h/s)	2.75	1.99	16.7	1.81 - 3.68
ED_{50} (µg)	15.7	2.24	51.4	-0.783 - 32.1
E_0	0	1.45	NC	NC
Standard Error	1.08	NC	10.7	0.842 - 1.31

BSV: Between-subject variability, CV%: coefficient of variability, NC: Not Calculated

Source: important-documents-referenced-pt0010801.pdf, Page 475

Table 6 Dose-Response Parameters for ΔFEV1 AUC_{0-24} Estimated by E_{max} Model

PD Parameters	△ FEV_1 AUC_{0-24} vs Glycopyrrolate MDI Dose			
	Estimate	BSV%	CV %	95% CI
E_{max}(L.h/s)	4.68	5.28	18.7	2.89-6.47
ED_{50} (µg)	19.0	0.198	44.3	1.80-36.2
E_0	0	9.37	NC	NC
Standard Error	2.11	NC	9.82	1.68-2.53

BSV: Between-subject variability, CV%: coefficient of variability, NC: Not Calculated

Source: important-documents-referenced-pt0010801.pdf, Page 475

Reviewer's comments:
The sponsor also conducted an exposure-response analysis to justify the selection of BID dosing regimen. However, the exposure-response relationship for a locally-acting drug product may hardly be interpreted.

1.1.3 What is the characteristic of exposure-response (E-R) relationship for safety? Does it support the proposed dose regimen?

The exposure-response analysis for safety was not conducted by the Sponsor.

1.2 Recommendations

The Division of Pharmacometrics in Office of Clinical Pharmacology has reviewed the information contained in NDA 208294. This NDA is considered acceptable from a pharmacometrics perspective.

In label section 12.3, Special Populations, "Population pharmacokinetic analysis showed no evidence of a clinically significant effect of age, sex, race/ethnicity, or body weight on the pharmacokinetics of glycopyrrolate" replaced (b) (4)

In label section 12.3, Special Populations, the results of a study evaluating glycopyrrolate PK in renal transplantation patients from reference product (NDA021912 Robinul) were inserted to replace (b) (4)

1.3 Label Statements

See section 3 of Clinical Pharmacology review for detailed label recommendation.

2. RESULTS OF SPONSOR'S ANALYSIS

2.1 Population PK analysis

Datasets for the population PK analysis of plasma glycopyrrolate and formoterol were provided by Pearl Therapeutics. The population PK analysis was performed using Phoenix® NLMETM Version 1.3. The quality-of-fit of compartmental models was assessed using a standard model discrimination process including statistical criteria (e.g., Akaike information criterion, objective function value, etc.) as well as pertinent graphical representations of goodness-of-fit (e.g., fitted and observed concentrations versus time).

The structural model for GP and formoterol consisted of a 2-compartment disposition with a first-order absorption and linear elimination. The final model resulted in adequate quality of fit indicating no time dependency of PK of GP and formoterol following multiple doses.

- GP: A covariate analysis was performed to assess sources of variability in GP primary PK parameters and identify clinically relevant intrinsic and extrinsic covariates (Table 7):
    - Age effect on Ka: older subjects are expected to display slower absorption than younger subjects.
    - There was a slight departure from dose linearity at the highest dose level of 144 µg GP. Typical values of CL/F, CL2/F and Vc/F at dose levels of 28.8 and 57.6 µg were approximately 15% lower relative to the 14.4 µg dose. Typical values of CL/F, CL2/F and Vc/F for the highest dose (144 µg) were approximately 35% lower than the 14.4 µg dose. Therefore, there is a departure from dose linearity at the highest dose level.
    - BCRCL on CL/F: Subjects with moderate renal impairment (45 mL/min creatinine clearance) are expected to display CL/F values approximately 17% lower than subjects with normal renal function (creatinine clearance of 94.2 mL/min).
    - Age effect on CL/F: 40- and 79-year old subjects are expected to display CL/F values approximately 79% higher and 28% lower than those in a typical 62-year old subject.
    - Effect of Monotherapy: The CL/F of GP following administration of GP MDI (monotherapy) was approximately 15% lower than that following administration of GP-FF MDI (combination therapy).
    - Effect of ICS: the typical Vc/F of GP in subjects taking ICS at baseline was 36% larger than subjects who did not take ICS.
    - Effect of weight on Vc/F: the Vc/F of GP in 43- and 158-kg subjects would be ~27% lower and ~36% higher than in a typical 83.3-kg subject, respectively.

Table 7 Final Population PK Parameters of Glycopyrrolate

Population Pharmacokinetic Parameter	Typical Values (RSE%)	Between Subject Variability (%)	Shrinkage (%)
Ka (h^{-1})	**45.2 (8.8)**	**56.5 (19.2)**	**51.4**
Effect of Age	x $(AGE/62)^{-2.44\ (34.4)}$		
CL/F (L/h)	**217 (5.7)**	**71.2 (5.6)**	**8.0**
Effect of Creatinine Clearance	x $(CRCLBSLC/94.2)^{0.250\ (46.5)}$		
Effect of Age	x $(AGE/62)^{-1.33\ (28.8)}$		
Effect of DDI (GP MDI)	x 0.847 (4.0)		
*Effect of Dose level 28.8 ug	x 0.835 (5.6)		
*Effect of Dose level 57.6 µg	x 0.865 (5.4)		
*Effect of Dose level 115.2 µg	x 0.653 (5.6)		
Vc/F (L)	**951 (8.3)**	**82.5 (5.4)**	**5.0**
Effect of ICS	x 1.36 (19.2)		
Effect of Weight	x $(WTSCR/83.3)^{0.480\ (47.6)}$		
CL2/F (L/h)	**456 (8.3)**	**78.1 (8.9)**	**30.4**
Effect of Weight	x $(WTSCR/83.3)^{0.794\ (35.9)}$		
V2/F (L)	**2019 (8.0)**	NA	NA
Error Model			
Proportional (%)	23.6 (4.6)	NA	NA
Additive (pg/mL)	1.74 (2.6)		

Source: from pop-pk-analysis.pdf, Page 28, Table 6.4:1

The standard goodness-of-fit plots for the GP final model are shown in the Figure 1.

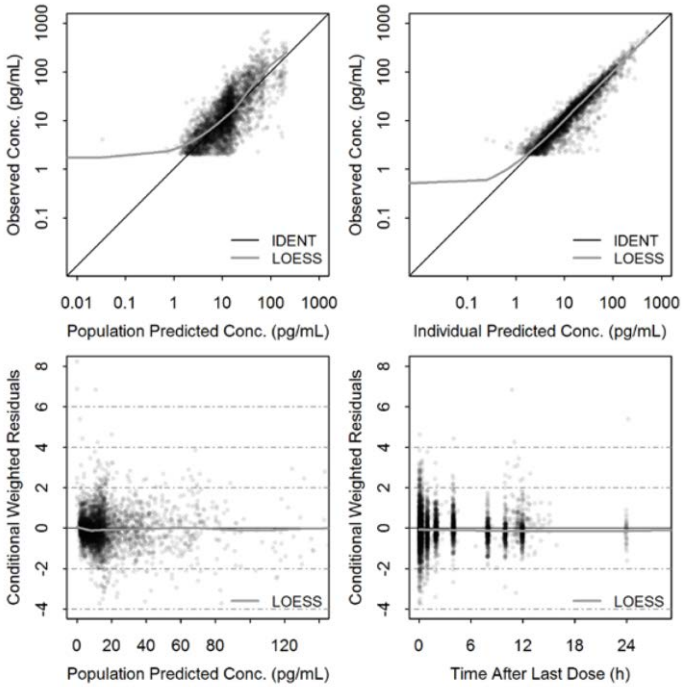


Figure 1 Diagnostic plots for the GP final population PK Model. (Source: pop-pk-analysis.pdf, Page 27, Table 6.3.1)

A visual predictive check (VPC) was performed to allow visual comparison between the distributions of simulated concentrations from the final model and those obtained from the original dataset (Figure 2). These simulations were replicated a total of 1000 times so that within each bin, nonparametric 95% CIs of the 5th, 50th and 95th prediction percentiles of concentration could be computed. These were displayed graphically and overlaid with the corresponding percentiles of the observed data.

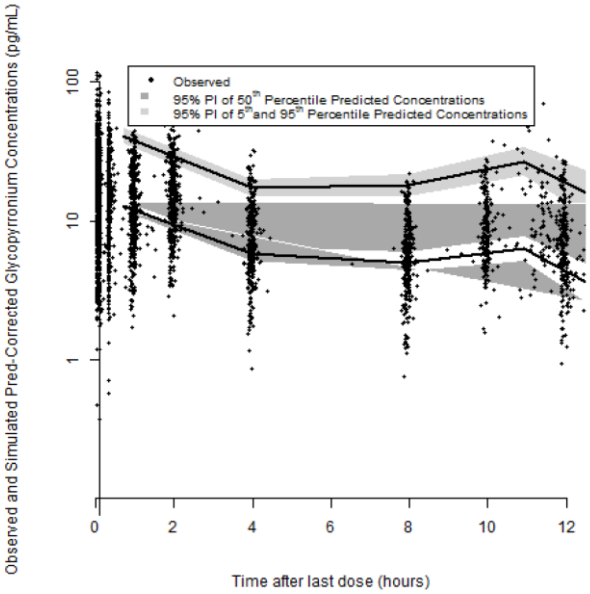


Figure 2 Model-predicted typical value PK profiles overlaid on observed GP concentrations versus time. (Source: pop-pk-analysis.pdf, Page 100)

- Formoterol: A covariate analysis was performed to assess sources of variability in formoterol primary PK parameters and identify clinically relevant intrinsic and extrinsic covariates (Table 8):
    - COPD severity explained the variability of Ka, while BCRCL and PVFEV1 explained the variability of CL/F.
        - Effect of COPD severity on Ka: Subjects with severe and very severe COPD (Ka = 6.8 /hr) are expected to display slower absorption than that in subjects with moderate COPD (Ka = 10.9 /hr).
        - Effect of baseline creatinine on CL/F: Subjects with moderate renal impairment (45 mL/min creatinine clearance) are expected to display a CL/F value approximately 31% lower than subjects with normal renal function (creatinine clearance of 94 mL/min).
        - Effect of PVFEV1 on CL/F: Subjects with COPD and low post-Ventolin forced expiratory volume in one second (PVFEV1) values displayed a lower CL/F.

- The typical Vc/F and V2/F of formoterol were 948 and 434 L, respectively. The Vc/F of formoterol was dependent on the use of ICS at baseline, and body weight at screening.
  - The typical Vc/F of formoterol in subjects taking ICS at baseline was 32% larger than subjects who did not take ICS.
  - Effect of WTSCR on Vc/F: 36.3- and 167-kg subjects are expected to display Vc/F values approximately 29% lower and 36% higher those in a typical 81.5-kg subject.

- No DDI was detected following administration of formoterol as monotherapy or combination therapy.

Table 8 Final Population PK Parameters of Formoterol

Population Pharmacokinetic Parameter	Typical Values (RSE%)	Between Subject Variability (%)	Shrinkage (%)
Ka (h^{-1})	**10.9 (9.8)**	**93.2 (5.8)**	**17.4**
Effect of COPD Severe and Very Severe	x 0.628 (14.7)		
CL/F (L/h)	**102 (3.6)**	**57.3 (4.6)**	**4.0**
Effect of Creatinine Clearance	x $(CRCLBSLC/94.0)^{0.502\ (23.3)}$		
Effect of $PVFEV_1$	x $(PVFEV1/1.52)^{0.303\ (37.1)}$		
Vc/F (L)	**948 (5.9)**	**66.7 (4.6)**	**5.6**
Effect of ICS	x 1.32 (14.5)		
Effect of Weight	x $(WTSCR/81.5)^{0.428\ (42.0)}$		
CL2/F (L/h)	**56.9 (9.0)**	NA	NA
V2/F (L)	**434 (9.1)**	NA	NA
Error Model		NA	NA
Proportional (%)	29.2 (11.8)		
Additive (pg/mL)	0.224 (7.7)		

Source: from pop-pk-analysis.pdf, Page 35, Table 7.4:1

The standard goodness-of-fit plots for the formoterol final model are shown in the Figure 3.

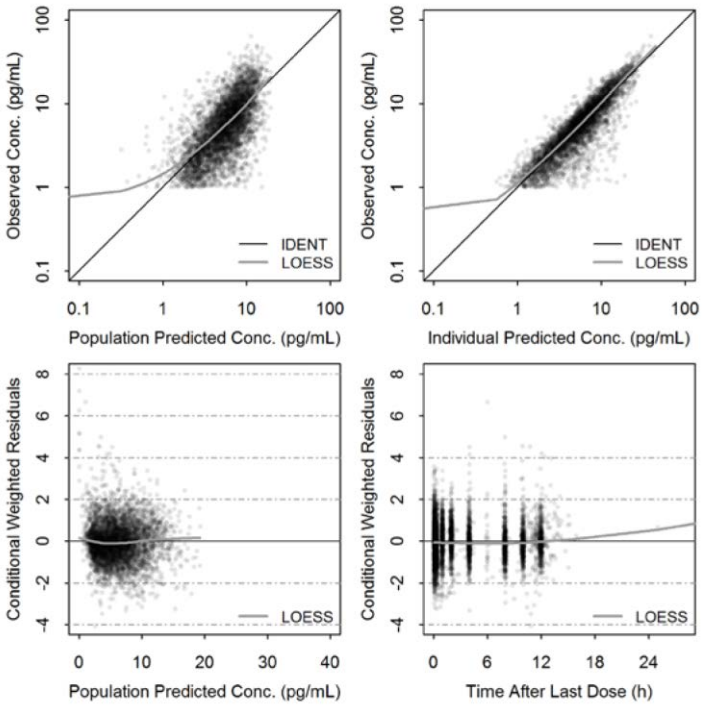


Figure 3 Diagnostic plots for the GP final population PK Model. (Source: pop-pk-analysis.pdf, Page 27, Table 6.3.1)

A visual predictive check (VPC) was performed to allow visual comparison between the distributions of simulated formoterol concentrations from the final model and those obtained from the original dataset (Figure 4).

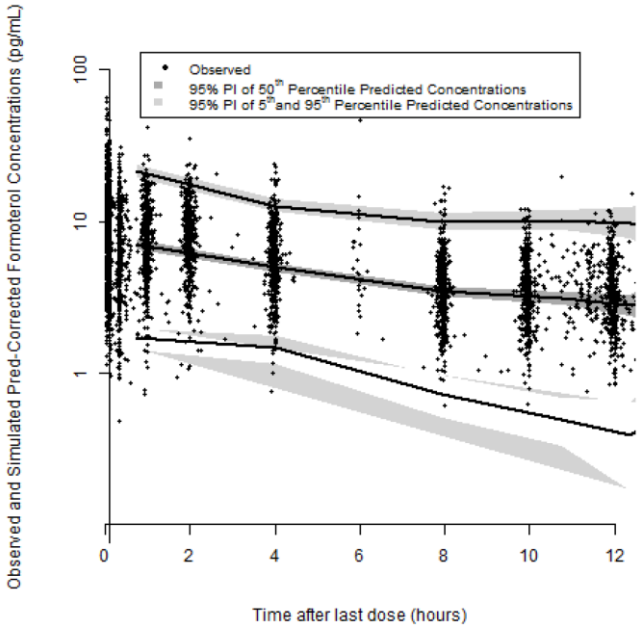


Figure 4 Model-predicted typical value PK profiles overlaid on observed formoterol concentrations versus time. (Source: pop-pk-analysis.pdf, Page 157)

2.2 Dose-Response analysis

Among 33 randomized COPD patients in Study 0010801, PK and efficacy (FEV1) data from 30 patients of modified intention-to-treat population (mITT) were analyzed. Due to the partial crossover schedule, there were 21 to 22 patients assigned to each of six the treatments. PK samples were collected at pre-dose, and at 2, 6, 20 min as well as 1, 2, 4, 8, 12, and 24 hours post-dose. FEV1 values were measured at 1 hour and 30 min pre-dose and at 15, 30 min as well as 1, 2, 4, 6, 8, 10, 12, 16, 22, 23 and 24 hours post-dose.
The population PK analysis, the dose-response and exposure-response analysis were performed by Phoenix NLME 1.0 (Pharsight, Mountain View, CA).

In general, a trend of greater improvement of FEV1 $AUC_{0\text{-}12h}$ and $AUC_{0\text{-}24h}$ with increase of GP dose was observed in Study 0010801 (Table 9).

Table 9 Descriptive Summary of ΔFEV1 $AUC_{0\text{-}12h}$ and $AUC_{12\text{-}24h}$ following Placebo and Glycopyrrolate MDI Treatment

Glycopyrrolate MDI Dose (µg)	Arithmetic Mean (CV%)	
	△ FEV_1 $AUC_{0\text{-}12}$ (L.h/s)	△ FEV_1 $AUC_{0\text{-}24}$ (L.h/s)
0	0.084 (1952%)	-0.943 (-395%)
18	1.643 (124%)	2.043 (190%)
36	2.145 (113%)	2.744 (174%)
72	1.796 (122%)	2.373 (182%)
144	2.87 (65.2%)	3.875 (89.9%)

Source: important-documents-referenced-pt0010801.pdf, Page 475

The dose-response relationship was explored by four E_{max} models (Table 10). Statistical criterion such as Akaike Information (AIC) and Log likelihood (-2 LL) were used to assess the goodness-of-fit of the above dose-response model. When comparing several models, the model associated with the smallest AIC and -2 LL was selected during the model discrimination process.

Table 10 Candidate E_{max} models for Dose-Response Modeling for ΔFEV1 $AUC_{0\text{-}12h}$ and $AUC_{0\text{-}24h}$

Model	Equations
Simple E_{max} Model	$E = E_{max} \times Dose / (Dose + ED_{50})$
Simple E_{max} Model with E_0	$E = E_0 + (E_{max} - E_0) \times Dose / (Dose + ED_{50})$
Sigmoid E_{max} Model	$E = (E_{max} \times Dose^{\gamma}) / (Dose^{\gamma} + ED_{50}^{\gamma})$
Sigmoid E_{max} Model with E_0	$E = E_0 + (E_{max} - E_0) \times Dose^{\gamma} / (Dose^{\gamma} + ED_{50}^{\gamma})$

E = effect, E_{max} = maximal effects, ED_{50} = dose associated to 50% of E_{max}, E_0 = baseline effects (placebo effect), γ = sigmoidicity factor.

Source: important-documents-referenced-pt0010801.pdf, Page 475

The simple E_{max} model provided the best quality of fit for the dose-response analysis of ΔFEV1 $AUC_{0\text{-}12h}$ (Table 7) and ΔFEV1 $AUC_{0\text{-}24h}$ (Table 8). An additive error model

was used for the final dose-response analyses. Model performances of dose-response models are presented in Figure 5.

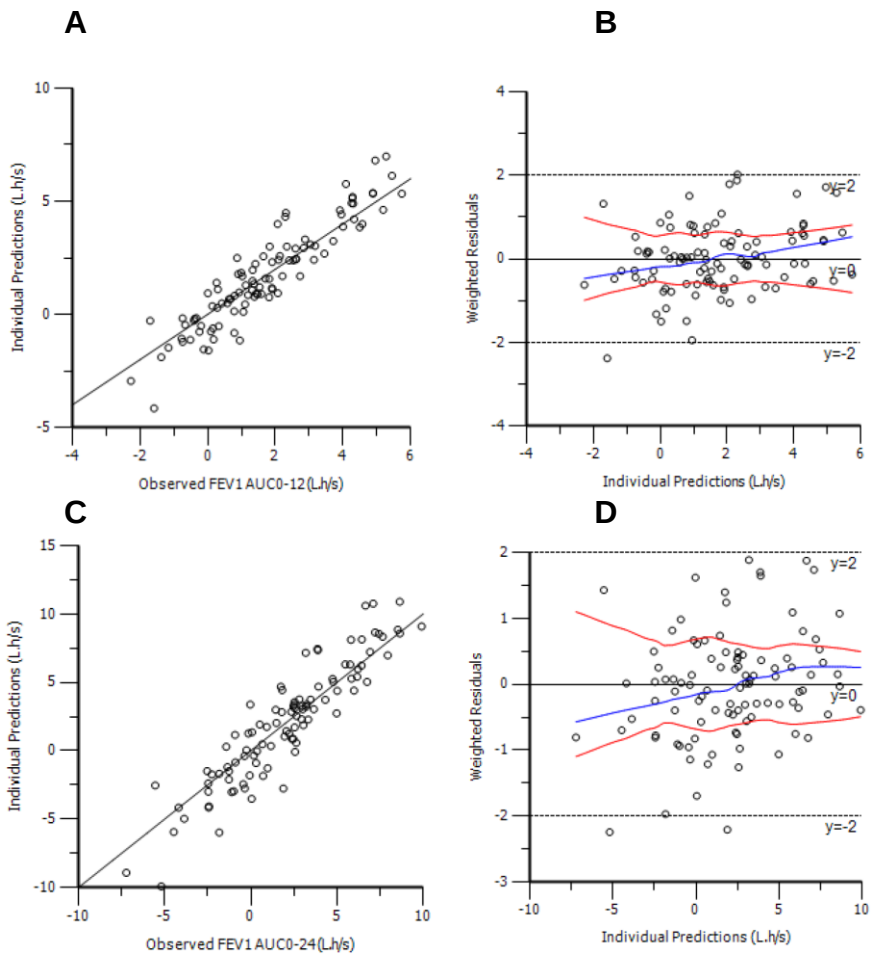


Figure 5 Simple E_{max} model performance plots for dose-response relationship: Goodness-of-fit plots of model-predicted ΔFEV1 $AUC_{0\text{-}12h}$ (A) and ΔFEV1 $AUC_{0\text{-}24h}$ (C); weighted residue plots derived from models of ΔFEV1 $AUC_{0\text{-}12h}$ (B) and ΔFEV1 $AUC_{0\text{-}24h}$ (D). (Source: important-documents-referenced-pt0010801.pdf, Page 487)

3. RESULTS OF REVIEWER'S ANALYSIS

3.1 Introduction

Sponsor conducted popPK analysis using Phoenix® NLMETM. Herein, reviewer used NONMEN to evaluate the sponsor-discovered significant covariates on the CL/F of GP and formoterol. Reviewer agreed with most of the major conclusions drawn by the Sponsor except the magnitude of the effect of age and creatinine on CL/F of GP. The discussions and comments were reflected in the Pharmacometrics Key Review Questions.

3.2 Objectives

The reviewer's analysis objective is to use NONMEM for evaluation of the effect of the sponsor-discovered significant covariates on the CL/F of GP and formoterol.

3.3 Methods

3.3.1 Software

NONMEM 7.3 was used for the reviewer's analysis.

3.3.2 Data Sets and Control stream

Review folder and Data set are summarized in Table 11 (folder location: \\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Bevespi_NDA208294_YR\popPK)

Table 11 Summary of Reslizumab Pharmacometrics Reviewer Folder and Data Set

	Sponsor's Data Set	Adapted Data Set*	Sponsor's Control Stream	Sponsor's output	Adapted Control Stream*
Formoterol	glycdat.xpt	glycol.csv	glfimod.txt	glfiout.txt	run003.mod run005.mod run006.mod
Glycopyrrolate	formdat.xpt	form.csv	fofimod.txt	fofiout.txt	run0013 mod run0014 mod run0015 mod run0016 mod run0017 mod run0018 mod run0021 mod run0022 mod

*** Adapted for changes of directory, input and output format**

3.4 Results

- To assess covariates' effect on GP CL/F

The Sponsor identified 4 significant covariates on GP CL/F: dose, BCRCL, age, and effect of formoterol.

- Dose effect: Actually the Sponsor imposed the dose effect on CL/F, Vc/F and Q/F with the same estimation. This is equivalent to introduce of a bioavailability factor on different doses, rather than CL/F-specific covariates. In single-dose ascending crossover Study PT005801, the GP C_{max} and AUCs generally increase in a dose-proportional manner by non-compartmental analysis (Table 12). Therefore, the dose effect was not further evaluated in the reviewer's model.

Table 12 Summary of Glycopyrrolate PK Parameters following Single Dose Administration

Parameter	Arithmetic Mean (CV%)			
	GP 144 µg	GP 72 µg	GP 36 µg	GP 18 µg
N	20	20	18	18
AUC_{0-24} (pg•h/mL)	498 (82.0)	202 (74.5)	120 (67.2)	34.5 (101.2)
AUC_{0-12} (pg•h/mL)	398 (79.8)	163 (70.6)	89.9 (57.7)	31.9 (88.8)
AUC_{12-24} (pg•h/mL)	102 (100.9)[a]	41.0 (91.3)[b]	32.0 (147.0)[c]	4.34 (250.5)[d]
$AUC_{0-tlast}$ (pg•hr/mL)	491 (84.4)	196 (78.8)	113 (74.4)	30.7 (112.5)
AUC_{0-inf} (pg•h/mL)	598 (84.0)[a]	252 (70.8)[b]	127 (68.7)[d]	66.2 (72.2)[e]
C_{max} (pg/mL)	160 (73.8)	62.9 (72.3)	27.3 (51.5)	15.6 (72.0)
t_{max}[f] (h)	0.100 (0.0330, 0.933)	0.100 (0.0330, 0.917)	0.100 (0.0330, 0.383)	0.333 (0.0330, 0.350)
$t_{1/2}$ (h)	9.61 (36.6)[a]	8.76 (59.4)[b]	6.28 (62.6)[d]	5.09 (82.0)[e]
CL/F (L/h)	422 (75.6)[a]	510 (81.3)[b]	494 (89.6)[d]	416 (77.0)[e]
Vz/F (L)	4697 (49.7)[a]	4627 (50.9)[b]	3320 (56.9)[d]	1995 (32.2)[e]

[a]n=16, [b]n=19, [c]n=12, [d]n=11, [e]n=10, [f] Median (Min, Max)
Source: CSR pt0010801.pdf, Page 71, Table 13

- BCRCL is a significant covariate of GP CL/F (Table 13). There is a clear trend of increasing of unexplained inter-subject variability (ETA) on CL/F over increasing of BCRCL if BCRCL is not introduced as a covariate (Figure 6). CL/F of a subject with mild (CRCL=75 mL/min) and moderate (CRCL=45 mL/min) renal impairment is expected to be approximately 11% and 31% lower than a subject with normal renal function (CRCL=94 mL/min), respectively. (Figure 7).

Table 13 Evaluation of GP CL/F covariates from Reviewer's Model by Backward Elimination

Covariates on GP CL/F	Sponsor's Estimate[1]	Reviewer's Estimate[1]	Change of OF by Removing Covariate in Reviewer's Models
Baseline CRCL	0.250 (0.116)[2]	0.502 (0.121)[2]	7.827
Age	-1.33 (0.384)[3]	-1.06 (0.389)[3]	7.544
Co-administration with Formoterol	-0.166 (0.0396)[4]	-0.144 (0.0394)[5]	19.439

[1] Typical value (SE)
[2] as the power of [baseline CRCL/94]
[3] as the power of [Age/62]
[4] as the power of e when formoterol is administered
[5] as the proportion change when formoterol is administered
Source: Reviewer's analysis and summary from run013 lst and glfiout.txt

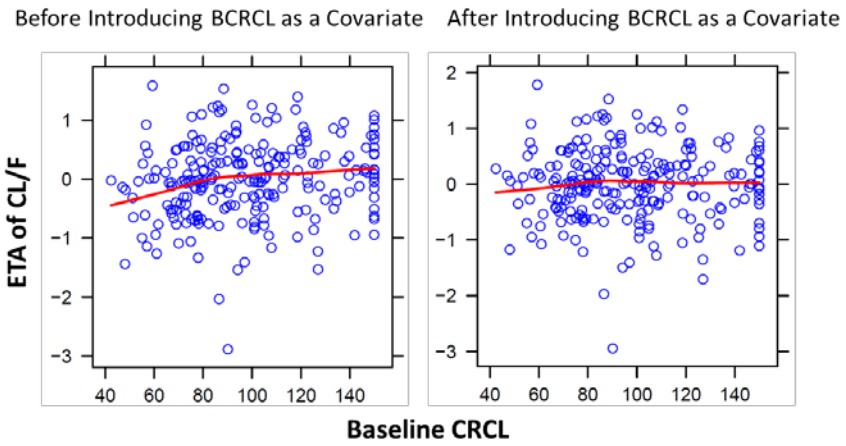


Figure 6 Scatter plot of inter-subject variability (ETA) of GP CL/F over baseline creatinine clearance before and after introduction of the BCRCL as a covariate (reviewer's analysis).

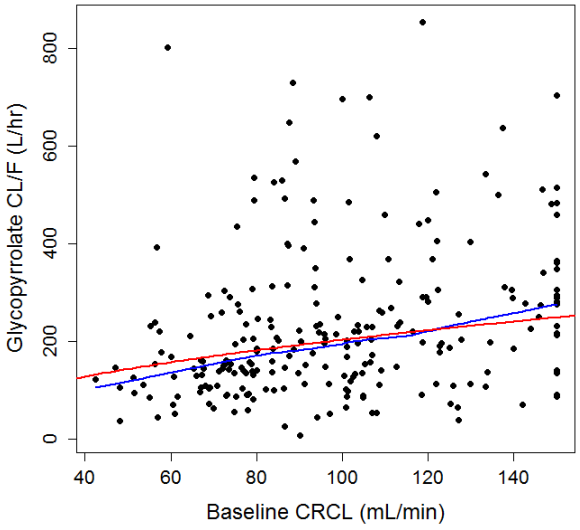


Figure 7 Scatter plot of glycopyrrolate CL/F over baseline creatinine clearance. The red line represents $CL/F_{tv} \times (CRCL/94)^{0.502}$ prediction curve. The blue line represents local smoothing curve (reviewer's analysis).

- Age is a significant covariate of GP CL/F (Table 13). There is a clear trend of decreasing of unexplained inter-subject variability (ETA) on CL/F over increasing of age if age is not introduced as a covariate (Figure 8). It is known that CRCL decreases with age increase; and age is a variable for CRCL estimation. Therefore the age effect on CL/F is usually confounded by the effect of CRCL. The following two pieces of evidence support that age is a CRCL-independent covariate on GP CL/F:
  - The trend of inter-subject variability on CL/F over age persists in a moderate way after introduction of CRCL as a covariate. The trend only disappears after introduction of age as a covariate (Figure 8).
  - The power value of baseline creatinine clearance on CL/F was 0.687 $[(CRCLBSLC/94.2)^{0.687}]$ when age was removed as a covariate from the final model. With this value fixed, introducing age back to the model resulted in reduction of objective function of 6.463. The power value of age on CL/F was -0.912 $[(AGE/62)^{-0.912}]$ when CL/F was fixed at 0.687, and -1.06 $[(AGE/62)^{-1.06}]$ when both covariates were estimated (Table 14).

Table 14 Evaluation of Age Effect on GP CL/F in the Context of $CL_{creatinine}$

Model	Baseline Creatinine Clearance	Age	Change of OF
Model 14	Estimated as 0.687 (0.146)[1]	Not introduced	-
Model 20	Fixed at 0.687	Not introduced	0
Model 21	Fixed at 0.687	Estimated as 0.912 (0.371)[1]	-6.463
Model 13	Estimated as 0.502 (0.121)	Estimated as -1.06 (0.389)[1]	-7.544

[1] power value (RSE)
Source: Reviewer's analysis and summary from run014 lst, run20 lst, and run 21 lst

The CL/F of a subject 71 years of age (median of 4th quartile) is expected to be approximately 31% lower than a subject 50 years of age (median of 1st quartile) (Figure 9).

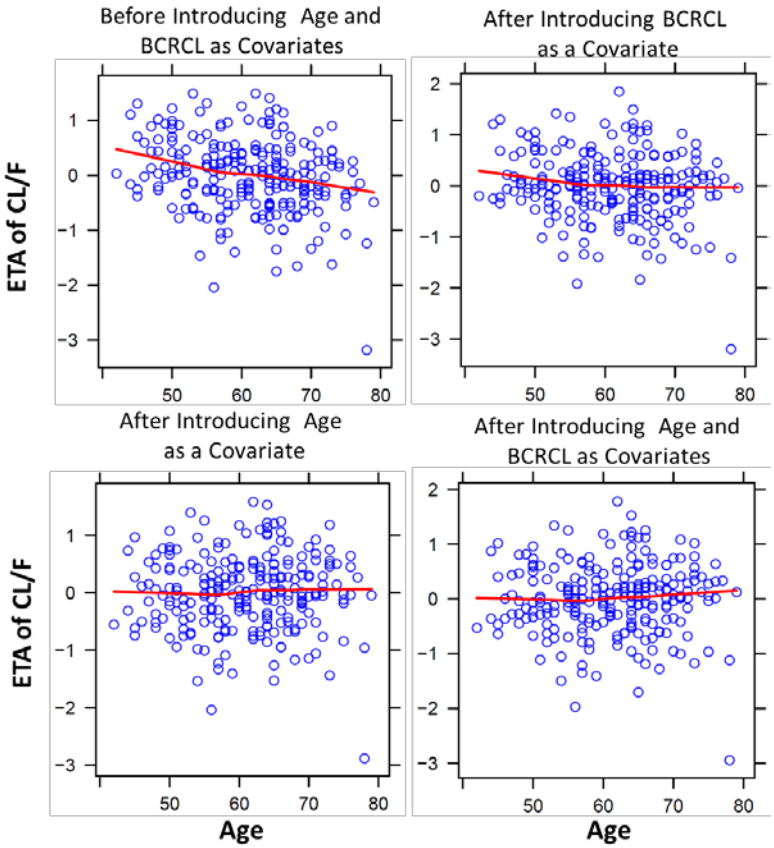


Figure 8 Scatter plot of inter-subject variability (ETA) of GP CL/F over age before and after introduction of BCRCL and/or age as covariates (reviewer's analysis).

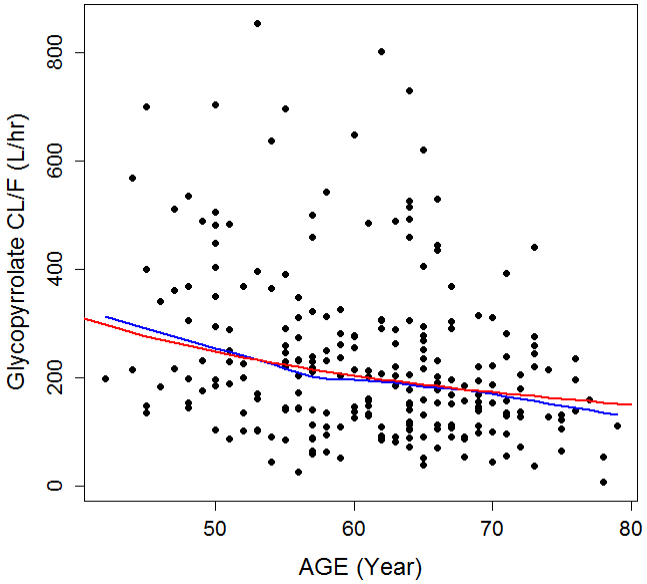


Figure 9 Scatter plot of glycopyrrolate CL/F over age. The red line represents $CL/F_{tv} \times (AGE/62)^{-1.06}$ prediction curve. The blue line represents local smoothing curve (reviewer's analysis).

- Co-administration of formoterol has a significant effect on of GP CL/F (Table 17). The model estimated that formoterol would reduce GP CL/F by 14%.

- To assess covariates' effect on formoterol CL/F

The Sponsor identified 2 significant covariates on formoterol CL/F: BCRCL and PVFEV1.

- BCRCL is a significant covariate of formoterol CL/F (Table 15). There is a clear trend of increasing of inter-subject variability on CL/F over increasing of BCRCL if this BCRCL is not introduced as a covariate (Figure 10). The CL/F of a subject with mild (CRCL=75 mL/min) and moderate (CRCL=45 mL/min) renal impairment is expected to be approximately 11% and 32% lower than a subject with normal renal function (CRCL=94 mL/min), respectively (Figure 11).

Table 15 Evaluation of Formoterol CL/F covariates from Reviewer's Model by Backward Elimination

Covariates on GP CL/F	Sponsor's Estimate[1]	Reviewer's Estimate[1]	Change of OF by Eliminating covariate
Baseline CRCL	0.502 (0.117)[2]	0.531 (0.0907)[2]	35.254
Post-Ventolin FEV1	0.303(0.112)[3]	0.357 (0.0933)[3]	26.021

[1] Typical value (SE)
[2] as the power of [baseline CRCL/94]
[3] as the power of [PVFEV1/1.52]
Source: Reviewer's analysis and summary from run003 lst and fofiout.txt

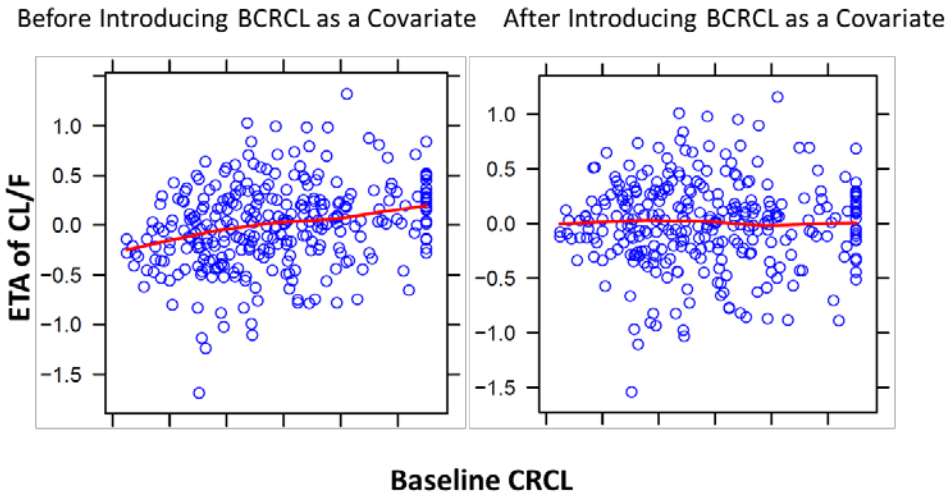


Figure 10 Scatter plot of inter-subject variability (ETA) of formoterol CL/F over baseline creatinine clearance before and after introduction of the BCRCL as a covariate (reviewer's analysis).

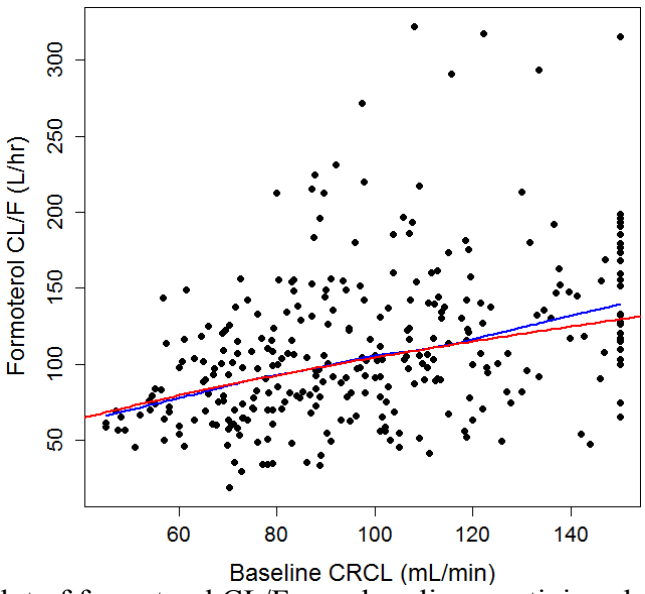


Figure 11 Scatter plot of formoterol CL/F over baseline creatinine clearance. The red line represents $CL/F_{tv} \times (CRCL/94)^{0.531}$ prediction curve. The blue line represents local smoothing curve (reviewer's analysis).

- PVFEV1 is a significant covariate of formoterol CL/F (Table 18). There is a clear trend of increasing of inter-subject variability on CL/F over increasing of PVFEV1 if this BCRCL is not introduced as a covariate (Figure 12). The power function of PVFEV1 on formoterol CL/F was 0.357 $[(PVFEV1/1.52)^{0.357}]$ (Figure 13). PVFEV1 values reflected COPD patients' response to albuterol, a short-acting β-adrenergic agonist. The clinical meaning and the mechanism of effect of PVFEV1 on formoterol CL/F is not clear.

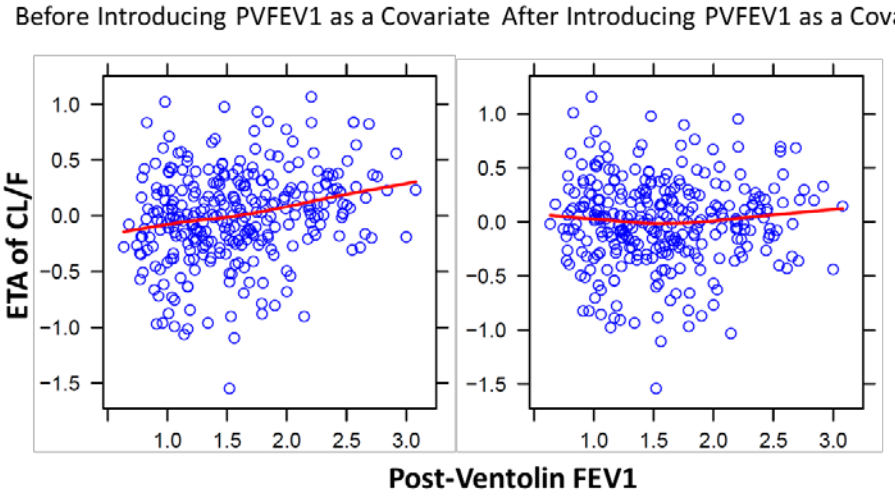


Figure 12 Scatter plot of inter-subject variability (ETA) of formoterol CL/F over baseline creatinine clearance before and after introduction of the BCRCL as a covariate (reviewer's analysis).

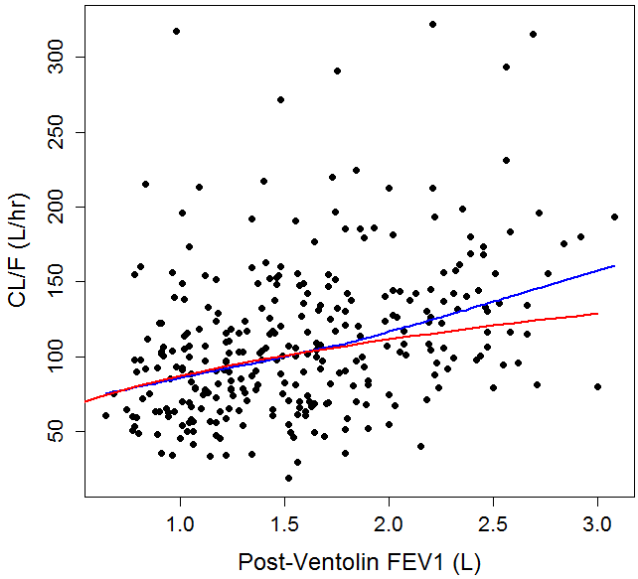


Figure 13 Scatter plot of formoterol CL/F over post-ventolin FEV1 values. The red line represents $CL/F_{tv} \times (PVFEV1/1.52)^{0.357}$ prediction curve. The blue line represents local smoothing curve (reviewer's analysis).

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SHEETAL S AGARWAL
03/14/2016

YUNZHAO REN
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03/14/2016

SURESH DODDAPANENI
03/14/2016

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA/BLA Number	208294	**SDN**	
Applicant	Pearl Therapeutics	**Submission Date**	06/25/2015
Generic Name	glycopyrrolate and formoterol	**Brand Name (Proposed)**	Bevespi Aerosphere
Drug Class	formoterol: Long-acting β2-adrenergic agonist glycopyrrolate: Long-acting muscarinic antagonist		
Indication (Proposed)	Long-term, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema		
Dosage Regimen	Two inhalations (i.e. 18 µg of glycopyrrolate [glycopyrronium bromide], equivalent to 14.4 µg of glycopyrronium, and 9.6 µg of formoterol fumarate) twice daily (BID)		
Dosage Form	Metered Dose Inhaler	**Route of Administration**	Oral
OCP Division	DCP2	**OND Division**	DPARP

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	Sheetal Agarwal, Ph.D., RAC	Suresh Doddapaneni, Ph.D.
Pharmacometrics	Anshu Marathe, Ph.D.	Yaning Wang, Ph.D.
Genomics		

Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	8/24/2015	**74-Day Letter Date**	9/4/2015
Review Due Date	3/21/2016	**PDUFA Goal Date**	4/25/2016

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

☐ Yes

☑ No

If yes explain

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type	**Count**	**Comment(s)**
In Vitro Studies		
☐ Metabolism Characterization		

☐ Transporter Characterization			
☐ Distribution			
☐ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☑ Relative Bioavailability		5	5 clinical pharmacology studies that also included assessments of relative BA of GFF MDI to monoproducts and relative BA of GFF MDI to the loose combination as secondary objectives will be reviewed by the Biopharm review team as this NDA was submitted before the new MOU was implemented. PT0030901 (counted as DDI study), PT003009 (counted as TQT study), PT003010 (counted as Race study), PT0031002 and PT003006 (counted as multiple dose PK studies)
☐ Bioequivalence			
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☑ Single Dose	1	PT010001
	☐ Multiple Dose		
Patients	☑ Single Dose	1	Dedicated studies + Pop PK Phase 3 Study PT0010801
	☑ Multiple Dose	2	Dedicated studies + Pop PK Phase 3 Studies PT003006, PT0031002
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☑ Race		1	Study PT003010 (Caucasians vs. Japanese)
☑ Sex			Pop PK Phase 3
☑ Geriatrics			
☐ Pediatrics			
☑ Hepatic Impairment			No studies, information borrowed from reference drugs and literature
☑ Renal Impairment			Pop PK Phase 3
☐ Genetics			
Extrinsic Factors			
☑ Effects on Primary Drug		1	DDI (Study PT0030901)
☐ Effects of Primary Drug			
Pharmacodynamics			
☐ Healthy Subjects			
☑ Patients		8	Dose ranging studies with the individual monotherapy and the combination product
Pharmacokinetics/Pharmacodynamics			
☐ Healthy Subjects			
☑ Patients		1	Pop PK Phase 3 (Pop PK report counted as 1 study)
☑ QT		1	Study PT003009 (Study review consulted to the TQT team for

		review, not counted in OCP review)			
Pharmacometrics					
☑ Population Pharmacokinetics		Effect of co-variates Phase 3			
☐ Exposure-Efficacy					
☐ Exposure-Safety					
Total Number of Studies		**In Vitro**		**In Vivo**	16
Total Number of Studies to be Reviewed					15

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☐No ☑N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☑Yes ☐No ☐N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☑Yes ☐No ☐N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	

Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ☐No ☐N/A	
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☑Yes ☐No ☐N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐Yes ☐No ☑N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☑Yes ☐No ☐N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	

Filing Memo

In this NDA, the sponsor, Pearl Therapeutics, seeks marketing approval for a fixed-dose combination of glycopyrrolate (glycopyrronium bromide) 9 µg and formoterol fumarate 4.8 µg (GFF MDI) to be administered via oral inhalation. The product is indicated for the long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema at the recommended dose of two inhalations (i.e. 18 µg of glycopyrrolate [glycopyrronium bromide], equivalent to 14.4 µg of glycopyrronium, and 9.6 µg of formoterol fumarate) twice daily (BID). The proposed brand name is Bevespi Aerosphere.

The individual components of GFF MDI are available commercially for multiple indications. Glycopyrronium is a LAMA which exerts its bronchodilatory effect via muscarinic receptors located on smooth muscle cells within the trachea and bronchi. Glycopyrronium is approved in many countries including the US in multiple formulations for different indications, including for COPD in the EU and Japan; however, it is not currently available as an orally-inhaled product in the US for COPD. Formoterol fumarate is a potent and selective LABA approved in many countries worldwide for use in asthma and COPD. It is available in the US as a dry powder inhaler (Foradil Aerolizer inhalation powder) and as an inhalation solution (Perforomist) for the maintenance treatment of bronchoconstriction in patients with COPD. Formoterol fumarate is also available in the US as a combination product, Symbicort Inhalation Aerosol, containing formoterol fumarate dihydrate and budesonide for the treatment of COPD.

The NDA is a 505(b)(2) NDA referencing approved NDAs 17558 for glycopyrrolate (Robinul) and 21929 (Symbicort) for formoterol furoate for some nonclinical and some human PK (for e.g., some ADME and special populations data) information. Most of the PK information included in the product label is with the combination product itself.

The sponsor has had several interactions with the Agency before submitting the NDA during which the Agency agreed with the sponsor's choice of the final dose to be carried into Phase 3, i.e., 18/9.6 µg of glycopyrrolate and formoterol fumarate resp. (b) (4) .

The proposed dosage form is a single pressurized metered dose inhaler (MDI) of 9/4.8 µg actuation strength of glycopyrrolate and formoterol fumarate resp. The 7.2 µg ex-actuator of glycopyrronium base is equivalent to 9.0 µg ex-actuator glycopyrrolate (i.e., glycopyrronium bromide) and 4.8 µg ex-actuator of formoterol fumarate is equivalent to (b) (4) The MDI is formulated (b) (4) with micronized glycopyrronium bromide and/or micronized formoterol fumarate cosuspended with a porous particle excipient in a hydrofluoroalkane (HFA) propellant. The table below includes the formulation contents as provided by the sponsor:

Table 1. Composition of GFF MDI, 7.2/4.8 µg per Actuation, 120 Inhalations

Component	Manufacturing Concentration (% w/w)	Quantity per Canister[1]	Metered dose (ex-valve)[2]	Delivered dose (ex-actuator)	Function	Reference to Standard
Glycopyrronium Bromide, micronized		(b) (4)	8.32 µg[3]	7.20 µg[3]	Active Ingredient	Pearl
Formoterol Fumarate, micronized			5.55 µg	4.80 µg	Active Ingredient	Pearl
Porous Particles				(b) (4)	Cosuspending Agent	Pearl
HFA-134a					Propellant	(b) (4)
						(b) (4)

[2] Formulation overages include drug overages of (b) (4)% to account for losses to the valve and actuator upon actuation. Refer to 3.2.P.2.2.2 Overages for details regarding formulation overages.

[3] Metered and delivered dose are expressed as the active moiety (i.e. glycopyrronium).

The clinical pharmacology package for the NDA includes single and multiple dose PK assessments, TQT assessment, DDI assessment between the 2 components when administered together and a pop PK assessment for effect of co-variates such as age, gender, creatinine clearance etc., on the PK of both the drugs. In addition 8 dose ranging studies with the combination product as well as the monotherapy products will be evaluated.

No filing issues have been identified with this NDA package and no clinical pharmacology related comments need to be included in the 74-day filing letter.

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

/s/

SHEETAL S AGARWAL
08/04/2015

SURESH DODDAPANENI
08/04/2015