AstraZeneca

Statistical Analysis Plan

Study Code	PT003014
Date	07 March 2017
NCT#	NCT02343458

A Randomized, Double-Blind, Chronic Dosing (24 Weeks), Placebo-Controlled, Parallel Group, Multi-Center Study to Assess the Efficacy and Safety of PT003, PT005, and PT001 in Subjects with Moderate to Very Severe COPD, Compared with Placebo

STATISTICAL ANALYSIS PLAN FOR STUDY PT003014

Study Number:	PT003014
Investigational Drug and Drug Number:	Glycopyrronium and Formoterol Fumarate Inhalation Aerosol (GFF MDI); PT003 Glycopyrronium Inhalation Aerosol (GP MDI); PT005 Formoterol Fumarate Inhalation Aerosol (FF MDI); PT001
Indication:	COPD
Dosage Form/Strength:	GFF MDI 14.4/9.6 µg ex-actuator BID GP MDI 14.4 µg ex-actuator BID FF MDI 9.6 µg ex-actuator BID

PT003014 Protocol Title: A Randomized, Double-Blind, Chronic Dosing (24 Weeks), Placebo-Controlled, Parallel Group, Multi-Center Study to Assess the Efficacy and Safety of PT003, PT005, and PT001 in Subjects with Moderate to Very Severe COPD, Compared with Placebo

Date of Issue: 07 Mar 2017

Version: Final Version

Signed Agreement on Statistical Analysis Plan

FINAL SIGN-OFF SIGNATURES

Primary Biostatistician: [redacted]

Peer Review Biostatistician: [redacted]

Approved by: [redacted]

Approved by: [redacted]

Approved by: [redacted]

Approved by:

[redacted]

Change Log			
Version No.	**Effective Date**	**Reason for the Change / Revision**	**Supersedes**

TABLE OF CONTENTS

List of Tables

List of Figures

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AR (1)	First-order autoregressive
AST	Aspartate aminotransferase
ATS	American Thoracic Society
AUC	Area under the curve
BDI	Baseline Dyspnea Index
BID	bis in die, twice daily
BMI	Body mass index
BMP	Basic metabolic panel
BP	Blood pressure
BPM	Beats per minute
BUN	Blood urea nitrogen
CAT	COPD Assessment Test
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMP	Comprehensive metabolic panel
COPD	Chronic obstructive pulmonary disease
CTCAE	Common Terminology Criteria for Adverse Events
DBP	Diastolic blood pressure
dL	Deciliter
DMC	Data monitoring committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eDiary	Electronic diary
e.g.	Exempli gratia, for example
ER	Emergency room
ERS	European Respiratory Society
EU	European Union
ex-actuator	Dose delivered from the actuator (i.e., mouthpiece) of the MDI
FEV_1	Forced expiratory volume in 1 second
FF MDI	Formoterol fumarate MDI
FVC	Forced vital capacity
GFF MDI	Glycopyrronium and formoterol fumarate MDI
GP MDI	Glycopyrronium MDI
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HCG	Human chorionic gonadotropin
HCRU	Healthcare resource utilization
HLT	High level term
HO	Health Outcome
HR	Heart rate
HFA	Hydrofluoroalkane

i.e.	Id est, that is
ICU	Intensive care unit
ICS	Inhaled corticosteroid
ITT	Intention-to-treat
IWRS	Interactive web response system
L	Liter
LABA	Long-acting beta agonist
LAMA	Long-acting antimuscarinic antagonists
MAR	Missing at random
MCAR	Missing completely at random
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCID	Minimum clinically important difference
MCV	Mean corpuscular volume
MDI	Metered dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
mmHg	Millimeters of mercury
MMRC	Modified Medical Research Council
MNAR	Missing not at random
ms	Millisecond
NHANES III	Third National Health and Nutrition Examination Survey
NMAR	Not missing at random
OTC	Over-the-counter
PCS	Potentially clinically significant
PEFR	Peak expiratory flow rate
PFT	Pulmonary function test
PP	Per Protocol
QD	Quaque die; once a day
QT	Time from electrocardiogram Q wave to the end of the T wave corresponding to electrical systole
QTcF	QT corrected using Fridericia's formula [$QT/(RR^{1/3})$]
RM	Repeated measures
RR	Time from electrocardiogram R wave to the next R wave corresponding to electrical systole
SABA	Short-acting beta agonist
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SGRQ	St. George Respiratory Questionnaire
SMQ	Standard MedDRA Query
SOP	Standard operating procedure
STDM	Study Data Tabulation Model
TDI	Transition Dyspnea Index

US	United States

Trademark Information

Trademarks Not Owned By Pearl

Ventolin

Atrovent

1. INTRODUCTION

Pearl Therapeutics, Inc., a member of the AstraZeneca group of companies (hereafter referred to as Pearl) is developing a combination product, Glycopyrronium and Formoterol Fumarate Inhalation Aerosol (hereafter referred to as GFF MDI), as a twice daily (BID) maintenance bronchodilator treatment in patients with Chronic Obstructive Pulmonary disease (COPD). Pearl is also developing the individual products, Glycopyrronium Inhalation Aerosol (hereafter referred to as GP MDI) and Formoterol Fumarate Inhalation Aerosol (hereafter referred to as FF MDI) as BID maintenance bronchodilator treatments in patients with COPD.

This Statistical Analysis Plan (SAP) outlines the statistical methods for the display, summary and analysis of data to be performed at the end of Study PT003014.

The SAP should be read in conjunction with the study Protocol and the electronic Case Report Forms (eCRFs) for this study. This version of the SAP has been developed using the PT003014-05 Protocol (Version 6.0, Amendment 5, dated Jan. 20, 2017) and the CRFs Revision 04 dated Sept. 4, 2015.

In this study, GFF MDI 14.4/9.6 µg represents a dose of 14.4 µg of glycopyrronium and 9.6 µg of formoterol fumarate and GP MDI 14.4 µg represents a dose of 14.4 µg of glycopyrronium. FF MDI 9.6 µg represents a dose of 9.6 µg of formoterol fumarate. GFF MDI, GP MDI, and FF MDI are administered twice daily (BID).

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

The overall objective of Study PT003014 is to assess the efficacy and safety of treatment with GFF MDI (14.4/9.6 µg ex-actuator, BID), FF MDI (9.6 µg ex-actuator, BID), and GP MDI (14.4 µg ex-actuator, BID) compared with each other and Placebo MDI over 24 weeks in subjects with moderate to very severe COPD.

2.1.1 Primary Objective

The primary objective is to compare the efficacy of treatment with GFF MDI, FF MDI, and GP MDI to Placebo MDI and to compare the efficacy of GFF MDI to its components on lung function using trough forced expiratory volume in 1 second (FEV_1) in subjects with moderate to very severe COPD.

2.1.2 Secondary Objectives

- To compare the effects of GFF MDI, FF MDI, GP MDI, and Placebo MDI on dyspnea using the Transition Dyspnea Index (TDI) focal score.
- To compare the effects of GFF MDI, FF MDI, GP MDI, and Placebo MDI on quality of life using the change in St. George Respiratory Questionnaire (SGRQ) score.

- To compare the effects of GFF MDI, FF MDI, GP MDI, and Placebo MDI on symptoms using the change in rescue Ventolin HFA use as an indirect measure of COPD symptom control.
- To determine the time to onset of action on Visit 4 (Day 1).

2.1.3 Other Efficacy Objectives

- To evaluate the effects of GFF MDI, FF MDI, GP MDI, and Placebo MDI on pulmonary function test (PFT) parameters.
- To assess the effects of GFF MDI, FF MDI, GP MDI, and Placebo MDI on COPD exacerbations.
- To evaluate the effect of treatments on nighttime awakenings, daytime and nighttime rescue Ventolin HFA use, breathlessness, cough, and sputum production as assessed by subjects' electronic diary (eDiary) entries.

2.1.4 Safety Objectives

- To assess the safety of GFF MDI, FF MDI, and GP MDI relative to Placebo MDI based on adverse events (AEs), vital sign measurements, electrocardiograms (ECGs), and clinical laboratory evaluations.

2.1.5 Healthcare Resource Utilization Objective

- To assess overall and COPD-specific healthcare resource utilization (HCRU) between treatment groups.

2.2 STUDY ENDPOINTS

2.2.1 Efficacy Endpoints

2.2.1.1 Primary Efficacy Endpoint

The primary endpoint differs by approach but is always based on morning pre-dose trough FEV_1.

The three different registration approaches will be called: 1) US/China, 2) Japan, and 3) EU/South Korea/Taiwan. The primary endpoint is identical for the US and China.

The Japan approach is for registration purposes based on the agreement with the Japan Health Authority for which endpoints assessed over weeks 12 to 24 are required.

The EU/South Korea/Taiwan approach is for endpoints assessed over 24 weeks.

The delineation of multiplicity controls for the primary and secondary measures is separated by approach and detailed in Section 6.4.4.

All inferential results will be based on analyses using the Intent-to-Treat (ITT) Population unless otherwise noted. In addition to the ITT analysis, symptom endpoints will also be analyzed using the Symptomatic Population. The primary analyses of rescue Ventolin usage will be conducted in the Rescue Ventolin User Population (refer to Section 5.1).

Primary Endpoint (US/China)

- The primary endpoint will be the change from baseline in morning pre-dose trough FEV_1 at Week 24 of treatment.

Primary Endpoint (Japan)

- The primary endpoint will be the change from baseline in morning pre-dose trough FEV_1 over Weeks 12 to 24 of treatment.

Primary Endpoint (EU/ South Korea/Taiwan)

- The primary endpoint will be the change from baseline in morning pre-dose trough FEV_1 over 24 weeks of treatment.

2.2.1.2 Secondary Efficacy Endpoints

- TDI score over 24 weeks (US/China and EU/South Korea/Taiwan approaches) and over Weeks 12 to 24 (Japan approach)
- TDI score over 24 weeks (US/China and EU/South Korea/Taiwan approaches) and over Weeks 12 to 24 (Japan approach) in the Symptomatic Population
- Change from baseline in morning pre-dose trough FEV_1 over 24 weeks (US/China approach)
- Peak change from baseline in FEV_1 within 2 hours post-dosing at Week 24 (US/China approach), over 24 weeks (EU/South Korea/Taiwan approach), and over Weeks 12 to 24 (Japan approach)
- Change from baseline in SGRQ total score at Week 24 (US/China approach) and over Weeks 12 to 24 (Japan and EU/South Korea/Taiwan approaches)
- Change from baseline in SGRQ total score at Week 24 (US/China approach and over Weeks 12 to 24 (EU/South Korea/Taiwan and Japan approaches) in the Symptomatic Population
- Change from baseline in average daily rescue Ventolin (albuterol sulfate) HFA use over 24 weeks (all approaches) in the Rescue Ventolin User Population
- Time to onset of action on Day 1 (all approaches)

2.2.1.3 Other Efficacy Endpoints

Day 1 Assessments

- Change from baseline at each post-dose time point in FEV_1, forced vital capacity (FVC), and FEV_1 AUC_{0-2}

- Proportion of subjects achieving an improvement from baseline in FEV_1 using different thresholds (i.e., ≥10%, ≥12%, ≥100 mL, ≥200 mL, and ≥12% and ≥200 mL)

Assessments Over 24 Weeks (Unless Otherwise Stated)

- Rate of moderate or severe COPD exacerbations
- Time to the first moderate or severe COPD exacerbation
- Rate of all COPD exacerbations
- Time to the first COPD exacerbation of any severity
- Time to treatment failure
- Time to first clinically important deterioration (CID)
- Time to first sustained CID
- Change from baseline in morning pre-dose trough for FVC as well as FEV_1 AUC_{0-2} at each post-randomization visit, over 24 weeks, and over Weeks 12-24
- Peak change from baseline in FEV_1 and FVC, through 2 hours post-dose over 24 weeks, over Weeks 12-24, and at each post-randomization visit
- Percentage of days with 'no rescue Ventolin (albuterol sulfate) HFA use'
- Change from baseline in mean daily total symptom score as well as each individual symptom (cough, shortness of breath, sputum volume, nighttime awakenings and rescue Ventolin HFA use), the mean morning total and individual symptom scores, and the mean evening total and individual symptom scores over 24 weeks, over Weeks 12-24, and over each 4-week interval of the 24-week Treatment Period
- TDI focal score at each post-randomization visit
- Individual components of the TDI: functional impairment, magnitude of task, and magnitude of effort over 24 weeks, over Weeks 12-24, and at each post-randomization visit
- Percentage of subjects achieving a minimal clinically important difference (MCID) threshold of ≥1 unit on average in TDI focal score over 24 weeks and separately over Weeks 12-24
- Changes from baseline at each post-randomization visit for SGRQ total score
- Change in individual domain scores of SGRQ: Symptoms, Activity, and Impacts over Weeks 12-24, and at each post-randomization visit
- Percentage of subjects achieving an MCID threshold of ≥4 units on average in SGRQ total score over Weeks 12-24 and separately at Week 24

2.2.1.4 Healthcare Resource Utilization Endpoints

Healthcare resource utilization (HCRU) endpoints will include the following: the number of days missed from work, and COPD-related and non-COPD related telephone calls and visits to health care providers, Emergency Room (ER) visits, and hospitalizations including days in

hospital, days in Intensive Care Units (ICUs), days in Coronary Care Units (CCUs), and subject intubation events.

2.2.2 Safety Endpoints

The safety endpoints include:

- AEs
- 12-Lead ECG: change from baseline for heart rate, PR interval, QRS axis, QRS interval, QT interval, and QTcF (Fridericia Corrected QT) interval
- Clinical laboratory testing
- Vital sign measurements

3. STUDY DESIGN AND ANALYTICAL CONSIDERATIONS

3.1 Study Design

Study PT003014 is a multicenter, randomized, double-blind, parallel group, chronic dosing (24 weeks), placebo-controlled study to assess the efficacy and safety of GFF MDI (14.4/9.6 µg ex-actuator, BID), GP MDI (14.4 µg ex-actuator, BID), and FF MDI (9.6 µg ex-actuator, BID) compared with Placebo MDI in subjects with moderate to very severe COPD.

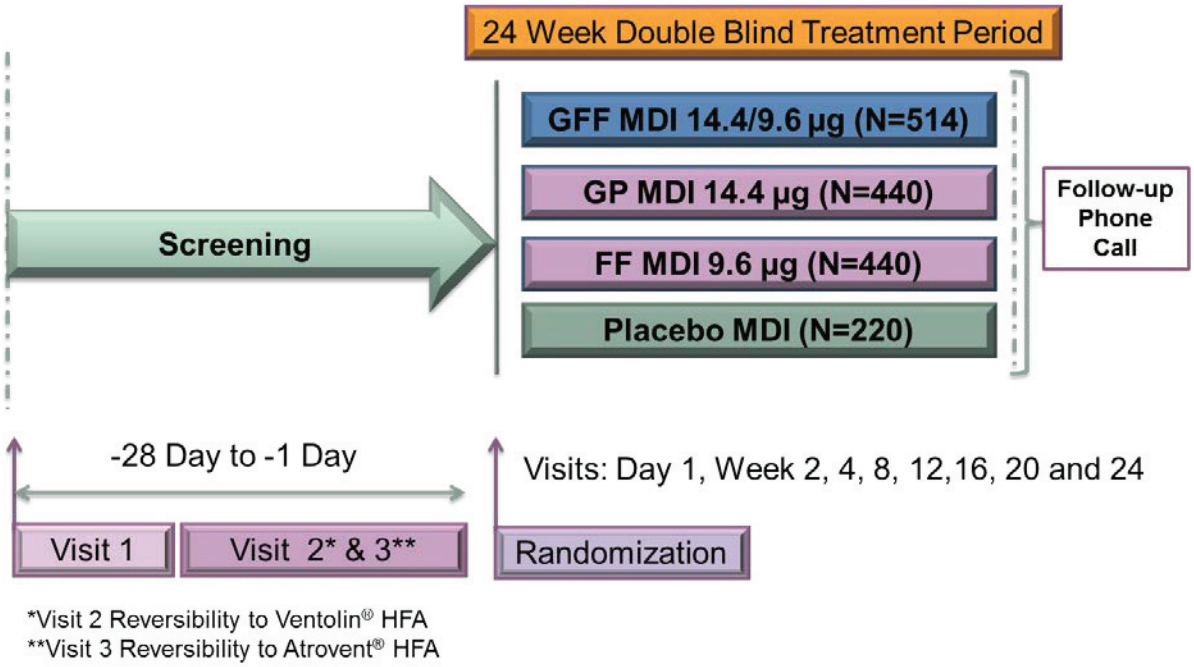
3.1.1 Overall Study Design and Plan

Study PT003014 will be conducted at approximately 180 sites, contributing approximately 10 subjects per site. Across these sites, it is planned that 1614 subjects with moderate to very severe COPD will be randomized into the study to provide approximately 1300 subjects to complete the study (see Study Flow Diagram Figure 1). Subjects will be randomized in a 7:6:6:3 scheme [GFF MDI, FF MDI, GP MDI, and Placebo MDI]. Approximately 514 subjects will be enrolled into the GFF MDI treatment group, 440 subjects each into the FF MDI and GP MDI treatment groups and approximately 220 subjects will be enrolled in the Placebo MDI treatment group.

Randomization will be stratified by reversibility to Ventolin® (albuterol sulfate) (yes or no) and by disease severity (moderate vs. severe or very severe) to ensure a distribution of subjects in a 7:6:6:3 (GFF MDI:FF MDI:GP MDI:Placebo MDI) ratio within each stratum.

The entire study period is scheduled to take a maximum of 30 weeks for each individual subject (see Figure 1). The study is anticipated to run for approximately 18 months and should not exceed 24 months.

Figure 1 PT003014 Study Flow Diagram



Section 4 of the Protocol provides details on study design and plan. The Schedule of Events for the study is shown in Table 1.

Table 1 Schedule of Events

Procedures	Screening Period			Treatment Period									Follow-Up
	Visit 1	Visit 2	Visit 3	Visit 4 Day 1	Visit 5 Week 2	Visit 6 Week 4	Visit 7 Week 8	Visit 8 Week 12	Visit 9 Week 16	Visit 10 Week 20	Visit 11 Week 24	Discon[§] Visit	14 days Post-Dose
Study Day/Week[a]	Day -28 to -9	Day -21 to -2	Day -19 to -1	Day 1	Wk 2 ±2Days[a]	Wk 4 ±2Days[a]	Wk 8 ±2Days[a]	Wk 12 ±2Days[a]	Wk 16 ±2Days[a]	Wk 20 ±2Days[a]	Wk 24 ±2Days[a]		
Obtain Informed Consent	X												
Review Incl/Excl Criteria	X	X	X	X									
Verify Continued Eligibility					X	X	X	X	X	X	X		
Reversibility[b]		X	X										
Demographics & Medical/Surgical History	X	X	X	X									
Smoking Status	X	X	X	X	X	X	X	X	X	X	X		
COPD Assessment Test (CAT)[c]		X											
MMRC[c]		X											
Prior/Concomitant Medications[d]	X	X	X	X	X	X	X	X	X	X	X	X	X
Spirometry[e]	X	X	X	X	X	X	X	X	X	X	X		
Physical Examination[f]	X										X	X	
Vital Signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	
12-Lead ECG[h]	X	X	X	X	X	X		X			X	X	
Pregnancy Test[i]	X							X			X	X	
Clinical Laboratory Testing[i]	X			X		X		X			X	X	
Chest X-ray or CT[j]	X												
Adjust COPD Medications[k]	X										X	X	
COPD Exacerbations and Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X
Inhalation Device Training[l]	X												
Study Drug Dispensing/Collection	X[m]			X		X	X	X	X	X	X	X	

Procedures	Screening Period			Treatment Period									Follow-Up
	Visit 1	Visit 2	Visit 3	Visit 4 Day 1	Visit 5 Week 2	Visit 6 Week 4	Visit 7 Week 8	Visit 8 Week 12	Visit 9 Week 16	Visit 10 Week 20	Visit 11 Week 24	Discon[§] Visit	14 days Post-Dose
Study Drug Administration [n]				X	X	X	X	X	X	X	X		
BDI/TDI [o]				X		X	X	X	X	X	X	X	
SGRQ [o]				X				X	X	X	X	X	
eDiary (electronic diary) Training [p]	X												
Review of eDiary [q]		X	X	X	X	X	X	X	X	X	X	X	
Review/Record Dose Indicator Reading [r]				X	X	X	X	X	X	X	X	X	
HCRU [s]					X	X	X	X	X	X	X	X	
Telephone Contact [t]		X	X	X	X	X	X	X	X	X	X		X

a. Scheduling Visits: The maximum Screening Period is 28 days; the earliest a subject can be randomized from Visit 1 Date is 9 Days (7 days for LABA washout plus 1 day between Visit 2 and 3 plus 1 day between Visit 3 and Visit 4) or 16 days if subject is washing off of tiotropium; Site should make every effort to maintain subjects within the scheduled visit window. Subjects who fall outside the visit window will be placed in the appropriate visit window at the next scheduled visit.

b. Subjects will be tested for reversibility to albuterol (Ventolin HFA) at Visit 2 and reversibility to Atrovent HFA at Visit 3; Refer to Protocol Section 7.1.1 for additional details.

c. CAT and MMRC will be used to characterize the subject population only and not to be used to determine eligibility to participate in the study.

d. At all visits beyond Visit 1 (Screening), note time of last dose of short-acting bronchodilator and other COPD medications (if <6 hours, visit should be rescheduled).

e. Refer to Protocol Section 7.1 for spirometry assessments and specific time points to be performed at each treatment visit.

f. Includes evaluation weight at Visit 1 (Screening) and Visit 11 (Final Visit) and height at Visit 1 (Screening) only.

g. Refer to Protocol Section 7.2.2 for vital signs assessments and specific time points to be performed at each treatment visit. Weight will be obtained at Visit 1 (screening) and Visit 11 (Final Visit) only.

h. Refer to Protocol Section 7.2.3 for ECG assessments and specific time points to be performed at each treatment visit.

i. Refer to Protocol Section 7.2.4 for clinical laboratory assessments (hematology, chemistry and urinalysis) and specific time points to be performed at each treatment visit. Serum pregnancy test will be performed at Visit 1 (Screening) and Visit 11 (Week 24) and a urine pregnancy test will be done at Visit 8 (Week 12).

j. Obtain a new Chest X-ray if Chest X-ray or CT performed within the 6 months prior to Visit 1 (Screening) is not available except in countries with restrictive radiology assessment practice (e.g., Germany) where only subjects who have had an x-ray or CT scan (thorax) performed outside of the study in the last 6 months are allowed to be enrolled. Alternatively, in these countries, an MRI should be used instead of a CT scan or x-ray as per local practice assessment.

k. At Visit 1 (Screening), stop prohibited COPD medications and change COPD medications as specified in Protocol Section 5.4 (i.e., Sponsor-provided Atrovent HFA with or without ICS). At the end of Visit 11, return subject to pre-study or other appropriate inhaled maintenance COPD.

l. Sites may use sponsor provided Atrovent HFA or Ventolin HFA to train subjects on the use of MDIs.

m. Sponsor provided Atrovent HFA or Ventolin HFA is dispensed only after a subject is determined to be eligible to proceed to Visit 2 (i.e., only if a subject meets COPD definition following spirometry assessments at screening).

n. In clinic dosing time is recorded as time of the second puff/inhalation. The in clinic dosing time should be timed to be within 12±2 hours of the prior evening dosing time.

o. When BDI/TDI and SGRQ are obtained at the same visit, it is recommended that the BDI/TDI should be collected first, followed immediately by the SGRQ. The BDI/TDI and SGRQ should be completed prior to any other visit procedures.

p. Issue and train subjects on eDiary use only after a subject is determined to qualify to proceed to Visit 2.

q. Refer to Protocol Section 7.1.3 for details of electronic diary review.

r. Refer to Protocol Section 7.1.6 for details and instructions on recording dose indicator readings.

s. Refer to Protocol Section 7.3 for details on HCRU collection.

t. It is recommended that sites call the subject on the day before a scheduled visit and remind the subject of the expectations for the upcoming visit (e.g., Dosing appropriately the day before the visit, withholding COPD medications the morning of the scheduled visit, bring all study drug and eDiary to the visit, etc.).

§ - Illustrates the procedures that may be required at a premature discontinuation visit. N**ote:** Premature discontinuation visits will be captured as unscheduled visits (Refer to Protocol Section 8.7).

Note: When data collection time-points are concurrent, it is recommended that variables be collected in the following order: BDI/TDI, SGRQ, vital signs, ECG, clinical laboratory assessments, and spirometry.

Table 2 Timed Assessments During Treatment Period (Visits 4-11)

	Pre-dosing		Post-dosing				
Clinical Variable[a]	**-1 hour**	**-30 minutes**	**5 minutes**	**15 minutes**	**30 minutes**	**1 hour**	**2 hours**
BDI/TDI[b]	X[†]						
SGRQ[b]	X[†]						
Review of Electronic Diary Data	X[†]						
Vital Signs[c]	X				X		X
12- Lead ECG[d]	X[d]				X		X
Clinical Laboratory Testing[e]	X[†]						
Spirometry (FEV_1, FVC, PEFR)[f]	X[g]	X[g]	X[h]	X	X	X	X
Study Drug Collection[i]	X[†]						
Record Dose Indicator Reading[j]		X[†]					
Study Drug Dispensing[k]							X

a. In clinic dosing time is recorded as time of the second puff. Safety assessments (vital signs, and ECG) should be started approximately 5 - 10 minutes ahead of the specified time point to ensure that spirometry for FEV_1, FVC and PEFR assessments will be conducted as close to the specified time points as possible (i.e., FEV_1, FVC, and PEFR assessments need to be conducted within ± 15 minutes of specified time prior to study drug administration; ± 5 minutes of specified time for the first 60 minutes post study drug administration; ± 15 minutes of specified time point for assessments obtained thereafter).

b. When BDI/TDI and SGRQ are obtained at the same visit, it is recommended that the BDI/TDI will be collected first, followed immediately by the SGRQ. The BDI/TDI and SGRQ should be completed prior to any other visit procedures. The questionnaires must be completed prior to any other visit procedures. BDI/TDI will be obtained at all visits except Visit 5 (Week 2). SGRQ will be obtained at Visit 4 (Day 1), Visit 8 (Week 12), Visit 9 (Week 16), Visit 10 (Week 20), Visit 11 (Week 24) or Premature Discontinuation Visit.

c. At Visit 4 only, pre-dose vital signs will be collected twice at least five minutes apart. Vital signs will be obtained within one hour pre-dosing and at 30 minutes post study drug administration at all treatment visits. At all visits post randomization except Visit 6 (Week 4) and Visit 9 (Week 16) only, vital signs will be obtained at 2 hours post study drug dosing. Temperature will be obtained pre-dose; no further temperature assessments are required unless clinically indicated.

d. At Visit 4 only, pre-dose ECG will be collected twice at least five minutes apart. An ECG will be obtained once pre-dose and at 30 minutes and 2 hours post-dose at Visit 4 (Day 1), Visit 5 (Week 2) , Visit 8 (Week 12), and Visit 11 (Week 24). At Visit 6 (Week 4), only a pre-dose ECG will be obtained.

e. Clinical laboratory tests (hematology, chemistry and urinalysis) will be obtained prior to dosing at Visit 4 (Day 1), Visit 6 (Week 4), Visit 8 (Week 12) and Visit 11 (Week 24) only. Serum pregnancy test will be performed at Visit 11 (Week 24) and a urine pregnancy test will be done at Visit 8 (Week 12).

f. Post-dose spirometry assessment will be obtained at all visits except Visit 6 (Week 4) and Visit 9 (Week 16).

g. To be randomized, all subjects must meet FEV_1 Baseline Stability criteria. Refer to Protocol Section 7.1.2 for additional details.

h. The 5-minute post-dose spirometry assessment will be obtained at Visit 4 (Treatment Day 1) only.

i. At the start of each treatment visit, subject must withhold all COPD medications, prior to the study visit. Short-acting bronchodilators, rescue Ventolin HFA should be withheld for at least 6 hours prior to start of test day procedures.

j. Site staff will record the dose indicator reading at each visit. The dose indicator reading recorded by the site staff will be dose indicator count observed prior to subject dosing. For new MDIs the recorded count will be the count following the priming of the device but before the subject dose. Refer to Protocol Section 7.1.6 for more details

k. Dispense study drug for at home use to subject following completion of all post-dose assessments. Refer to Protocol Section 6.6 for Instructions for Preparation of Treatments for Administration and Dispensing

† This is not a timed assessment. Sites should plan to perform these activities so as not to interfere with collection of timed assessments such as spirometry.

Note: Where data collection time-points are concurrent, variables must be collected in the following order: BDI/TDI, SGRQ, vital signs, ECG, clinical laboratory assessments, and spirometry.

Inclusion criteria for the study are listed in Section 5.1 of Protocol PT003014. Subjects eligible for enrollment in the study must meet all of the inclusion criteria.

Exclusion criteria for the study are listed in Section 5.2 of Protocol PT003014. Subjects meeting any of the exclusion criteria are to be excluded from the study.

3.1.2 Prior, Concomitant, Post-Treatment, Prohibited Medications, and Other Restrictions

All concomitant medications taken during the study will be recorded on the Concomitant Medications eCRF page with indication, dose, dose regimen, and dates of drug administration. Medications are considered concomitant if they were reported as being taken at any point from the start of randomized study medication to the date of Visit 11, the date of the Discontinuation Visit, or the date of the last in-clinic or diary data. Medications with an onset date of the date of Visit 11, the date of a Discontinuation Visit, or the last in-clinic or diary data collection or after will not be considered concomitant, but will be considered post-treatment medications.

Prohibited medications are identified in Section 5.4 of Protocol PT003014. Other restrictions are identified in Section 5.5 of Protocol PT003014.

3.2 Treatment Blinding and Randomization

The subject, clinical site personnel and Pearl will be unaware of the treatment assigned to a subject when the treatment is GFF MDI, GP MDI, FF MDI, or Placebo MDI. If a subject is assigned GFF MDI, GP MDI, FF MDI, or Placebo MDI, it will not be possible to differentiate between these 4 treatments since they will be identical in all aspects.

Subjects will be randomly assigned to one of the 4 treatment arms using an interactive web-response system (IWRS) in a 7:6:6:3 ratio with less subjects being assigned to the Placebo MDI arm and more subjects being assigned to the GFF MDI arm. Randomization will be stratified by disease severity (moderate vs. severe or very severe) and reversibility to Ventolin (albuterol sulfate) HFA (yes or no). Center will not be used as a stratification factor given the impracticality of enrolling a large enough number of subjects to ensure balance in each of the four strata formed by combining disease severity and reversibility.

3.3 Hypothesis Testing

For the primary comparisons, the null hypothesis for each pairwise comparison will be that the mean test treatment effect is equal to that of Placebo MDI (or an individual component); the alternative hypothesis is then that the test treatment effect and that of Placebo MDI (or an individual component) are not equal. P-values will thus be reported as two-sided.

The primary null (H_0) and alternative (H_1) hypotheses with μ representing the mean are:

- H_0: $\mu_{FF} = \mu_{placebo}$
  H_1: $\mu_{FF} \neq \mu_{placebo}$

- H_0: $\mu_{GP} = \mu_{placebo}$
  H_1: $\mu_{GP} \neq \mu_{placebo}$
- H_0: $\mu_{GFF} = \mu_{placebo}$
  H_1: $\mu_{GFF} \neq \mu_{placebo}$
- H_0: $\mu_{GFF} = \mu_{FF}$
  H_1: $\mu_{GFF} \neq \mu_{FF}$
- H_0: $\mu_{GFF} = \mu_{GP}$
  H_1: $\mu_{GFF} \neq \mu_{GP}$

Secondary and other efficacy analyses will involve the above hypotheses applied to secondary efficacy endpoints.

3.4 Interim Analysis

Interim analyses for the purpose of evaluation of efficacy are not planned for this study. However, as specified in the Data Monitoring Committee (DMC) Charter for this study, the DMC members will be provided pre-specified safety analyses at pre-determined intervals which will use semi-blinded treatment codes (A, B, C, and Placebo MDI). As such, the DMC may require the unblinding key if they feel such actions are necessary to evaluate the safety of study subjects.

3.5 Sample Size

It is estimated that a sample size of 1614 subjects (514 subjects in the GFF MDI arm, 440 subjects each in the GP MDI and FF MDI arms, and 220 subjects in the Placebo MDI arm) will provide approximately 91% power with Type I error controlled at a two-sided alpha level of 0.05 to detect differences for all five primary comparisons if the true differences from placebo are 90 mL for FF MDI, 100 mL for GP MDI, and 150 mL for GFF MDI resulting in corresponding differences between GFF MDI and FF MDI and GP MDI of 60 mL and 50 mL, respectively, in morning pre-dose trough FEV_1 at Week 24, approximately 99% power for morning pre-dose trough FEV_1 over 24 weeks and approximately 99% power for morning pre-dose trough FEV_1 over Weeks 12 to 24. Assumptions regarding variability for the primary endpoint are based on Pearl's experience with Phase IIb clinical studies and on published data for within-subject variation (D'Urzo, 2001, van Noord , 2005; Maesen, 1995) and between-subject variation (Dahl, 2001, Calverley, 2003). A composite value standard deviation (SD) of 200 mL has been assumed. A within-subject correlation structure has been assumed combining a block diagonal structure induced by using subject as a random effect with an AR (1) structure with ρ=0.5. Differential dropout rates have been assumed with increased dropout due to lack of efficacy ranging up to 25% in the Placebo MDI arm. Under these assumptions, based on this sample size, the study will have approximately 99% power with Type I error controlled at a two-sided alpha level of 0.05 to detect differences between FF MDI and Placebo MDI and between GP MDI and Placebo MDI in morning pre-dose trough FEV_1 at Week 24, over 24 weeks or over Weeks 12-24.

4. DATA AND ANALYTICAL QUALITY ASSURANCE

The overall quality assurance procedures for the study data, statistical programming and analyses are described in Standard Operating Procedures (SOPs) of Everest Clinical Research (hereafter referred to as Everest). Detailed data management procedures are documented in the study Data Management Plan, Data Validation Check Specifications, and Integrated Safety Data Review Plan. Detailed statistical and programming quality control and quality assurance procedures are documented in the Statistical Analysis and Programming QC/QA Plan.

Transfer of PFT data from the central PFT laboratory (iCardiac Technologies, Inc.) to Everest will be defined in the iCardiac Technologies DMP (Data Management Plan), and data handling rules related to this data are included in Appendix 1 of this SAP. The quality of all PFTs obtained at each timepoint will be graded independently at iCardiac Technologies by qualified personnel. Quality grading assessments will be based on ATS/ERS criteria and will be included in data transfers.

5. ANALYSIS POPULATIONS

5.1 Population Definitions

5.1.1 Intent-to-Treat (ITT) Population

The **Intent-To-Treat (ITT) Population** is defined as all subjects who are randomized to treatment and receive at least one dose of the study treatment. Subjects will be analyzed according to the treatment they were assigned to at randomization. (Note that a subject who used a study treatment, but took less than one full dose of treatment will qualify for this population.)

5.1.2 Per Protocol (PP) Population

The **Per Protocol (PP) Population** is a subset of the ITT Population defined as all subjects with post-randomization data obtained prior to a major protocol deviation. Data obtained after any major protocol deviation will be excluded. Since receiving the wrong treatment will be a major protocol deviation, subjects in the PP Population will be analyzed as randomized (which for this population is identical to analysis by the actual treatment received). Post-randomization visits will be excluded from the Per Protocol set if there is no evidence in the e-diary that the as-randomized study medication was used the evening prior to the scheduled visit.

Any evaluability criteria with a potential impact on efficacy results will be identified in a blinded fashion aided by a review of data listings prior to database lock. Major protocol deviations (protocol violations), therefore, can result in exclusion of all data from a particular subject from the PP Population or require exclusion of data from a specific timepoint and/or subsequent timepoints for an endpoint. Protocol deviations for exclusion of data from the ITT Population will be agreed by the study team and documented prior to database lock.

Reasons for exclusion from the PP Population will documented in the Blinded Data Review meeting minutes prior to database lock; these minutes will be included in an appendix to the Clinical Study Report.

5.1.3 Symptomatic Population

The **Symptomatic Population** is defined as all subjects in the ITT Population with CAT scores of ≥15 at Visit 4.

5.1.4 Rescue Ventolin User Population

Regional differences in rescue Ventolin HFA usage are expected with some regions using virtually no rescue medication at study entry. Therefore, the **Rescue Ventolin User (RVU) Population** is defined as all subjects in the ITT Population with average baseline Rescue Ventolin use of ≥ 1 puff/day.

5.1.5 Safety Population

The **Safety Population** is similar to the ITT Population (all subjects who are randomized to treatment and receive at least one dose of the study treatment). However, subjects will be analyzed according to treatment received rather than randomized. If a subject received more than one randomized treatment, they will be analyzed and included in summaries according to the treatment they received the most. (Note that a subject who used a study treatment, but took less than one full dose of treatment will qualify for this population). **Note:** The statement that a subject had no adverse events also constitutes a safety assessment.

5.2 Populations for Primary and Sensitivity Analyses

Demographics will be summarized for the ITT, PP, Symptomatic, Rescue Ventolin User and Safety Populations and the Non-Randomized analysis set. The Safety Population will be used to summarize safety and healthcare resource utilization. The Safety and Rescue Ventolin User Populations will be used to summarize extent of exposure. Efficacy analyses will be performed for the ITT Population. The PP Population will be used to perform sensitivity analyses of trough FEV_1 only. The Symptomatic Population will be used for the efficacy analysis of symptom endpoints. Rescue medication endpoints will be analyzed with the Rescue Ventolin User Population.

5.3 Populations for Subjects with Multiple Subject IDs

Every effort will be made to prevent subjects from participating at more than 1 site within the study or in more than one Pearl study. However, in the event that there are subjects with multiple subject identification numbers (IDs) who participated at more than 1 site within the study or in more than one Pearl study, the following rules will be used to determine into which efficacy and safety population analyses the collected data will be included.

In the event that there are subjects with multiple subject identification numbers (IDs) who participated at more than 1 site within Study PT003014, but who did overlap in Investigational Product (IP) exposure, these subjects will be included in the All Subjects Randomized tabulations and listings only. The safety of these subjects will be summarized separately in a narrative in the Clinical Study Report and identified in the CSR as not reported in the analysis output.

In the event that there are subjects with multiple IDs who participated at more than 1 site within Study PT003014, but who did not overlap in treatment exposure; these subjects will be included in the ITT, Safety, RVU, and PP Populations for the treatment received at the first site/exposure and only in the Safety Population for the treatment received at the second site/exposure. The subjects' data from the second or higher exposure(s) will be excluded from the ITT, RVU, and PP Populations as intra-subject correlation (i.e., subject in the same study more than once) would not be modeled correctly in statistical analyses.

For subjects who did not have overlap in IP exposure and participated in more than one Pearl efficacy/study, the subjects' data will be included in the ITT, PP, RVU, and Safety Populations for the first exposure. For the second and higher exposure(s), the subjects' data will be included in the ITT, RVU, and Safety Populations and excluded from the PP Population.

Table 3 summarizes the approach for handling data analysis for these subjects by Pearl.

Table 3 Approach for Handling Data Analysis for Subjects Who Participated More Than Once in Study PT003014 at Different Sites or in More than One Pearl Efficacy/Safety Study

Subject Type	Analysis Population Inclusion for Subject Data	
	First Study Exposure	**Second or Higher Study Exposure**
Overlap in IP Exposure	Exclude data from ITT, PP, Symptomatic, RVU, and Safety Populations	Exclude data from ITT, PP, Symptomatic, RVU, and Safety Populations
No overlap in IP exposure but participated in Study PT003014 more than once	Include data in ITT, PP, Symptomatic, RVU, and Safety Populations	Include data in Safety Population and exclude data from ITT, PP, Symptomatic, and RVU Populations
No overlap in IP exposure but participated in more than one Pearl efficacy/safety study	Include data in ITT, PP, Symptomatic, RVU, and Safety Populations	Include data in ITT, Symptomatic, RVU, and Safety Populations and exclude data from PP Population

Abbreviations: IP=Investigational Product; ITT=Intent-to-Treat, PP=Per Protocol, RVU=Rescue Ventolin User

5.4 China and Asia Populations

The **China Population** is defined as all subjects enrolled in sites in China.

The **Asia Population** is defined as all subjects enrolled in sites located in Japan, China, South Korea, and Taiwan.

Corresponding ITT, PP, Symptomatic, RVU and Safety analysis populations, as well as other relevant analysis sets, for the China and Asia Populations are defined as described in Section 5.1 and restricted to the China/Asia Populations. China/Asia-specific primary and sensitivity

analysis populations are defined as described in Section 5.2, specifically for the US/China approach, and restricted to the China/Asia Populations.

6. STATISTICAL ANALYSIS

All data collected on eCRFs and contributing to the analysis will be provided in listings, except for data collected only for confirmation of study entry criteria and for study management purposes. Data for all subjects who are randomized will be included in the subject data listings. Data for non-randomized subjects will be listed where available.

All safety and efficacy parameters will be summarized by treatment (unless specified otherwise). Summary statistics for safety will be provided for the Safety Population.

Continuous variables will be summarized with descriptive statistics (the number of non-missing values, mean, standard deviation, median, minimum, and maximum). Additionally, the 25th and 75th percentiles will be presented when appropriate based on historical knowledge of the distribution of underlying data.

Categorical variables will be summarized with frequency counts and percentages (where appropriate).

6.1 General Data Handling Rules and Definitions

6.1.1 Data Exclusion and Missing Data Imputation

The exclusion of data from the PP Population has been discussed in Section 5.1. Unless excluded as specified in Section 5.1, all lung function assessments analyzed that have at least one effort that meets ATS/ERS criteria for acceptability will be considered acceptable and contribute to the post-dose assessments for a population. If the PFT assessments at a specific timepoint were deemed to be unacceptable quality, i.e., none of the efforts met ATS/ERS criteria for acceptability, the PFT assessments obtained at the timepoint will not be included in any efficacy analysis and will be considered missing (Miller et al., 2005). Thus, all observed data will be included in the ITT Population analysis, with the exception of data at a timepoint which had unacceptable quality based on ATS/ERS criteria.

Change from baseline in morning pre-dose trough FEV_1 and other lung function measures at each visit is defined as the average of all available pre-dose values minus baseline. In subjects with only one pre-dose assessment, the value will be calculated from the single measurement. In subjects with no pre-dose values, the pre-dose trough FEV_1 value at that visit will not be calculated and will be considered missing with two exceptions: non-missing pre-dose data from an unscheduled visit will be mapped to a scheduled visit, if a dose is taken at that scheduled visit; and if there is no clinic dose at the scheduled visit or the scheduled visit is not done, unscheduled data on a single day will be mapped to the scheduled visit with the pre-dose trough FEV_1 calculated as the average of all data for that day.

For the ITT Population, the determination of peak change from baseline in FEV_1 requires at least one non-missing FEV_1 value during the first 2 hours post-dose.

All observed data will be used with the trapezoidal rule to calculate AUC_{0-2} for a spirometry parameter using change from baseline values. For the purpose of AUC calculations, the value of the spirometry parameter at time 0 will be the change from baseline in morning pre-dose trough at the visit. To aid in interpretation, all AUC values will be normalized by dividing the AUC by the time from the first to the last non-missing value (typically 2 hours). If AUC is based on just one 1 assessment, that value will be the value of the AUC (the trapezoidal rule and normalization will not apply as the area is 0 and the time interval is 0).

For the final analysis, the primary efficacy endpoint data will be examined to determine if the nature and magnitude of the missing data leads to concerns about potential biases in the evaluation of treatment effects. It is expected that the amount of missing data will be sufficient enough to warrant a sensitivity analysis (with missing data imputation) to determine the robustness of the primary endpoint analysis (National Research Council of National Academy of Sciences, 2010). A discussion of the impact of missing data will be included in the clinical study reports.

The imputation approach used for assessing the robustness of the primary endpoints is described in Section 6.4.1.

For the TDI, at each visit, if a response to any of the three questions is missing, then the focal score will also be considered missing. For the TDI responder analyses, subjects without post-baseline data will be considered to be non-responders for the analysis.

For the SGRQ, scoring and handling of missing items will be conducted in accordance with the user's guide for the SGRQ. For the SGRQ responder analyses, subjects without post-baseline data will be considered to be non-responders for the analysis.

For rescue Ventolin HFA use, for every period of time for which the mean number of puffs of rescue Ventolin HFA will be calculated, missing values will be ignored in both the numerator and denominator. As such, the denominator will be adjusted based on the number of days (including half days) with non-missing values.

Missing data will be maintained as missing in the analysis datasets, unless specified otherwise. For variables where missing data are imputed, another analysis dataset will contain a variable with the imputed value. Thus, the original variable value will be maintained as missing in one of the analysis datasets.

Data Imputation for Adverse Events Summaries by Severity and Relationship to Study Drug

For the AE summaries by severity, an AE with missing severity will be deemed as severe. For the AE summaries by relationship to study drug, an AE with a missing relationship to study drug will be deemed as definitely related. Imputed values will not be listed in data listings.

Data Imputation for Laboratory, Vital Sign, and ECG Summaries (Continuous Parameters)

Data from unscheduled visits will not be used for this analysis, unless a prior or subsequent visit is missing where a value was scheduled to be collected. That is, data obtained during unscheduled visits will be allocated to the scheduled visit prior to the unscheduled visit if it was missed or to the next missing scheduled visit (not more than 4 weeks subsequent) if the previous scheduled visit was not missing.

Data Imputation (All Laboratory Summaries)

Laboratory values of '>=x' or '<=x' will be taken as the value of x in the analyses. If a laboratory value is prefixed with'>': the available original value +0.001 will be used for table summaries; if a laboratory value is prefixed with '<', then the original value –0.001 will be used in table summaries.

6.1.2 Study Dates and Day of Assessment or Event

Study Day and Day of Assessment or Event definitions are provided in Appendix 1, Data Handling Rules.

6.2 Subject Disposition and Analysis Populations

A disposition table for all subjects randomized will be provided *(Table 1.1.1 and Listing 1.2).* This tabulation will include the number of subjects in each randomized treatment who were not treated, who received the study treatment, who were withdrawn prematurely, and who completed Week 12, Week 24, and the Follow-up Telephone Call of the study. The number and percentage of randomized subjects who were included in the ITT, PP, Symptomatic, Rescue Ventolin User, and Safety Populations will also be tabulated *(Table 1.1.1)*.

The number of subjects randomized will be provided by treatment for each country and regional subgroup (*Table 1.1.2*). The numbers of subjects randomized and in the analysis populations will be provided for each country/regional subgroup and treatment overall and also by country, center, and treatment in Table 1.1.3. If there are any subjects who took study treatment other than what was randomized during the study, both the treatment assigned at randomization and actual treatment(s) received during the Treatment Period will be listed *(Listing 1.3)*. The duration of actual treatment will be listed (*Listing 1.3)*.

Note that the date of Discontinuation (withdrawal) shown in Listing 1.2 is designed to be useful in narrative writing and is different than the definition of the end of the treatment period. For this listing, the date of withdrawal for discontinued subjects is defined as the later of the last visit date, the date of the last dose of study medication, or the date of last contact for subjects lost-to-follow-up; the date of death will be listed separately for this listing.

A summary table (*Table 1.1.4*) and a listing *(Listing 1.4)* of reasons subjects were not randomized will be provided for the Non-Randomized analysis set. Reasons for early discontinuation will be summarized for all subjects randomized *(Table 1.2.1).* The number and

percentage of subjects withdrawn for each reason for early discontinuation will be tabulated by randomized treatment for the ITT, Rescue Ventolin User, and PP Populations *(Table 1.2.2 overall and by CAT Score Subpopulation, including Symptomatic Population [CAT Score ≥15])and Table 1.2.3)*; and by treatment actually received for the Safety Population *(Table 1.2.4)*.

The reason for exclusion from the PP Population will be tabulated by study treatment for all ITT subjects *(Table 1.3)*. The reason for exclusion from the PP Population of a subject or of partial data for a subject will be listed for all randomized subjects, in addition to any subjects excluded from the ITT, Symptomatic, Rescue Ventolin User, and Safety Populations *(Table 1.1.5)*. A listing of subjects who did not comply with restrictions on smoking, use of rescue Ventolin, and xanthine (and/or xanthine analogue)-containing products (protocol deviations requiring removal of data from the PP Population analysis) just prior to spirometry will be provided in Listing 6.1.1. Use of rescue Ventolin at pre-dose or during the post-dose assessments on each specific test day (yes/no), will be provided in Listing 6.1.3. In addition, the eligibility information (inclusion/exclusion criteria with any waivers granted) of all subjects who are randomized will be listed *(Listing 2.1)*.

The number and percentage of subjects with changes in smoking status after the start of study treatment will be tabulated by randomized treatment and across all treatments, by visit during the study, in Table 1.13 *(Listing 1.5)*.

6.3 Demographic and Baseline Characteristics and Extent of Exposure

The definitions for the derived demographic or characteristic variables can be found in Appendix 1.

6.3.1 Demography, Physical Characteristics, CAT, and MMRC

Subject demographics and smoking status/history will be summarized for the ITT, PP, Rescue Ventolin User, and Safety Populations and for the Non-Randomized analysis set *(Tables 1.4.1 through 1.4.5, respectively, and Listing 1.2)*. A summary of subject demographics and smoking status/history by CAT Score Subpopulation will also be provided for the ITT Population, including the CAT Score Subpopulation of ≥15 (i.e., Symptomatic Population)*(Table 1.4.1*). Inhaled corticosteroid use (yes/no) will be summarized for all populations except for the Non-Randomized analysis set. The Pearl Medical Monitoring team will identify which medications captured on the eCRF are ICS medications.

The COPD Assessment Test (CAT) is a short self-administered questionnaire designed to assess the condition of subjects and overall impact of COPD. The CAT will be done at Screening Visit 2. It will be utilized to describe the burden and symptomatic impact of COPD in the study populations.

The MMRC scale is a five-point scale that considers certain activities, such as walking or climbing stairs, which provoke breathlessness (Fletcher 1959). At Screening Visit 2, in one minute, the subject selects a grade on the MMRC scale that most closely matches his/her severity

of dyspnea. The MMRC scale is considered a discriminative instrument that can categorize subjects with COPD in terms of their disability. The MMRC grade will be used to describe the symptomatic burden in the study populations. The MMRC Scale uses a simple grading system to assess a subject's level of dyspnea, shortness of breath, as follows:

Table 4 MMRC Dyspnea Scale

Grade	Description of Breathlessness
0	I only get breathless with strenuous exercise.
1	I get short of breath when hurrying on level ground or walking up a slight hill.
2	On level ground, I walk slower than people of the same age because of breathlessness, or have to stop for breath when walking at my own pace.
3	I stop for breath after walking about 100 yards or after a few minutes on level ground.
4	I am too breathless to leave the house or I am breathless when dressing.

Demographic and baseline characteristic variables summarized will include the following:

- Age
- Gender
- Race
- Ethnicity
- BMI
- Weight
- Height
- Smoking status (current vs. former smoker)
- Used inhaled corticosteroids at Baseline (all populations except for the Non-Randomized analysis set)
- Number of years smoked
- Average number of cigarettes smoked per day
- Number of pack years smoked, calculated as (number of cigarettes per day/20) x number of years smoked
- COPD Assessment Test (CAT) total score and total score category (<10, ≥10, <15, ≥15, <20, ≥20)
- Modified Medical Research Council (MMRC) Scale grade.

Screening CAT data will be listed *(Listing 4.2)*. The categories of the CAT total score (<10, ≥10, <15, ≥15, <20, and ≥20) will be summarized *(Tables 1.4.1 through 1.4.5 for the ITT, PP, Rescue Ventolin User, and Safety Populations and for Non-Randomized analysis set, respectively)*; this summary will also be provided by CAT Score Subpopulation for the ITT

Population *(Table 1.4.1*). The MMRC grade will also be summarized similarly *(Tables 1.4.1 through 1.4.5 and Listing 4.3)*.

6.3.2 COPD History, Screening/Baseline Spirometry, and Reversibility

The number of years prior to the start of study medication that COPD was first diagnosed calculated as (Date of First Dose of Study treatment in the study – Date COPD First Diagnosed) /365.25 will be summarized for the ITT, PP, Rescue Ventolin User, and Safety Populations by treatment and listed *(Tables 1.5.1 through 1.5.4 and Listing 4.1).* Severity of COPD (GOLD 2014 grade) and GOLD 2017 categories (A, B, C, and D) at Screening Visit 2 post-Ventolin (albuterol sulfate) HFA will also be included in these summaries. These summaries will also be provided by CAT Score Subpopulation for the ITT Population, including for the CAT Score Subpopulation of ≥15 (i.e., Symptomatic Population) *(Table 1.5.1)*. History of moderate or severe COPD exacerbation in the prior year will be summarized for the ITT Population and listed *(Table 1.9.3 and Listing 4.4).*

Descriptive statistics will be provided for Screening Period pre-bronchodilator and post-bronchodilator and baseline spirometry parameters *(Tables 1.6.1 and 1.6.3 for the ITT, PP, and Rescue Ventolin User Populations, respectively, and Listing 2.2)*; descriptive statistics will also be provided by CAT Score Subpopulation for the ITT Population, including for the CAT Score Subpopulation of ≥15 (i.e., Symptomatic Population) *(Table 1.6.1)*.

Characterization of Reversibility:

Reversibility to Ventolin (albuterol sulfate) HFA (SABA) will be evaluated at Visit 2. Reversibility to Atrovent (ipratropium bromide) HFA (short-acting anticholinergic) will be evaluated at Visit 3. The procedure will be as follows:

Reversibility testing to Ventolin (albuterol sulfate) HFA (Visit 2 Only):

- Perform pre-bronchodilator PFTs (-60 min and -30 min) prior to administration of Ventolin (albuterol sulfate) HFA.
- Administer 4 puffs of Ventolin (albuterol sulfate) HFA.
- Perform post-bronchodilator PFT 30 min after the administration of Ventolin (albuterol sulfate) HFA.

Reversibility testing to Atrovent (ipratropium bromide) HFA (Visit 3 Only):

- Perform pre-bronchodilator PFTs (-60 min and -30 min) prior to administration of Atrovent (ipratropium bromide) HFA.
- Administer 4 puffs of Atrovent (ipratropium bromide) HFA.
- Perform post-bronchodilator PFT 30 minutes after the administration of Atrovent (ipratropium bromide) HFA.

Reversibility will be a comparison of the average of all best FEV_1 efforts obtained at -60 min and -30 min pre-bronchodilator to the best FEV_1 effort obtained at 30 minutes post-bronchodilator. A subject is determined to be reversible to Ventolin (albuterol sulfate) HFA if the improvement in FEV_1 approximately 30 minutes following administration of 4 puffs of Ventolin (albuterol sulfate) HFA is ≥12% and ≥200 mL. A subject is determined to be reversible to Atrovent (ipratropium bromide) HFA if the improvement in FEV_1 approximately 30 minutes following administration of 4 puffs of Atrovent (ipratropium bromide) HFA is ≥12% and ≥200 mL. However, if the subject fails the reversibility criteria at 30 minutes post-dose, any other available post-dose timepoint will be used instead to determine if reversibility was achieved.

Bronchodilator reversibility to Ventolin (albuterol sulfate) HFA at Screening Visit 2 and reversibility to Atrovent (ipratropium bromide) HFA at Screening Visit 3 will be summarized for the ITT, PP, and Rescue Ventolin User Populations *(Tables 1.7.1 through 1.7.3 for Ventolin HFA reversibility, respectively, and Tables 1.8.1 through 1.8.3 for Atrovent HFA reversibility, respectively; a summary will also be provided by CAT Score Subpopulation, including CAT Score ≥15 [i.e., Symptomatic Population][Tables 1.7.1 and 1.8.1]; Listing 2.2 for Ventolin HFA and Atrovent reversibility and Listing 5.1.2 for Ventolin HFA and Atrovent HFA dispensing)*. Also, the following will be summarized:

1. The percentage of reversible subjects
2. The change in FEV_1 from pre-dose FEV_1 to post-bronchodilator assessment
3. Percent reversibility, defined as 100 x (the change from pre-Ventolin HFA to post for FEV_1)/pre-Ventolin HFA FEV_1.

When multiple timepoints are available post-bronchodilator, the last assessment will be used. For Tables 1.7.1 through 1.7.3, if a subject is missing a Post-Ventolin or Pre-Ventolin FEV_1 value at Screening Visit 2, these values will be replaced by the Pre-Atrovent and Post-Atrovent values from Screening Visit 3. The percentage of subjects reversible to Ventolin HFA only, Atrovent HFA only, and to both Ventolin HFA and Atrovent HFA will be provided (*Table 1.8.4, ITT Population).*

Additionally, the percentage of subjects meeting each of the following response criteria will be summarized for both Ventolin (albuterol sulfate) HFA and Atrovent (ipratropium bromide) HFA bronchodilators:

- ≥12% improvement post-bronchodilator in FEV_1 from pre-bronchodilator
- ≥150 mL improvement post-bronchodilator in FEV_1 from pre-bronchodilator
- ≥200 mL improvement post-bronchodilator in FEV_1 from pre-bronchodilator

6.3.3 Medical and Surgical History at Screening, Reproductive Status and Pregnancy Testing, and COPD-related and non-COPD related Prior Medication for COPD

Medical and Surgical History at Screening will be summarized for the Safety Population and listed for all randomized subjects *(Table 1.9.1 and Listing 4.5.1)*. Cardiovascular risk factors of interest at Screening which are explicitly captured on the eCRF will be summarized for the Safety Population and listed for all randomized subjects *(Table 1.9.2 and Listing 4.5.2)*.

Screening Reproductive Status and Pregnancy Testing Results will be listed *(Listing 4.6)*.

6.3.4 Prior, Concomitant, and Post-Treatment Medications/Treatments

All prescription and over-the-counter (OTC) medications taken by the subject during 30 days before Screening will be recorded on the Concomitant Medications eCRF page. All concomitant medication/treatment taken by the subject while on study will be recorded in the eCRF.

Coding: Everest will be responsible for coding medication/treatment verbatim terms, using the latest version of the World Health Organization Drug Dictionary Enhanced and the Herbal Dictionary (WHO-DDE + WHO-HD, version 1Q2015 or later). Corresponding preferred terms (preferred base names) will be assigned to the medication/treatment verbatim terms along with appropriate ATC (Anatomic Therapeutic Chemical) drug classifications.

Multiple ATC assignments: If there are multiple ATC codes assigned to the same prior/concomitant medication, the "primary" one based on a Pearl medical evaluation will be used.

Prior medication/treatment is any medication/treatment taken prior to study treatment, even if this medication continued to be taken on the day of the start of study treatment in the study or afterward (Appendix 1).

Concomitant medication/treatment is any medication/treatment reported as being taken at any point from the date of randomization (Visit 4) to the date of Visit 11, the date of a Discontinuation Visit or the last contact date (the date of the last in-clinic or diary data collection or after). A medication with an onset date of the date of Visit 11, the date of a Discontinuation Visit or the last contact date will not be considered concomitant, but will be considered a **Post-Treatment medication/treatment**.

As a consequence of the definition of a concomitant medication, the rate of use of prohibited COPD medications may appear higher in the summary table of COPD concomitant medications, *(Table 1.11.1)*. This rate of prohibited medication use may appear higher since it will include subjects who used the prohibited medication after stopping study treatment but before the subjects had a discontinuation visit that would classify the medication as post-treatment.

Any medication/treatment which cannot be identified as Prior, Concomitant, or Post-Treatment will be considered as being in each of the categories that are possible from the available information.

Concomitant COPD and Non-COPD medications/treatments will be summarized by preferred term and actual treatment received for the Safety Population *(Tables 1.11.1 and 1.11.2, respectively)*. Prior, concomitant/post-treatment COPD and Non-COPD medications will be displayed in separate listings *(Listings 4.7 and 4.8, respectively)*.

Reported Prior Medication for COPD and non-COPD-Related Medications will be tabulated *(Tables 1.10.1 and 1.10.2, respectively)* and listed separately *(Listings 4.7 and 4.8, respectively)*.

6.3.5 Extent of Exposure to Study Medication and Compliance

Subject's exposure to a study treatment will be determined by the duration of time (days) for which the doses were administered, defined as "((End date of treatment – Date of first dose of treatment) + 1)".

Percent compliance is defined as (total number of puffs of study treatment taken on a study day/total puffs expected to be taken on a study day) averaged across all days of a subject's dosing between start of study treatment and last day on study treatment) x 100. The expected number of puffs for a test day which is the last date of treatment will be 2, the expected number of puffs for the last date of treatment which is not a test day will be 4 when a PM dose is taken and then 2 otherwise; the expected number of puffs on dates prior to the last date of treatment will be 4.

The number of days of exposure to study treatment and the number of puffs of study medication will be summarized for each treatment for the Safety Populations *(Table 1.12)*. The total person-years of exposure for a treatment group, defined as the total exposure in the study across all subjects in the treatment, will also be provided by treatment *(Table 1.12)*. These Safety Population tabulations will be done by actual treatment received most often in the study, as specified in Section 5.1.5.

In addition, a summary of treatment compliance will be provided. The treatment compliance will be categorized into 7 different groups depending on the degree of compliance: 0 – <20%, 20 – <40%, 40 – <60%, 60 – <80%, 80 – 100%, >100 – 120%, and >120% *(Table 1.12)*. Also provided in this summary will be descriptive statistics (n, mean, standard deviation, median, minimum and maximum) for percent compliance by treatment. Treatment compliance will be reported in Listing 5.2. A listing of treatment dosing information will be provided in Listing 5.1.1. Any comments related to study medication or any other additional study comments will be listed *(Listing 9.4)*.

6.4 Efficacy Analyses

Lung function measurements and symptom-based endpoints will be evaluated.

There are 6 possible pairwise comparisons of treatments. Five of the 6 comparisons are considered important as outlined in Section 6.4.4 Control of Type I Error. While all 6 comparisons will be presented for each efficacy endpoint, only the 5 key comparisons will be

performed for the purpose of testing superiority. Summary statistics will be provided by randomized treatment and for each treatment difference for all possible comparisons.

Baselines for Analysis:

The mean of all available evaluable 60- and 30-minute pre-dose spirometry assessments conducted at Day 1 (Visit 4) will be used to establish baseline for all FEV_1 and FVC parameters.

For the diary symptom score parameters and rescue Ventolin HFA usage, baseline will be the average of the non-missing values from the e-diary data collected in the last seven days of the Screening Period.

For the SGRQ scores, baseline will be the value of the score calculated using the Day 1 questionnaire data collected prior to the start of study treatment.

The BDI assessment will be the baseline for the TDI analyses.

Visits and Time Windows for Spirometry Assessments

Efficacy data obtained during unscheduled visits will not be used in analyses but will be listed.

For efficacy analysis or derivation of AUC based on timepoints, the change from baseline in FEV_1 assessments will be allocated to derived nominal collection time windows using the time intervals specified for each below.

Table 5 Analysis Study Time Windows for Spirometry Assessments

Calculated Study Time Window	Time Interval for the Study Time Window
Pre-dose 60 min	≥45 min prior to dose
Pre-dose 30 min	≥0 to <45 min prior to dose
Post-dose 5 min	>0 to 9 min Post-dose
Post-dose 15 min	10 to 22 min Post-dose
Post-dose 30 min	23 to 44 min Post-dose
Post-dose 1 hr	45 to 89 min Post-dose
Post-dose 2 hrs	90 min Post-dose or more

Note: The time of the study drug dose will be available to the minute. The time of the spirometry assessment, will be available to the second, and will be truncated downward to whole minutes prior to calculation of the study time window. Any assessments for which the time interval is 0 due to truncation but are marked as post-dose nominally, will be assigned to the 5 min post dose time window.

If there are multiple spirometry values for the same parameter within the same post-dose study time window on the same day, the last value will be chosen for analysis with one exception: if multiples with the exact same time (in minutes and seconds) occur within a window, then the last value based on the nominal time window will be chosen for analysis. Queries to the site (prior to database lock and unblinding) will be used to ascertain which assessment actually occurred first.

6.4.1 Primary Efficacy Analyses

Analyses for the primary endpoints for each approach are presented in this section along with analyses for any of the secondary or other efficacy endpoints related to the primary endpoints.

6.4.1.1 Change From Baseline in Morning Pre-dose Trough FEV_1

The change from baseline in morning pre-dose trough FEV_1 will be analyzed using a repeated measures (RM) linear model. Data from all study treatments will be included in the modeling.

The linear RM model will include baseline FEV_1 and reversibility to Ventolin (albuterol sulfate) HFA as continuous covariates and visit, treatment, and the treatment by visit interaction as categorical covariates. Baseline is defined as the average of all available evaluable 60- and 30-minute values obtained prior to dosing at Visit 4. An unstructured matrix will be used to model the variance-covariance structure within subject. If this model fails to converge, the heterogeneous Toeplitz (TOEPH) structure will be used to model correlation between time points from the same subject. Contrasts will be used to obtain estimates of the treatment differences at Week 24, over Weeks 12-24, and over 24 weeks. The over 24 weeks treatment difference is a model-based estimate of the average treatment effect using all scheduled visits. The over 12-24 weeks treatment difference is a model-based estimate of the average treatment effect using all scheduled visits within the 12-24 week interval. The analysis of the average over the entire 24 weeks is a secondary endpoint for the US/China approach and a primary endpoint for the EU/South Korea/Taiwan approach. The analysis of the average over Weeks 12-24 is a primary endpoint for the Japan approach. Two-sided p-values and point estimates with two-sided 95% confidence intervals will be produced for each treatment difference. The primary analysis will be conducted using the ITT Population. All non-missing data will be used.

Additional supportive analyses of morning pre-dose trough FEV_1 will include the change from baseline at Week 24, over Weeks 12-24, and over the entire 24-week treatment period in the PP Population and treatment differences at individual timepoints estimated by the RM model.

The least squares (LS) mean and the standard error of this mean with the corresponding two-sided 95% confidence interval will be provided for each treatment based on the models. The LS mean difference for all of the possible pairwise treatment comparisons, as well as the corresponding two-sided 95% confidence interval will be provided based on the models. The LS means presented for the population will be estimated assuming arithmetic mean levels of baseline FEV_1 and reversibility to Ventolin (albuterol sulfate) HFA. In addition, descriptive statistics for unadjusted change from baseline in morning pre-dose trough FEV_1 will be presented for each treatment by scheduled week of assessment. Summary statistics and the results of statistical testing for this analysis will be provided in Table 2.1.1 with the LS Mean

change from baseline plotted by treatment and study week, along with the LS Mean estimates at Week 24 and over 24 weeks for each treatment *(Figure 2.1.1.1)* for the ITT Population *(Table 2.1.2 and Figure 2.1.2 for the PP Population analysis)*. Differences from Placebo MDI will be plotted for change in trough FEV_1 *(Figure 2.1.1.2 for the ITT Population).* The results of the ITT Population analysis will be considered primary; the PP Population analysis will be a supportive analysis.

Assumptions Checks and Removal of Outliers in Sensitivity Analyses

In general the distribution of spirometry measures is well-approximated by a normal distribution. Under some circumstances, however, (for example during a COPD exacerbation, unrelated to treatment) extreme and atypical values can arise. Such values have high influence on estimation of variance parameters and on standard errors of fixed effect estimates. Prior to database lock and unblinding, the change from baseline values for efficacy endpoints will be examined as part of data quality management. This will include production of normal probability plots, kernel density estimates, and normal order outlier statistics. Based on this blinded evaluation, if extreme values are identified, nonparametric methods or data transformations (e.g., Logarithmic or normal rank transformation) will be considered. If erroneous values are detected, every effort will be made to correct them prior to database lock, however if these values cannot be corrected, they will be considered for removal from analysis. These analyses will be conducted if warranted to demonstrate the robustness of the primary and secondary results and reported in the statistical methods appendix.

The assumption of normality in the change from baseline in the morning pre-dose trough FEV_1 data will be checked by visually inspecting the distribution of the residuals. Also, model fit and the assumption of homogeneity of variance among treatments will be verified by inspection of scatter plots of predicted vs. residuals, residuals vs. treatment, and by box plots of residuals for model variables with a potential effect on variance (treatment and visit). Plots for scaled (marginal) residuals will be prepared (option=VCIRY on the model statement and ODS graphics option allows the production of plots using these residuals). As a sensitivity analysis, if appropriate, the linear RM model analysis will be conducted by allowing for heterogeneity of variance between treatments and visits (if unstructured covariance model failed to converge). Note that the unstructured covariance structure allows for heterogeneity among the visits.

Sensitivity Analyses

Sensitivity analyses will be conducted to evaluate the robustness of the primary analysis findings to missing data. The estimand of interest in this study is the effect of treatment compared to control (for example GFF MDI vs. GP MDI) at Week 24 of treatment, or over 24 weeks of treatment, or over Weeks 12-24. Since the primary analyses of morning pre-dose trough FEV_1 use maximum likelihood based approaches, they are valid under the missing at random (MAR) assumption (Little and Rubin, 2002). The MAR assumption means that missingness is independent of the unobserved outcome values after accounting for the appropriate observed data and covariates in the model. In order to evaluate the robustness of the findings to this assumption, sensitivity analyses will be performed under varying assumptions for data

considered likely to be missing not at random (MNAR). MNAR means that missingness depends on the unobserved values, and cannot be predicted solely based on the subject's observed data.

Several types of statistical models have been proposed to analyze clinical study data under such assumptions. The first approach that will be implemented for this study is the use of pattern-mixture models (PMMs). PMMs have the advantages of allowing transparent and clinically interpretable formulations of the assumptions regarding unobserved data (Little and Rubin 2002). The second approach will implement a cumulative responder analysis.

Pattern Mixture Models

The details for implementation of a sensitivity analysis within the PMM framework were recently summarized by Ratitch et al. (2013) and are described below as implemented for this study. Multiple imputation (MI) methods for imputing missing data available in PROC MI are incorporated. Using MI as an integral part of a PMM-based analysis has a great advantage in that MI procedures produce correct variance estimates that account for uncertainty associated with the imputation process.

Methodology for Missing Data Imputation

The methods employed for missing data imputation are dependent on whether the reason for missingness is MAR (missing at random) or MCAR (missing completely at random) vs. MNAR (missing not at random). Thus, reasons for discontinuation as captured on the eCRF will have been classified as MCAR/MAR or MNAR. Additionally, in order to impute missing data for a visit prior to the discontinuation visit, the reasons for having missed the visit (captured on the eCRF) will be classified as COPD Related (MNAR), Not COPD Related (MAR/MCAR), and Unknown *(Listing 6.1.2)*. For the purpose of the sensitivity analysis, an Unknown reason for having missed a visit will be considered to be MNAR. Also, if the spirometry data quality obtained for a subject at any timepoint does not meet minimal acceptability requirements per ATS/ERS criteria, as determined during the blinded spirometry over read process, data for that timepoint will be considered MNAR. If both of the 60- and 30-minute pre-dose spirometry assessments are missing at a visit, but the visit is not missing, then this will be considered MNAR.

Unique patterns of missing values across visits will be summarized for change from baseline in FEV_1 *(Table 2.1.3.2 for the ITT Population)* with numbers and percentages by treatment. These and all reasons for missing values at a visit will be listed *(Listing 6.1.2)* and summarized in Table 2.1.3.1 for the change from baseline in morning pre-dose trough FEV_1. Additionally, these summary tables will provide a breakdown of the total missing count by MAR/MCAR and MNAR.

It is expected that the great majority of missing data will be caused by subjects discontinuing from the trial prematurely. The resulting missing data will have a monotone pattern, meaning that, once a subject has missing data for some visit, data will be missing for all subsequent visits.

The methodology described below will be used to address this type of missing data pattern. It is also expected that a small amount of non-monotone missing data (when subjects skip intermediate visits, but return for evaluations at subsequent visits) will be present. The intermittent missing data will be imputed prior to the imputation of the monotone missing data. Intermittent missing data classified as MNAR will be imputed using the Monte Carlo Markov Chain (MCMC) approach and then the imputed values will be decreased by delta as defined in the following section. Intermittent missing data classified as MAR/MCAR will be imputed using MCMC imputation without decreasing the imputed values by delta. Using the MCMC approach, missing visits will be imputed from the posterior distributions, derived from the joint distribution of morning trough FEV_1 at all visits within each treatment. There will be no conditioning on the covariates for this intermittent imputation. Intermittent missing values will not be used to define separate patterns. Patterns will be defined on the basis of the nature of the missingness in addition to completion status (completer or dropout). Each pairwise comparison will be evaluated separately. For purposes of explaining the procedure, the treatment with the presumed larger benefit will be labeled as Treatment, while the treatment to which it is being compared will be labeled Comparator. For example, for the comparison of GFF MDI to FF MDI, GFF MDI will be labeled Treatment and FF MDI will be labeled Comparator. The patterns used for analysis will be Treatment Completers, Comparator Completers, Treatment Dropouts MAR/MCAR, Treatment Dropouts MNAR, and Comparator Dropouts. This will be implemented through running separate sets of imputations and analyses for each of the 3 treatments (GFF, GP and FF), which are being considered for delta adjustment. The set where GFF will be delta-adjusted will provide estimates for the 3 key comparisons with GFF, i.e., GFF-FF, GFF-GP and GFF-Placebo. The set where FF will be delta-adjusted will provide estimates for the key comparison FF-Placebo, and the set where GP will be delta-adjusted will provide estimates for the key comparison GP-Placebo.

Each single imputation will be performed on the entire ITT set, regardless of the key comparison being evaluated. The key comparison will only determine the treatment to which the delta adjustment will be applicable (GFF, FF or GP). Accordingly, the analysis (RM ANCOVA) will be performed on the full ITT set with the observed and imputed values. Since the same set of subjects will be used as the main analysis, the results can be compared.

For each key comparison and each value of delta, 10 independent imputations will be done. The resulting 10 estimates of the treatment effect will then be combined into the final estimate for this combination of the key comparison and delta, using SAS PROC MIANALYZE.

Pattern Mixture Modeling with Delta Adjustment

Delta-adjusted PMM imputation will be used for sensitivity analysis under a clearly formulated clinical assumption about an MNAR mechanism. More specifically, the assumption is that subjects from the GFF MDI arm for the comparisons of GFF MDI to its components and Placebo MDI, or the GP MDI and FF MDI arms used for comparisons to Placebo, who discontinue at a given timepoint would have, on average, their unobserved efficacy score worse by some amount δ compared with the observed efficacy score of subjects who continue to the next assessed timepoint. For purposes of the sensitivity analyses, subjects who discontinue from the

Comparator arm are treated as if they would have exhibited the same evolution of the disease and same benefit from treatment with the comparator as comparator subjects that stayed on the study.

Delta values will be based on the estimated treatment difference from comparator taken from the primary analysis in the ITT Population where values will vary from 0 to the estimated treatment difference in increments of 0.010 L for change from baseline in FEV_1 trough.

For datasets with monotone missingness, regression-based imputation for monotone missingness (Rubin, 1987) will be applied and has the flexibility that it may be performed in a sequential manner using univariate models with a number of predictor variables. For example, the earliest visit will be imputed first, then the next one, and so on using outcomes from previous visits as predictors. This sequential approach is considered to perform well in practice with monotone missingness even when normality assumptions do not hold (Little, 2002; Molenberghs and Kenward, 2007; White, Royston, and Wood, 2011).

A sequential regression-based MI procedure was suggested for the implementation of the delta-adjustment strategy in the National Research Council (NRC) report on missing data (National Research Council of National Academy of Sciences, 2010) so that timepoints are imputed one at a time and that δ adjustment can be propagated through time by using the adjusted values as predictors. This procedure follows the general principles of PMM with identifying restrictions (assumptions) discussed above and is summarized as follows:

i. Missing values at timepoint 1 (Week 2 for FEV_1) will be imputed using a regression based MI method for monotone missingness (100 iterations per timepoint per delta). All covariates in the final RM ANCOVA model (except for visit and treatment by visit interaction) will be included in the modelling (baseline FEV_1, percent reversibility, and randomized treatment). At this stage, the imputed values will not yet be δ-adjusted for any subjects in the Treatment Dropouts MNAR pattern.
ii. After imputations are obtained in Step (i), for subjects missing data at timepoint 1 in the Treatment Dropouts MNAR pattern, the imputed value at timepoint 1 will be made worse by a value of δ. Since lower scores for the primary endpoints for this study represent worsening, δ will be subtracted from the previously imputed value. No adjustments will be made for the other patterns.
iii. All remaining timepoints will be imputed sequentially by repeating Steps (i–ii) for each timepoint including lag values from earlier timepoints in the imputation model (lag values will include imputed values from the previous step) in addition to the covariates specified above in Step (i). Data from subjects who have already had their responses decreased by δ in the previous step(s) will not be further decreased by δ again since the regression on the previous value carries this decrease forward. This principle also extends to the preliminary step of imputing intermittently missing visits. Thus, if an intermittent MNAR value is encountered for a subject, delta adjustment will not apply for the subsequent imputations of the monotone part of the missing visits, for that subject.

iv. Analyze multiply-imputed datasets by the same method used for the primary analysis (linear RM ANCOVA described above) and combine the results based on a standard MI methodology (Rubin, 1987).

Tipping Point Analysis

A series of analyses will be performed for each key pairwise comparison with a range of increasing δ values (from 0 to the estimated treatment difference from the primary analysis) so that one can assess at which point the study conclusions change from favorable to unfavorable, that is, so that one can find a tipping point. Then, a clinical interpretation regarding the δ value representing the tipping point will be considered to judge whether the corresponding differences between the dropouts and completers are plausible. Delta increments will be chosen to be 0.010 L for FEV_1 out of practicality concerns, with the intent to refine the grid around the tipping point, if it is observed. The largest value of delta considered for a given comparison will be the estimated treatment difference from the primary analysis, rounded upwards to the nearest 0.010 L.

A plot of p-values by δ will be provided for each of the 5 primary treatment comparisons and for each of the primary endpoints including the primary endpoint of change from baseline in trough FEV_1 at Week 24 for the US/China approach, the primary endpoint of change from baseline in trough FEV_1 for over Weeks 12-24 for the Japan approach, and the primary endpoint of change from baseline in trough FEV_1 over 24 Weeks for the EU/South Korea/Taiwan approach *(Tables 2.1.4.1 through 2.1.4.3 and Figures 2.1.4.1 through 2.1.4.15 for change in FEV_1 trough at Week 24, over 24 weeks, and over Weeks 12-24, ITT Population).* It is acknowledged that the process of imputation will incur a certain degree of noise due to the limited number of imputations (10). In order to better see the trend in the p-values with increasing delta, a smoother will be added to the graphs. Smoothing will be done by fitting a linear model (in delta) to the estimated standard errors, and then a weighted linear model to the estimated treatment effects. Smoothed p-values will then be derived from the smoothed treatment effects and standard errors.

Additionally, for a subset of specific δ's and for each of the 5 key pairwise comparisons (GFF MDI with comparators of Placebo and components, and for each component compared to the Placebo comparator) plots will be prepared displaying the mean adjusted estimates for each visit as well as over 24 weeks *(Figures 2.1.4.16 to 2.1.4.30 for change in trough FEV_1 at Week 24, for over 24 weeks, and for over Weeks 12-24, ITT Population).* For each key pairwise comparison, one model will be run for each imputation dataset generated for each of the δ's that represent roughly 0%, 25%, 50%, and 100% of the estimated treatment difference for the given comparison. The models used the same covariates as the primary analysis model, but the treatments were: Treatment Completers, Comparator Completers, Treatment Dropouts MAR/MCAR, Treatment Dropouts MNAR, and Comparator Dropouts *(Figures 2.1.4.16 to 2.1.4.30 for change in trough FEV_1 at Week 24, for over 24 weeks, and for over Weeks 12-24, ITT Population).* Table 6 identifies the models used to produce estimates plotted in these pattern figures.

Table 6 Models Used To Produce Estimates for Pattern Figures (Figures 2.1.4.16 to 2.1.4.30)

Models 1a, 1b, and 1c for plotting key comparisons of GFF to each Comparator	Model 1A: GFF vs. Placebo Key Comparison: Groups included in the model were: 1. GFF Completers 2. GFF MNAR 3. GFF MAR/MCAR 4. Placebo Completers 5. Placebo Dropouts	Model 1B: GFF vs. GP Key Comparison: Groups included in the model were: 1. GFF Completers 2. GFF MNAR 3. GFF MAR/MCAR 4. GP Completers 5. GP Dropouts	Model 1C: GFF vs. FF Key Comparison: Groups included in the model were: 1. GFF Completers 2. GFF MNAR 3. GFF MAR/MCAR 4. FF Completers 5. FF Dropouts
Model 2 for plotting key comparison of GP to Comparator	Groups included in the model were: 1. GP Completers 2. GP MNAR 3. GP MAR/MCAR 4. Placebo Completers 5. Placebo Dropouts		
Model 3 for plotting key comparison of FF to Comparator	Groups included in the model were: 1. FF Completers 2. FF MAR/MCAR 3. FF MNAR 4. Placebo Completers 5. Placebo Dropouts		

Cumulative Responder Analysis

US/China

Additional sensitivity analyses will be implemented based on a cumulative responder approach as described in Farrar et al. 2006 for the change from baseline in morning pre-dose trough FEV_1 at Week 24 *(Table 2.1.4.4)*. A cumulative distribution plot by treatment arm (Farrar et al., 2006) will also be produced. The observed change from baseline in morning pre-dose trough FEV_1 at Week 24 will be plotted on the X axis, while the proportion of responders (subjects that equal or exceed that level of change) will be plotted on the Y axis *(Figure 2.1.4.31)*. Subjects with missing data at Week 24 will be considered non-responders. The cumulative responder curves for each treatment will then be compared pairwise using Kolmogorov-Smirnov tests.

Japan

The methodology described above for the US/China approach will be applied using the mean change from baseline in morning pre-dose trough FEV_1 over Weeks 12-24 *(Table 2.1.4.6)*. The mean observed change from baseline in morning pre-dose trough FEV_1 over Weeks 12-24 will

be plotted on the X axis, while the proportion of responders (subjects that equal or exceed that level of change) will be plotted on the Y axis *(Figure 2.1.4.33)*. Subjects with missing data from Week 12 onward will be considered non-responders.

EU/South Korea/Taiwan

The methodology described above for the US/China approach will be applied using the mean change from baseline in morning pre-dose trough FEV_1 over 24 weeks *(Table 2.1.4.5)*. The mean observed change from baseline in morning pre-dose trough FEV_1 over 24 weeks will be plotted on the X axis, while the proportion of responders (subjects that equal or exceed that level of change) will be plotted on the Y axis *(Figure 2.1.4.32)*. Subjects with missing data after baseline will be considered non-responders.

6.4.2 Analysis of Secondary and Other Endpoints Related to Secondary

Secondary variables include TDI (over 24 weeks for US/China and EU/South Korea/Taiwan and over Weeks 12 to 24 for Japan), morning pre-dose trough FEV_1 over 24 weeks for the US/China (analysis described above), and onset of action on Day 1, peak FEV_1 (at Week 24 for US/China, over 24 weeks for EU/South Korea/Taiwan, and over Weeks 12 to 24 for Japan), rescue Ventolin HFA usage, and SGRQ (at Week 24 for US/China and over Weeks 12 to 24 for EU/South Korea/Taiwan and Japan). All analyses will be performed with the ITT Population except for rescue Ventolin usage which will be based on the Rescue Ventolin User Population. In addition, analyses of symptom endpoints of TDI and SGRQ will also be performed in the Symptomatic Population. Multiplicity will be controlled for the secondary variables as described in Section 6.4.4.

6.4.2.1 TDI

Assessments of dyspnea will be obtained using the BDI/TDI. The interviewer-administered version of the BDI/TDI questionnaire can be found in Appendix 9 of the Protocol. Previous Pearl studies utilized the SAC (self-administered computerized) version of the BDI/TDI.

At Visit 4, the severity of dyspnea at baseline will be assessed using the BDI. BDI components are functional impairment, magnitude of task, and magnitude of effort (*Listing 6.1.8)*. The possible range of values for each BDI component score is 0 (very severe impairment) to 4 (no impairment). The BDI component scores are summed to determine the BDI focal score (0 to 12) (i.e., the lower the score, the worse the severity of dyspnea).

At subsequent visits (as per schedule of events, Table 1) change relative to baseline will be assessed using the TDI. TDI components are: Change in Functional Impairment, Change in Magnitude of Task, and Change in Magnitude of Effort (*Listing 6.1.8)*. The TDI component score ranges from -3 (major deterioration) to +3 (major improvement). The sum of all component scores yields the TDI focal score (-9 to +9) (i.e., the lower the score, the more deterioration from baseline).

The difference between treatments in TDI focal score over 24 weeks and over Weeks 12-24 will be evaluated using a similar repeated measures approach as for the change from baseline in morning pre-dose trough. BDI will be included as a continuous covariate replacing baseline FEV_1 in the model. At each visit, if a response to any of the three questions is missing, then the focal score will also be considered missing. Two-sided p-values and point estimates with two-sided 95% confidence intervals will be produced for each treatment difference.

Primary analyses of the TDI will use the ITT Population *(Table 2.2.1 and Figures 2.2.1.1.1 and 2.2.1.1.2)* and Symptomatic Population (CAT score ≥15; *Table 2.2.1*). The analysis of the TDI focal score for the subpopulations of the CAT Score ≥10 and ≥20 will be similar to the primary analyses of the TDI focal score *(Table 2.2.1 and Figures 2.2.1.2.1 to 2.2.1.2.3)*. Analyses of the individual components of the TDI: functional impairment, magnitude of task, and magnitude of effort over 24 weeks, over Weeks 12-24, and by post-baseline visit will be summarized *(Table 2.2.2 for the ITT Population and by CAT Score Subpopulation; and Figures 2.2.2.1, 2.2.2.2., and 2.2.2.3 for the functional impairment, magnitude of task, and magnitude of effort components for the ITT Population overall and by CAT Score Subpopulation, including the CAT Score Population of ≥15 (i.e., Symptomatic Population).* Furthermore as supportive analyses, responder analyses will be performed where responders are defined as subjects who achieved a minimal clinically important difference (MCID) threshold of ≥1 unit on average in TDI focal score over 24 weeks (or separately over Weeks 12-24). Subjects without TDI data will be considered to be non-responders. Logistic regression, performed with PROC GENMOD, will be used to compare the treatments, adjusting for BDI and reversibility to Ventolin (albuterol sulfate) HFA as continuous covariates *(Table 2.2.3.1 for the ITT Population and by CAT Score Subpopulation, including CAT Score Population of ≥15 (i.e., Symptomatic Population).* The odds ratios for relative treatment differences will be determined, along with Wald two-sided 95% confidence intervals. The odds ratios presented will assume arithmetic mean levels of the BDI focal score and reversibility to Ventolin (albuterol sulfate) HFA. The Wald chi-square test will be used to calculate p-values for comparisons between treatments.

As additional supportive analyses, the difference between treatments at each of the individual post-baseline visits will also be evaluated and summarized *(Table 2.2.1 for the ITT Population and by CAT Score Subpopulation, including CAT Score Population of ≥15 (i.e., Symptomatic Population).* The difference between treatments over time will be plotted in Figures 2.2.1.1.1 and 2.2.1.1.2 for the ITT Population and Figures 2.2.1.2.1 through 2.2.1.2.3 for the CAT Score Subpopulations.

The assumption of normality in the TDI data will be checked by visually inspecting the distribution of the residuals. Also, model fit and the assumption of homogeneity of variance among treatments will be verified by inspection of scatter plots of predicted vs. residuals and residuals vs. treatment, and by box plots of residuals for model variables with a potential effect on variance (treatment and visit). Plots for scaled (marginal) residuals will be prepared (option=VCIRY on the model statement and ODS graphics option allows the production of plots using these residuals). As a sensitivity analysis, if appropriate, the linear RM model analysis will be conducted by allowing for heterogeneity of variance between treatments and visits (if

unstructured covariance model failed to converge). Note that the unstructured covariance structure allows for heterogeneity among the visits.

6.4.2.2 Peak FEV_1

The peak change from baseline in FEV_1 within 2 hours post-dosing at Week 24 (US/China), over 24 weeks (EU/South Korea/Taiwan), and over Weeks 12-24 (Japan) will be analyzed and summarized similarly to morning pre-dose trough FEV_1 *(Table 2.3.1 and Figure 2.3.1 for the ITT Population)*. The peak change from baseline on Day 1 and at each post randomization visit will also be analyzed. For the ITT, at each visit, the determination of peak value requires at least one non-missing value post-dose assessment.

6.4.2.3 St. George Respiratory Questionnaire (SGRQ)

The SGRQ will be used to provide the health status/health-related Quality of Life (QoL) measurements in this study (see Appendix 8 of the Protocol). The SGRQ contains 50 rated items divided into three domains: "Symptoms" concerned with respiratory symptoms, their frequency, and severity; "Activity" concerned with activities that cause or are limited by breathlessness; and "Impacts" which covers a range of aspects concerned with social functioning and psychological disturbances resulting from airway disease. A score will be calculated for each component and a "Total" score will also be calculated (*Listings 6.1.9 and 6.1.10)*. In each case, the lowest possible value is zero and the highest is 100. Higher values correspond to greater impairment of quality of life.

The differences between treatments in the change from baseline in SGRQ at Week 24 (US/China) and over Weeks 12-24 (EU/South Korea/Taiwan and Japan), will be evaluated using a similar RM approach as for the primary endpoint. Scoring and handling of missing items will be conducted in accordance with the user's guide for the SGRQ. Each response is to be given a unique empirically derived weight between 0 and 100, the weighted responses are then summed up and divided by the maximum possible score and expressed as a percentage. Missing data of the SGRQ total score will not be imputed. Two-sided p-values and point estimates with two-sided 95% confidence intervals will be produced for each treatment difference.

The primary analyses of the SGRQ will use the ITT Population *(Table 2.4.1 and Figure 2.4.1.1)* and Symptomatic Population *(CAT Score ≥15; Table 2.4.1).* The subpopulations of the CAT Score ≥10 and ≥20 will be analyzed similarly *(Table 2.4.1 and Figures 2.4.1.2 to 2.4.1.4)*. As additional supportive analyses, the differences between treatments at each of the individual post-baseline visits will also be evaluated and summarized *(Table 2.4.1 and Figure 2.4.1.1 for the ITT Population and Table 2.4.1 and Figures 2.4.1.2 to 2.4.1.4 for the CAT Score Subpopulations)*. Individual domains of the SGRQ (Symptoms, Activity, and Impacts) over Weeks 12-24 and for each post-baseline visit will also be analyzed in a similar fashion as for the overall score *(Table 2.4.2).* Furthermore as supportive analyses, responder analyses will be performed where responders are defined as subjects achieving an MCID threshold of ≥4 units on average in SGRQ total score over Weeks 12-24 (or separately at Week 24). Subjects without SGRQ data will be considered to be non-responders. Logistic regression, performed with PROC GENMOD, will be used to compare the treatments, adjusting for baseline SGRQ and reversibility to Ventolin

(albuterol sulfate) HFA as continuous covariates *(Table 2.4.3 for the ITT Population and by CAT Score Subpopulation, including for the CAT Score Subpopulation of ≥15 [i.e., Symptomatic Population])*. The odds ratios for relative treatment differences will be determined, along with the Wald two-sided 95% confidence intervals. The odds ratios presented will assume arithmetic mean levels of the baseline SGRQ and reversibility to Ventolin (albuterol sulfate) HFA. The Wald chi-square test will be used to calculate p-values for comparisons between treatments.

6.4.2.4 Rescue Ventolin HFA Use

The number of puffs of rescue Ventolin HFA taken in the previous 12 hours will be recorded in the subject diary in the morning and evening. The number of puffs of rescue Ventolin HFA used by subjects during the study will be provided in a diary data listing *(Listing 6.1.6)*.

For every period of time for which the mean number of puffs of rescue Ventolin will be calculated, missing values will be ignored in both the numerator and denominator. As such, the denominator will be adjusted based on the number of days (including half days) with non-missing values.

The mean daily number of puffs of rescue Ventolin HFA will be calculated overall and for each of the 4-week intervals during the Treatment Period. Diary data recorded during the last 7 days of the 10-14 day Screening Period will be used to calculate the baseline. The difference between treatments in the change from baseline in rescue Ventolin HFA use over 24 weeks will be evaluated using a similar RM approach as for the primary endpoint (*Table 2.5.1 and Figure 2.5.1.1 for the Rescue Ventolin User Population, the subset of subjects using an average of at least 1 puff per day of rescue Ventolin at baseline)*. Instead of visit, the number of the relevant 4-week interval (1-6) will be used as a categorical covariate in the model. As a supportive analysis, the treatment differences for each 4-week interval and over Weeks 12-24 will be evaluated and summarized similarly (*Table 2.5.1 and Figure 2.5.1.1 for the Rescue Ventolin User Population)*. Additionally as supportive analyses, daytime rescue Ventolin HFA use and nighttime rescue Ventolin HFA use will be evaluated and summarized in a similar fashion *(Table 2.5.1 and Figures 2.5.1.2 and 2.5.1.3)*. Two-sided p-values and point estimates with two-sided 95% confidence intervals will be produced for each treatment difference.

6.4.2.5 Time to Onset of Action

The onset of action will be determined for each treatment using the 5 and 15 minute post-dosing FEV_1 assessments from Day 1. The onset of action for each product (GP MDI, FF MDI, and GFF MDI) will be defined as the first timepoint where the difference from Placebo MDI for change from baseline in FEV_1 is statistically significant (the two-sided alpha level will be based on the Hochberg procedure for each comparison to Placebo MDI, see Section 6.4.4). ITT Population analyses will be performed to compare treatments using ANCOVA; the ANCOVA will include baseline FEV_1 and percent reversibility to Ventolin (albuterol sulfate) HFA as continuous covariates.

Results will be summarized and the adjusted mean change from baseline in FEV_1 will be plotted by treatment across timepoints *(Table 2.6.1 and Figure 2.6.1 for the ITT Population, and Listing 6.1.4)*.

6.4.3 Analysis of Other Endpoints

6.4.3.1 Other Spirometry Endpoints

FEV_1 AUC_{0-2} will be calculated using the trapezoidal rule and transformed into a weighted average by dividing by the time in hours from dosing of the last measurement included (typically 2 hours). FEV_1 AUC_{0-2} will be evaluated in a similar manner to the primary endpoint using the ITT Population. Summaries of analyses by visit, over Weeks 12-24, and over 24 weeks will be provided *(Table and Figure 2.7 for FEV_1 AUC_{0-2})*. The differences between treatments in FEV_1 AUC_{0-2} will be evaluated using an ANCOVA with baseline FEV_1 and Screening reversibility to Ventolin (albuterol sulfate) HFA as continuous covariates and treatment as a categorical covariate. Two-sided p-values and point estimates with two-sided 95% confidence intervals will be produced for each treatment difference at each timepoint.

Treatment differences in the peak change from baseline in FVC within 2 hours post-dose, FVC AUC_{0-2} and changes from baseline in morning pre-dose trough FVC will be evaluated in a similar manner *(Table and Figure 2.9 for peak change from baseline within 2 hours for FVC for the ITT Population; Table and Figure 2.8 for AUC_{0-2} for FVC for the ITT Population; and Table and Figure 2.10 for change from baseline in FVC trough, for the ITT Population, respectively)*.

Treatments will be compared using change from baseline at each post-dose timepoint over 2 hours for the following variables: FEV_1 and FVC *(Tables and Figures 2.6.1 for FEV_1 and 2.12 for FVC for the ITT Population using ANCOVA to compare treatments with baseline FEV_1 and percent reversibility to Ventolin (albuterol sulfate) HFA as continuous covariates and Listings 6.1.4 and 6.1.5; plots will display AUC_{0-2} estimates also)*.

On Day 1 during the first two hours post-dosing and by timepoint, the proportion of subjects achieving an improvement from baseline in FEV_1 using different thresholds (i.e., ≥10%, ≥12%, ≥100 mL, ≥200 mL, and ≥12% and 200 mL) will be estimated for each treatment. Subjects without post-baseline data will be considered to be non-responders. Logistic regression, performed with PROC GENMOD, will be used to compare the treatments, adjusting for baseline FEV_1 and reversibility to Ventolin (albuterol sulfate) HFA as continuous covariates. The odds ratios for the relative treatment differences will be determined, along with the Wald two-sided 95% confidence intervals. The odds ratios presented will use the arithmetic mean levels of baseline FEV_1 and reversibility to Ventolin (albuterol sulfate) HFA. The Wald chi-square test will be used to calculate p-values for comparisons between treatments *(Tables 2.11.1 through 2.11.5 for the ITT Population)*.

Percentage of Days With "No Rescue Ventolin Use" Over the Treatment Period

As a supportive analysis, percentage of days with 'no rescue Ventolin HFA use' over 24 weeks will be analyzed. A 'Day with no rescue use' is defined, using rescue Ventolin HFA usage data from days where rescue Ventolin HFA usage data is non-missing, as any day where the subject reported no puffs of rescue Ventolin HFA. The percentage of days with 'no rescue use' will be summarized by treatment and analyzed using ANCOVA to evaluate the treatment difference using baseline average daily rescue Ventolin HFA and percent reversibility to Ventolin HFA as covariates *(Table 2.5.2 for the Rescue Ventolin User Population)*.

COPD Exacerbations

The severity of exacerbations will be classified as follows:

Mild: exacerbations that do not require systemic steroids or antibiotics, and do not result in hospitalization or death

Moderate: exacerbations that requires treatment with systemic steroids and/or antibiotics, and do not result in hospitalization or death

Severe: exacerbations that result in hospitalization or death.

The number of exacerbations and the percentage of subjects who experience exacerbations will be summarized for all severities combined and by severity. The rate of all COPD exacerbations of any severity will be analyzed using negative binomial regression as implemented in PROC GENMOD. COPD exacerbations will be considered separate events provided that 7 or more days are between the recorded stop date of the earlier event and start date of the later. Exposure to randomized medication will be used as an offset variable. Time during an exacerbation or in the 7 days following an exacerbation will not be included in the calculation of exposure. For any subject with exposure calculated to be 0 due to removal of all exposure using this rule above, exposure for analysis purposes will be considered to be 1 day. Treatments will be compared adjusting for baseline percent predicted FEV_1, baseline CAT score, baseline COPD exacerbation history, smoking status at baseline, baseline continuous eosinophil count, and ICS use at baseline *(Table 2.13.1 for the ITT Population and by CAT Score Subpopulation, including the CAT Score Subpopulation of ≥15 [i.e., Symptomatic Population] and Listing 6.1.8)*.

Adjusted rates of exacerbations will be estimated using data-based weights from the study population for the categorical covariates of baseline COPD Exacerbation history, smoking status at baseline, and ICS use at baseline, and the arithmetic mean level of the continuous covariate, baseline percent predicted FEV_1 and baseline continuous eosinophil count.

The time to first COPD exacerbation of any severity will be analyzed up through Day 183 (Week 26) using a Cox regression model (ITT Population and by CAT Score Subpopulation, including the CAT Score Subpopulation of ≥15, i.e., Symptomatic Population). Treatment comparisons will be performed using the model, adjusting for baseline percent predicted FEV_1,

baseline COPD exacerbation history, baseline CAT score, smoking status at baseline, baseline continuous eosinophil count, and ICS use at baseline. SAS PROC PHREG will be used. Estimated adjusted hazard ratios relative to the comparator for each treatment comparison will be displayed along with the associated Wald two-sided 95% confidence intervals and p-values *(Table 2.14 and Listing 6.1.8)*. Hazard ratios will be estimated using the categorical covariates of baseline COPD Exacerbation history, smoking status at baseline, and ICS use at baseline, and the arithmetic mean level of the continuous covariates, baseline percent predicted FEV_1 and baseline continuous eosinophil count,

Time to first COPD exacerbation of any severity will be displayed graphically for each treatment using a Kaplan-Meier curve *(Figure 2.14.1.x for the ITT Population and by CAT Score Subpopulation, including the CAT Score Subpopulation of ≥15 [i.e., Symptomatic Population]).* Subjects who do not experience a COPD exacerbation will be censored at the Week 24 visit or Day 183, whichever is earlier. Subjects who withdraw from the study without experiencing a COPD exacerbation will be censored at the date of withdrawal or the last date of treatment, whichever is later (but on Day 183 or earlier).

The rate of moderate and severe COPD exacerbations and the time to first moderate or severe COPD exacerbation will be analyzed similarly to the rate of COPD exacerbations of any severity and the time to first COPD exacerbation of any severity *(Tables 2.13.1 and 2.14 and Figure 2.14.2 for the ITT Population and by CAT Score Subpopulation and Listing 6.1.8).*

Additional analyses of the rate of COPD exacerbations will be performed with imputation of a moderate exacerbation at the time of dropout for subjects withdrawing prematurely from the trial, unless an exacerbation has already been recorded at that time. Analyses with imputation will be provided in Table 2.13.2 *for the ITT Population and by CAT Score Subpopulation, including the CAT Score Subpopulation of ≥15 (i.e., Symptomatic Population)*.

Exacerbations starting after the end of treatment which are noted at the follow-up telephone call will not be included in the inferential analyses, but will be reported in the data listing *(Listing 6.1.8)*.

Time to Treatment Failure

Treatment failure will be defined as a moderate or severe COPD exacerbation or discontinuation from the study for any reason. The time to treatment failure up through Day 183 (Week 26) will be analyzed using a Cox regression model for the ITT Population and by CAT Score Subpopulation, including the CAT Score Subpopulation of ≥15 (i.e., Symptomatic Population). The model will include treatment, baseline percent predicted FEV_1, baseline COPD exacerbation history, baseline CAT score, smoking status at baseline (current vs former), baseline continuous eosinophil count, and ICS use at baseline. Estimated adjusted hazard ratios will be displayed along with associated 95% confidence interval and p-values *(Table 2.15)*. Time to treatment failure will be displayed graphically for each treatment group using a Kaplan-Meier curve *(Figure 2.15.x for the ITT Population and by CAT Score Subpopulation, including the CAT Score Subpopulation of ≥15 [i.e., Symptomatic Population])*. Subjects who did not experience a

treatment failure will be censored at the Week 24 visit or Day 183, whichever was earlier. The basic assumptions of the model including the proportional hazards assumption will be checked.

Time to First Clinically Important Deterioration (CID) and Time to First Sustained CID

First clinically important deterioration (CID) will be defined as the first occurrence of one of the following events: 1) ≥ 100 mL decline in trough FEV_1; 2) a treatment emergent moderate/severe COPD exacerbation; or 3) increase of ≥ 4 units on the SGRQ. A second definition of CID will include a 4th condition for death.

A sustained decline in trough FEV_1 will be defined as ≥100 mL decline in trough FEV_1 on 2 consecutive analysis visits or for ≥50% of all subsequent analysis visits with available trough FEV_1.

Likewise, a sustained SGRQ increase will be defined as ≥4 points increase in SGRQ on 2 consecutive analysis visits or for ≥50% of all subsequent analysis visits with available SGRQ.

First sustained CID will be defined as the first occurrence of one of the following events: 1) a sustained decline in trough FEV_1; 2) a sustained SGRQ increase; or 3) a treatment emergent moderate/severe COPD exacerbation.

Time to first event analysis will be produced for CID, CID with death, sustained CID, and each of their individual component events, using the Cox regression model for the ITT Population overall and by CAT Score Subpopulation, including CAT Score ≥15 (i.e., Symptomatic Population). The regression will adjust for baseline percent predicted FEV_1, baseline CAT score, baseline COPD exacerbation history (yes/no), smoking status at baseline (former smoker/current smoker), baseline continuous eosinophil count, and inhaled corticosteroid use at baseline (yes/no). Estimated adjusted hazard ratios will be displayed along with associated 95% confidence interval and p-values *(Tables 2.16.1, 2.16.2, and 2.17.1).* Median time to first CID will be provided. Time to first CID, first CID with death, and first sustained CID will be displayed graphically for each treatment group using a Kaplan-Meier curve *(Figures 2.16.1.x, 2.16.2.x, and 2.17.1., respectively, for the ITT Population and by CAT Score Subpopulation, including CAT* ≥15 *[i.e., Symptomatic Population]*). Subjects who did not experience a component event will be censored at the Week 24 visit or Day 183, whichever was earlier. The basic assumptions of the model including the proportional hazards assumption will be checked.

Time to first trough FEV_1 event will be the study day of the post-baseline analysis visit when change from baseline in trough FEV_1 was ≤ -100 mL. If this event did not occur, the observation will be censored at the last analysis visit where trough FEV_1 was evaluated. Time to first sustained decline in trough FEV_1 will be the study day of the initial decline, satisfying the sustained definition. If the subject did not experience a sustained trough FEV_1 decline, censoring will occur at the second-last analysis visit where trough FEV_1 was evaluated.

Similar considerations apply to time to first SGRQ event and first sustained SGRQ event.

Time to a CID event or sustained CID event will be based on the time of the component event which occurred first. Subjects who did not have a CID event will be censored at the earliest censoring day among the component censoring times. COPD exacerbations occurring past Day 183 will not be counted as CID events.

Symptom Scores (Daily, Daytime and Nighttime Symptom Scores)

All subjects will be provided with an electronic subject diary to record daytime and nighttime clinical symptoms: cough, shortness of breath, sputum volume, nighttime awakenings and medication (albuterol sulfate and salbutamol) use *(Listing 6.1.7)*.

For the purpose of statistical analysis, the following numeric scores will be assigned to responses for the symptoms questions:

Table 7 Numeric Scoring for Symptoms Diary Questions

Question	Response
How many times did you wake up last night?	**0** = None **1** = 1 **2** = 2 **3** = 3 **4** = 4 **5** = 5 or more times **6** = I was awake most or all of the night
How short of breath were you last night?	**0** = Not at all **1** = Mild **2** = Moderate **3** = Severe **4** = Very severe
How many puffs of rescue medication (Ventolin HFA) have you taken since you took your study medication last night (this morning)?	**0** = 0 **1** = 1 **2** = 2 **3** = 3 **4** = 4 **5** = 5 **6** = 6 **7** = 7 **8** = 8 **9** = 9 **10** = 10 Etc.

Question	Response
How often did you cough last night (today)?	**0** = Not at all **1** = Rarely **2** = Frequently **3** = Almost constantly
How much mucus (phlegm) did you cough up last night (today)?	**0** = None **1** = Less than 1 teaspoon (5 mL) **2** = 1-2 teaspoon (5-10 mL) **3** = More than 2 teaspoons (10 mL)
Did you feel short of breath today? and When did you feel short of breath? (highest response would be selected for analysis)	**0** = Not at all, and I was active **1** = Not at all, and I rested today *=Yes, I felt short of breath today **2** = During exercise **3** = Walking upstairs, uphill, or quickly **4** = Walking slowly or during light activity **5** = Washing or dressing **6** = Sitting or resting *Depends on response to follow up question

Individual missing scores for a symptom will be imputed in order to calculate the total symptoms score. Individual scores on a study day will be imputed using the average of the day prior and the day after. If data are not available for these days, the average of the score on the day will be imputed using the average of scores for the day for the subject's treatment group.

The analysis of rescue Ventolin HFA use has already been described in Section 6.4.2.4 above.

The mean daily total symptom score, the mean daytime symptom score and the mean nighttime symptom score will be calculated for each subject over 24 weeks, over Weeks 12-24, and for each 4-week interval of the 24-week Treatment Period. The last seven days of the 10-14 day Screening Period will be used to calculate the baseline. Calculation of the symptom scores will be based on scaled rescue Ventolin HFA use with the following categories:

Table 8 Scaling of Rescue Ventolin Use for Calculation of Symptom Scores

Variable	Scaling
Total Symptom Score	Using the total number of daytime and nighttime puffs of rescue Ventolin HFA: 0 = No rescue Ventolin HFA use 1=1-2 puffs 2=3-4 puffs 3=5-6 puffs 4=7-8 puffs 5=9-10 puffs 6=>10 puffs
Daytime Symptom Score	Using number of daytime puffs of rescue Ventolin HFA: 0 = No rescue Ventolin HFA use 1 = 1-2 puffs 2 = 3-4 puffs 3 = 5-6 puffs 4 = > 6 puffs
Nighttime Symptom Score	Using number of nighttime puffs of rescue Ventolin HFA: 0 = No rescue Ventolin HFA use 1 = 1-2 puffs 2 = 3-4 puffs 3 = 5-6 puffs 4 = > 6 puffs

The mean changes from baseline in the daily, daytime and nighttime symptom scores will be analyzed using a similar model as for morning pre-dose trough FEV_1 in Section 6.4.2.4 above in order to estimate treatment effects over 24 weeks and over Weeks 12-24 *(Table and Figure 2.18.1 for the ITT Population)*. In addition, summaries of the daily, daytime and nighttime symptom scores will be provided for each 4-week period *(Table and Figure 2.18.1 for the ITT Population)*. The above summaries will be repeated for each individual symptom score *(Tables and Figures 2.18.2 through 2.18.5 for cough, shortness of breath, sputum volume, and nighttime awakenings for the ITT Population; note that nighttime awakenings will be captured only in the morning and will be provided for morning summaries only)*.

Correlations Among Measures

Pearson and Spearman rank correlations within subjects will be estimated between pairs of variables (*Table 2.19.1 and 2.19.2 and Figures 2.19.1 through 2.23.55)*. Where appropriate, the variable averages across visits will be used to estimate the correlations using all data available.

The following variables will be correlated pairwise:

- Change from baseline in morning pre-dose trough FEV_1 at Week 24
- Peak change from baseline in FEV_1 at Week 24
- Change from baseline in SGRQ total score at Week 24
- Change from baseline in morning pre-dose trough FEV_1 over 24 weeks
- TDI focal score over 24 weeks
- Peak change from baseline in FEV_1 over 24 weeks
- Change from baseline in rescue Ventolin HFA use over 24 weeks

Additionally, the following variables will be correlated with the above variables and with each other separately:

- Change from baseline in morning pre-dose trough FEV_1 over Weeks 12-24
- Peak change from baseline in FEV_1 over Weeks 12-24
- Change from baseline in SGRQ total score over Weeks 12-24
- TDI focal score over Weeks 12-24

6.4.4 Control of Type I Error

There are three separate approaches for the control of Type I error: 1) US/China, 2) EU/South Korea/Taiwan, and 3) Japan.

6.4.4.1 US/China Approach

Strong control of the Type I error rate will be maintained at the two-sided 0.05 level for the primary endpoint across products using a sequential approach and then within each comparison for the secondary measures using a simultaneous approach as detailed below. Based on positive dependence of the test statistics (Sarkar, 2008; Sarkar, 1997), simultaneous control of Type I error for the secondary measures will be achieved using the Hochberg procedure (Hochberg, 1988). All endpoints will be tested using the ITT Population unless otherwise noted.

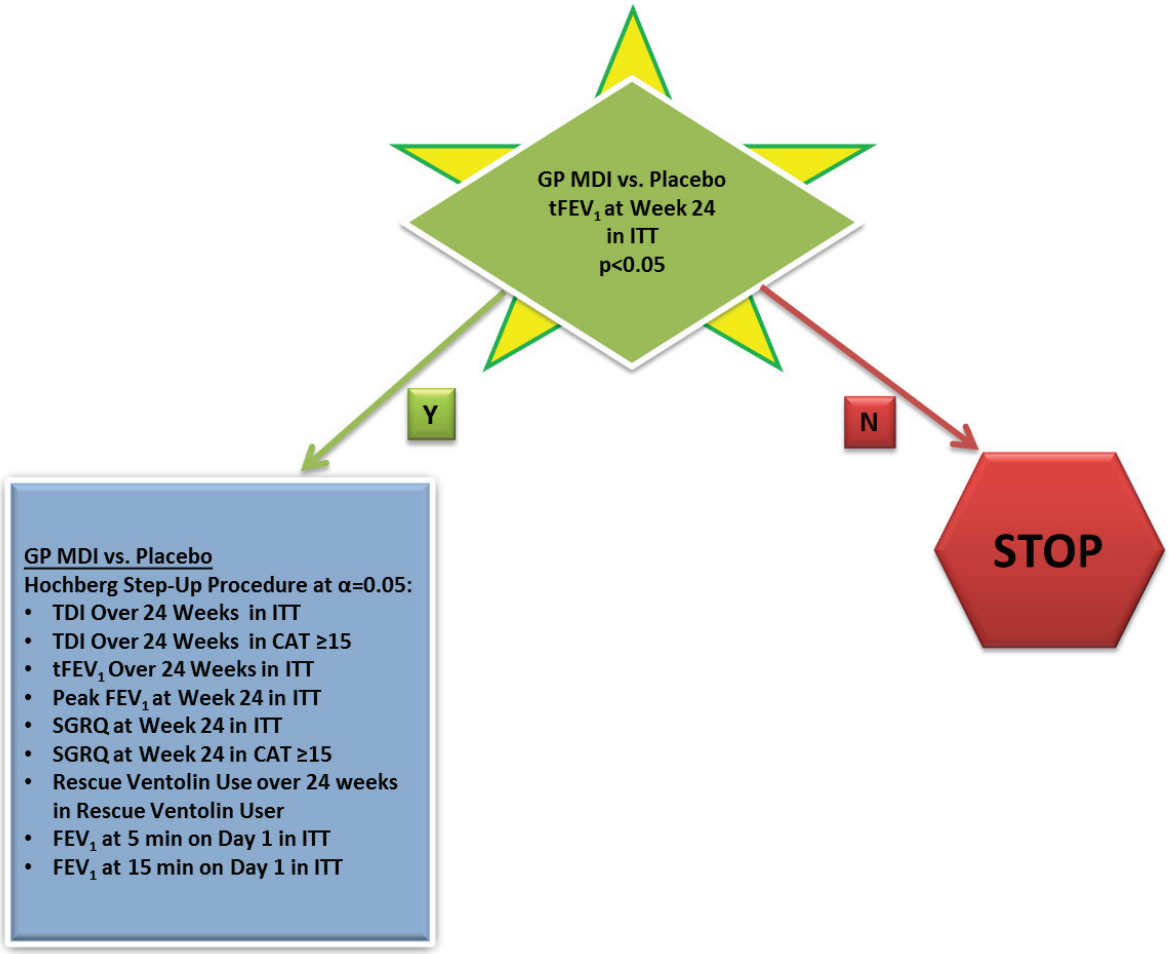
Control of Type I Error for GP MDI

For GP MDI, Type I error control will be achieved by comparing GP MDI to Placebo MDI using a two-sided alpha of 0.05 for the change from baseline in morning pre-dose trough FEV_1 at Week 24 first and continuing to assessment of secondary measures if this comparison is statistically significant. The secondary endpoints (TDI over 24 weeks, TDI over 24 weeks in the

Symptomatic Population, change in morning pre-dose trough FEV_1 over 24 weeks, peak change in FEV_1 at Week 24, change in SGRQ at Week 24, change in SGRQ at Week 24 in the Symptomatic Population, change in rescue Ventolin [albuterol sulfate] HFA use over 24 weeks in the Rescue Ventolin User Population, FEV_1 at 5 minutes post-dosing on Day 1, and FEV_1 at 15 minutes post-dosing on Day 1) will be tested simultaneously using the Hochberg procedure with a two-sided alpha of 0.05.

This strategy is illustrated in Figure 2.

Figure 2 Type I Error Control for GP MDI (US/China)



The CAT ≥15 population is the Symptomatic Population.

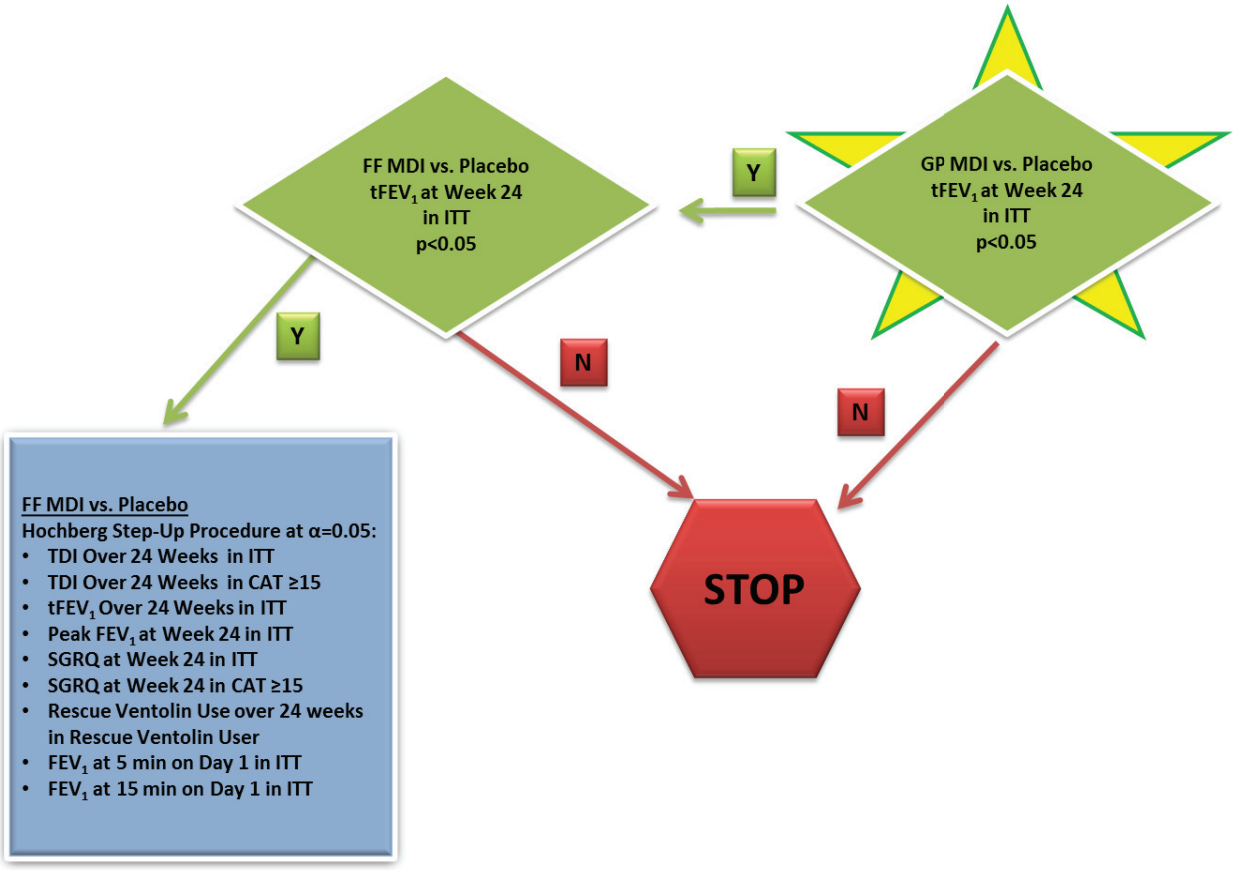
Control of Type I Error for FF MDI

Provided that the comparison between GP MDI and Placebo MDI is significant for the primary endpoint, comparisons using FF MDI will be interpreted inferentially. Type I error control will be achieved by comparing FF MDI to Placebo MDI using a two-sided alpha of 0.05 for the

change from baseline in morning pre-dose trough FEV_1 at Week 24 first and continuing to assessment of secondary measures if this comparison is statistically significant. The secondary endpoints (TDI over 24 weeks, TDI over 24 weeks in the Symptomatic Population, morning pre-dose trough FEV_1 over 24 weeks, peak FEV_1 at Week 24, SGRQ at Week 24, SGRQ at Week 24 in the Symptomatic Population, rescue Ventolin [albuterol sulfate] HFA use over 24 weeks in the Rescue Ventolin User Population, FEV_1 at 5 minutes post-dosing on Day 1, and FEV_1 at 15 minutes post-dosing on Day 1) will be tested simultaneously using the Hochberg procedure with a two-sided alpha of 0.05.

This strategy is illustrated in Figure 3.

Figure 3 Type I Error Control for FF MDI (US/China)



The CAT ≥15 population is the Symptomatic Population.

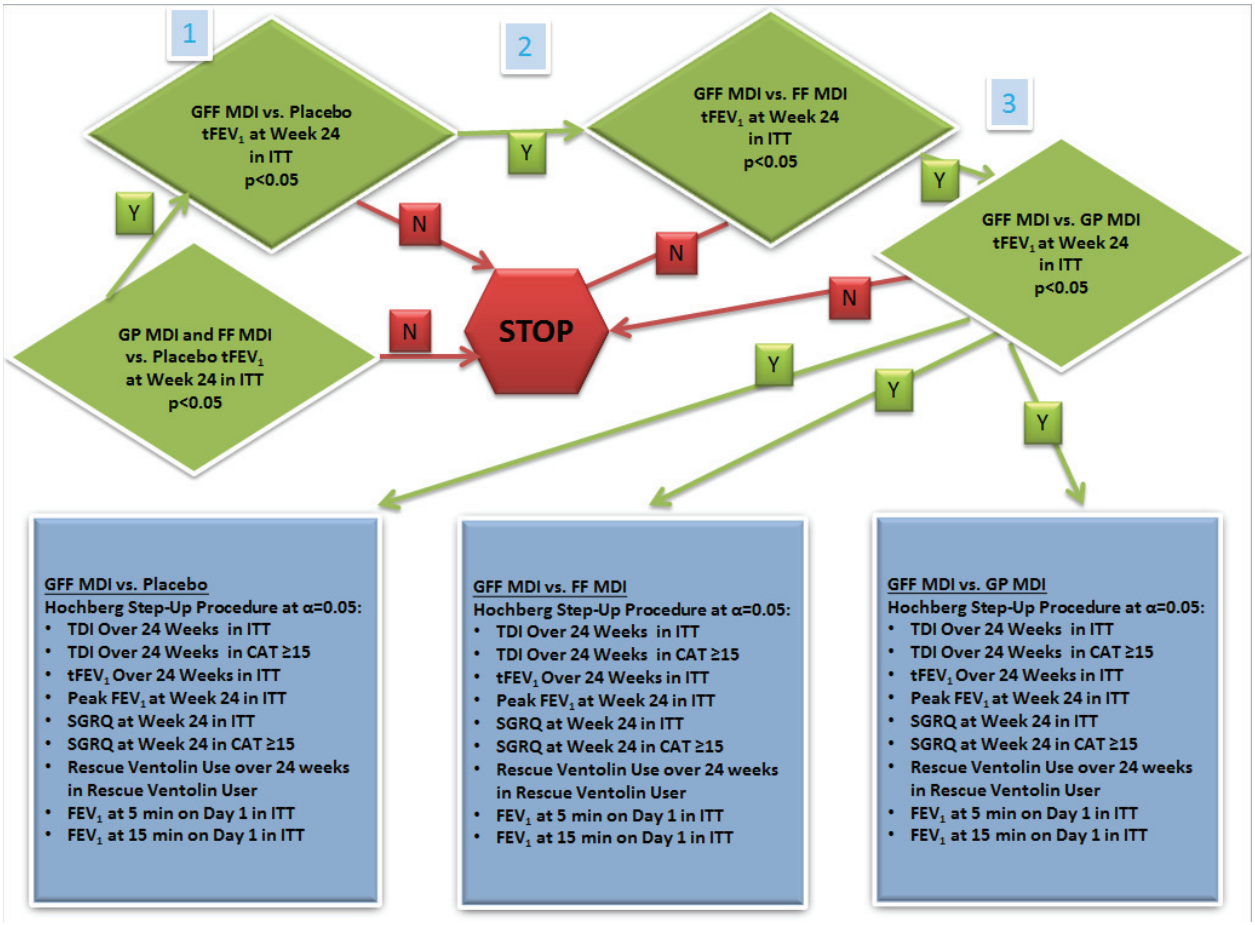
Control of Type I Error for GFF MDI

Provided that the comparisons between FF MDI and Placebo MDI and between GP MDI and Placebo MDI are significant for the primary endpoint, comparisons using GFF MDI will be interpreted inferentially. Type I error will be strictly controlled for the primary endpoint and will be controlled within each treatment comparison for the secondary assessments. GFF MDI will

be compared to Placebo MDI, then FF MDI, and finally GP MDI for morning pre-dose trough FEV_1 at Week 24 using a two-sided alpha level of 0.05 and continuing sequentially if each comparison is statistically significant. If GFF MDI is significantly superior to its components for the primary endpoint, the secondary measures of TDI over 24 weeks, TDI over 24 weeks in the Symptomatic Population, morning pre-dose trough FEV_1 over 24 weeks, peak FEV_1 at Week 24, SGRQ at Week 24, SGRQ at Week 24 in the Symptomatic Population, rescue Ventolin (albuterol sulfate) HFA use over 24 weeks in the Rescue Ventolin User Population, and for GFF MDI vs. Placebo MDI in order to evaluate onset of action, FEV_1 at 5 minutes post-dosing on Day 1 and FEV_1 at 15 minutes post-dosing on Day 1 will be evaluated for significance. Type I error will be controlled at the two-sided alpha of 0.05 within each comparison (GFF MDI vs. Placebo MDI, GFF MDI vs. FF MDI, and GFF MDI vs. GP MDI) using a simultaneous approach based on the Hochberg procedure.

This strategy is illustrated in Figure 4.

Figure 4 Type I Error Control for GFF MDI (US/China)



The CAT ≥15 population is the Symptomatic Population.

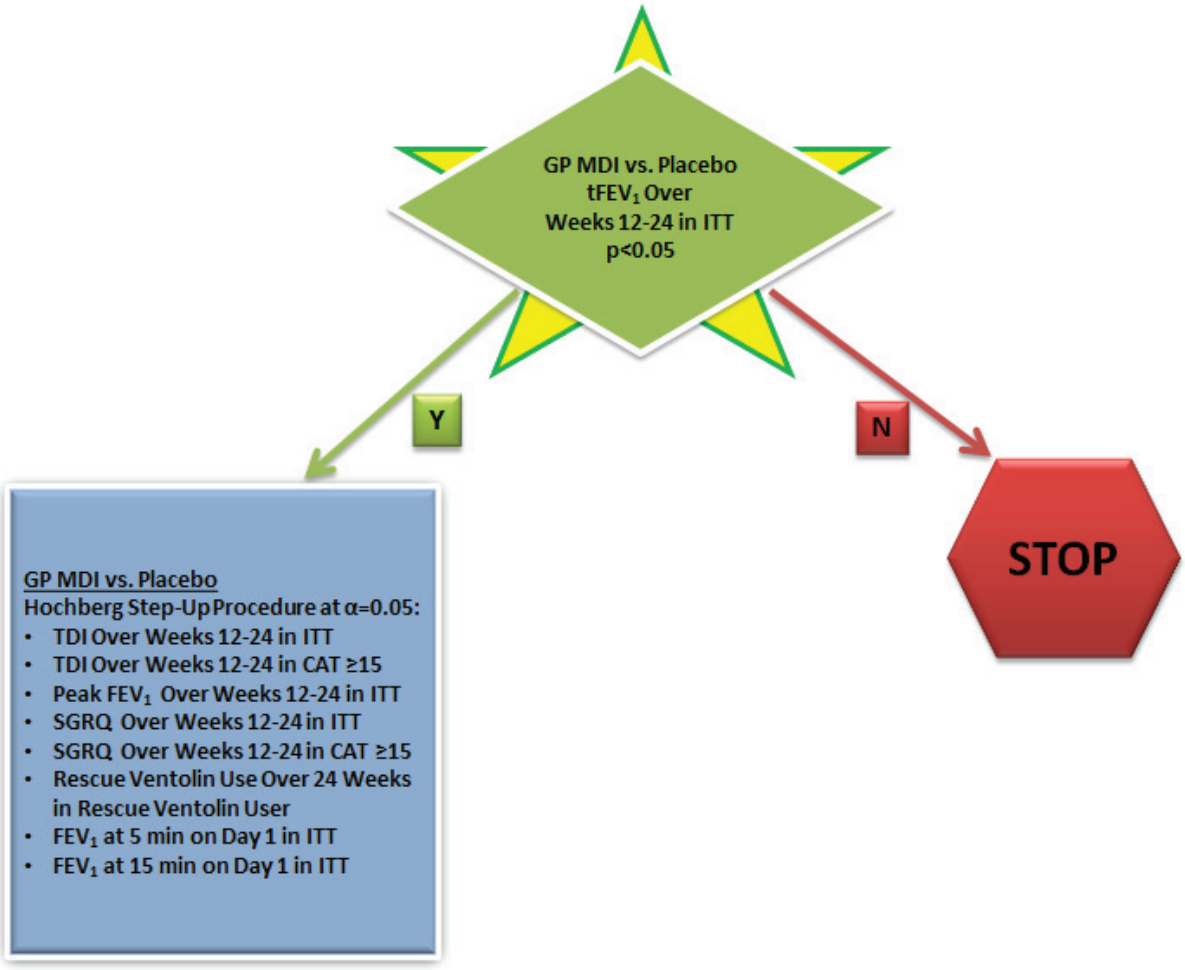
6.4.4.2 Japan Approach

Strong control of the Type I error rate will be maintained at the two-sided 0.05 level for the primary endpoint across products using a sequential approach and then within each comparison for the secondary measures using a simultaneous approach as detailed below. Based on positive dependence of the test statistics (Sarkar 2008; Sarkar, 1997), simultaneous control of Type I error for the secondary measures will be achieved using the Hochberg procedure (Hochberg, 1988). All endpoints will be tested using the ITT Population unless otherwise noted.

Control of Type I Error for GP MDI

For GP MDI, Type I error control will be achieved by comparing GP MDI to Placebo MDI using a two-sided alpha of 0.05 for the change from baseline in morning pre-dose trough FEV_1 over Weeks 12 to 24 first and continuing to assessment of secondary measures if this comparison is statistically significant. The secondary endpoints (TDI over Weeks 12 to 24, TDI over Weeks 12 to 24 in the Symptomatic Population, peak FEV_1 over Weeks 12 to 24, SGRQ over Weeks 12 to 24, SGRQ over Weeks 12 to 24 in the Symptomatic Population, rescue Ventolin [albuterol sulfate] HFA use over 24 weeks in the Rescue Ventolin User Population, FEV_1 at 5 minutes post-dosing on Day 1, and FEV_1 at 15 minutes post-dosing on Day 1) will be tested simultaneously using the Hochberg procedure with a two-sided alpha of 0.05. This strategy is illustrated in Figure 5.

Figure 5 Type I Error Control for GP MDI (Japan)



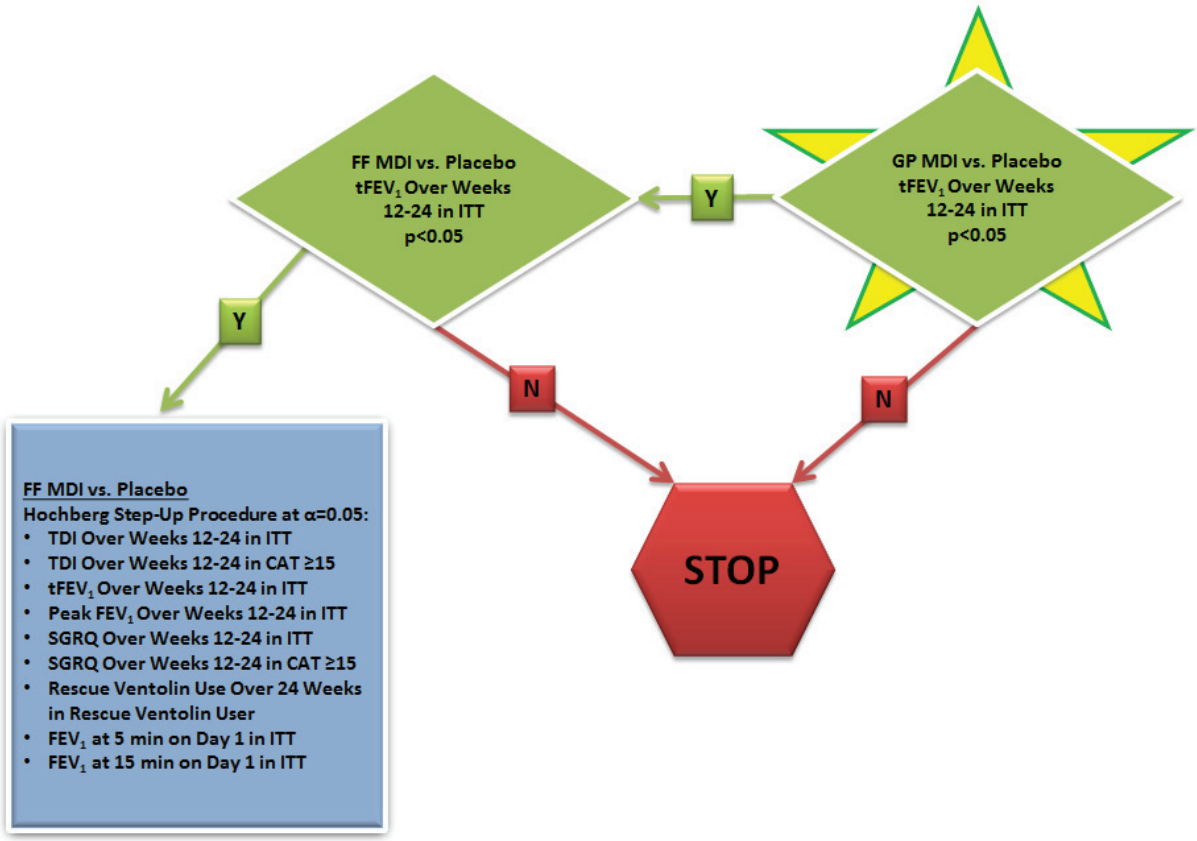
The CAT ≥15 population is the Symptomatic Population.

Control of Type I Error for FF MDI

Provided that the comparison between GP MDI and Placebo MDI is significant for the primary endpoint, comparisons using FF MDI will be interpreted inferentially. Type I error control will be achieved by comparing FF MDI to Placebo MDI using a two-sided alpha of 0.05 for the change from baseline in morning pre-dose trough FEV_1 over Weeks 12 to 24 first and continuing to assessment of secondary measures if this comparison is statistically significant. The secondary endpoints (TDI over Weeks 12 to 24, TDI over Weeks 12 to 24 in the Symptomatic Population, peak FEV_1 over Weeks 12 to 24, SGRQ over Weeks 12 to 24, SGRQ over Weeks 12 to 24 in the Symptomatic Population, rescue Ventolin [albuterol sulfate] HFA use over 24 weeks in the Rescue Ventolin User Population, FEV_1 at 5 minutes post-dosing on Day 1, and FEV_1 at 15 minutes post-dosing on Day 1) will be tested simultaneously using the Hochberg procedure with a two-sided alpha of 0.05.

This strategy is illustrated in Figure 6.

Figure 6 Type I Error Control for FF MDI (Japan)



The CAT ≥15 population is the Symptomatic Population.

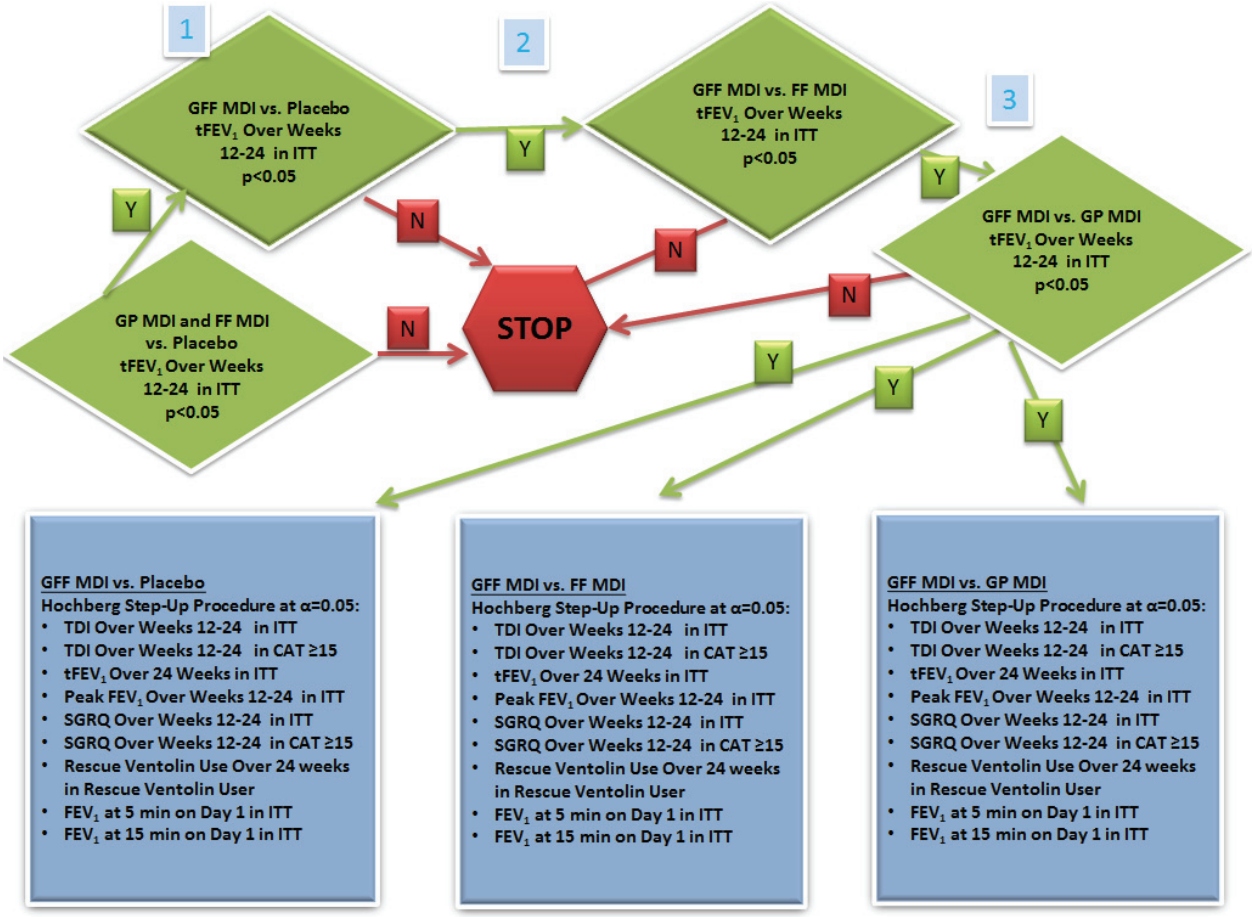
Control of Type I Error for GFF MDI

Provided that the comparison between FF MDI and Placebo MDI and between GP MDI and Placebo MDI are significant for the primary endpoint, comparisons using GFF MDI will be interpreted inferentially. Type I error will be strictly controlled for the primary endpoint and will be controlled within each treatment comparison for the secondary assessments. GFF MDI will be compared to Placebo MDI, then FF MDI, and finally GP MDI for morning pre-dose trough FEV_1 over Weeks 12 to 24 using a two-sided alpha level of 0.05 and continuing sequentially if each comparison is statistically significant. If GFF MDI is significantly superior to its components for the primary endpoint, the secondary measures of TDI over Weeks 12 to 24, TDI over Weeks 12 to 24 in the Symptomatic Population, peak FEV_1 over Weeks 12 to 24, SGRQ over Weeks 12 to 24, SGRQ over Weeks 12 to 24 in the Symptomatic Population, rescue Ventolin (albuterol sulfate) HFA use over 24 weeks in the Rescue Ventolin User Population, and for GFF MDI vs. Placebo MDI in order to evaluate onset of action, FEV_1 at 5 minutes post-dosing on Day 1 and FEV_1 at 15 minutes post-dosing on Day 1 will be evaluated for

significance. Type I error will be controlled at the two-sided alpha of 0.05 within each comparison (GFF MDI vs. Placebo MDI, GFF MDI vs. FF MDI, and GFF MDI vs. GP MDI) using a simultaneous approach based on the Hochberg procedure.

This strategy is illustrated in Figure 7.

Figure 7 Type I Error Control for GFF MDI (Japan)



The CAT ≥15 population is the Symptomatic Population.

6.4.4.3 EU/South Korea/Taiwan Approach

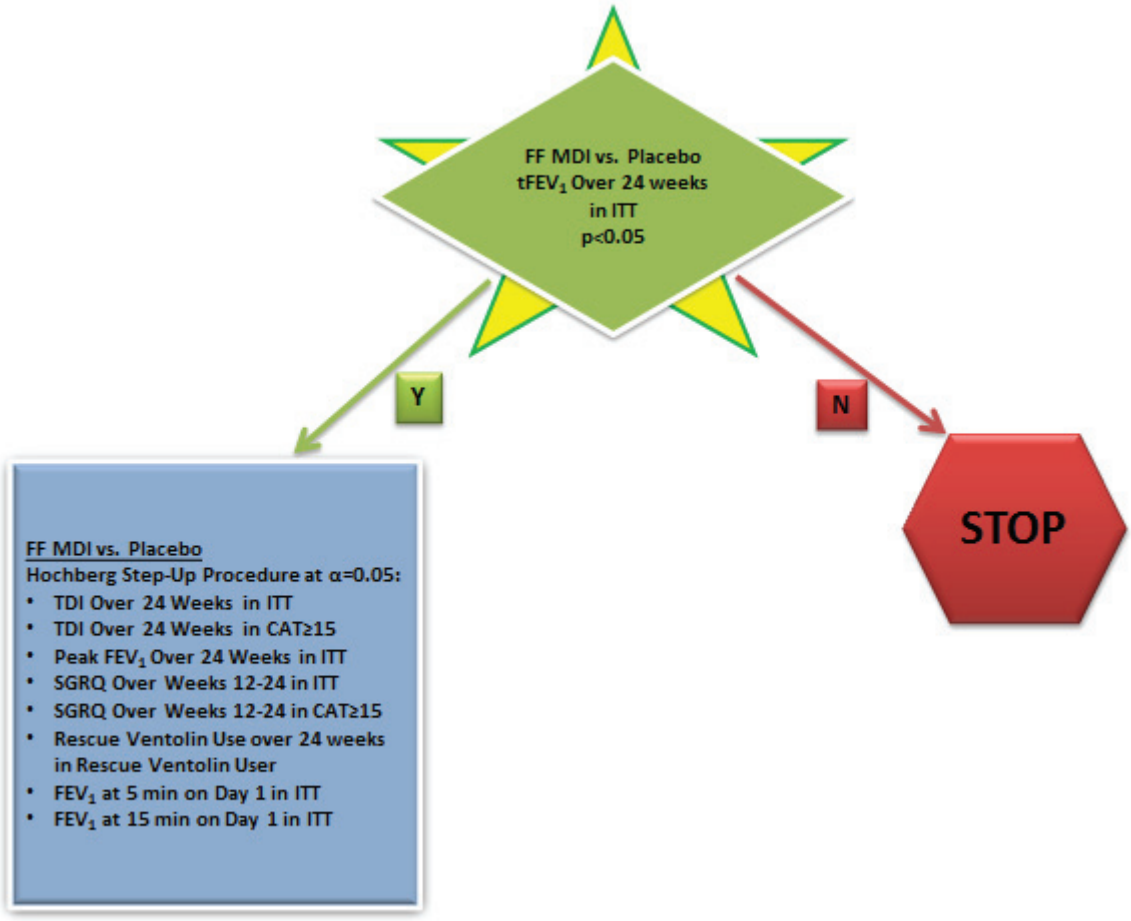
Strong control of the Type I error rate will be maintained at the two-sided 0.05 level for the key comparisons for each product using the approaches detailed below and across products for the primary endpoint for GFF MDI. All endpoints will be tested using the ITT Population unless otherwise noted.

Control of Type I Error for FF MDI

For FF MDI, Type I error control will be achieved by comparing FF MDI to Placebo MDI using a two-sided alpha of 0.05 for the change from baseline in morning pre-dose trough FEV_1 over 24 weeks first and continuing to assessment of secondary measures if this comparison is statistically significant. The secondary measures (TDI over 24 weeks, TDI over 24 weeks in the Symptomatic Population, peak FEV_1 over 24 weeks, SGRQ over Weeks 12-24, SGRQ over Weeks 12-24 in the Symptomatic Population, rescue Ventolin (albuterol sulfate) HFA use over 24 weeks in the Rescue Ventolin User Population, FEV_1 at 5 minutes post-dosing on Day 1, and FEV_1 at 15 minutes post-dosing on Day 1) will be tested simultaneously using the Hochberg procedure with a two-sided alpha of 0.05.

This strategy is illustrated in Figure 8.

Figure 8 Type I Error Control for FF MDI (EU/South Korea/Taiwan)



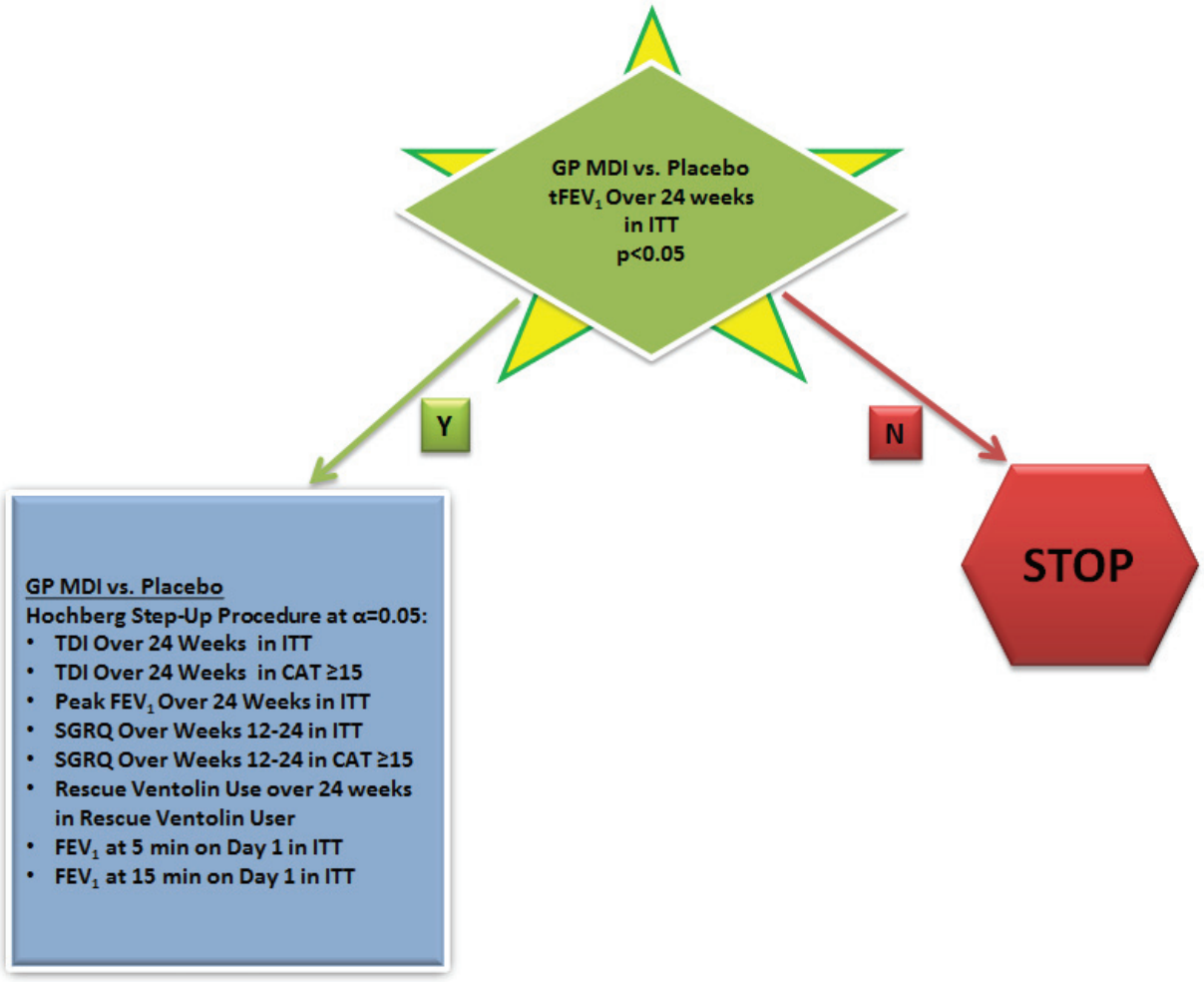
The CAT ≥15 population is the Symptomatic Population.

Control of Type I Error for GP MDI

For GP MDI, Type I error control will be achieved by comparing GP MDI to Placebo MDI using a two-sided alpha of 0.05 for the change from baseline in morning pre-dose trough FEV_1 over 24 weeks first and continuing to assessment of secondary measures if this comparison is statistically significant. The secondary measures (TDI over 24 weeks, TDI over 24 weeks in the Symptomatic Population, peak FEV_1 over 24 weeks, SGRQ over Weeks 12-24, SGRQ over Weeks 12-24 in the Symptomatic Population, rescue Ventolin [albuterol sulfate] HFA use over 24 weeks in the Rescue Ventolin User Population, FEV_1 at 5 minutes post-dosing on Day 1, and FEV_1 at 15 minutes post-dosing on Day 1) will be tested simultaneously using the Hochberg procedure with a two-sided alpha of 0.05.

This strategy is illustrated in Figure 9.

Figure 9 Type I Error Control for GP MDI (EU/South Korea/Taiwan)

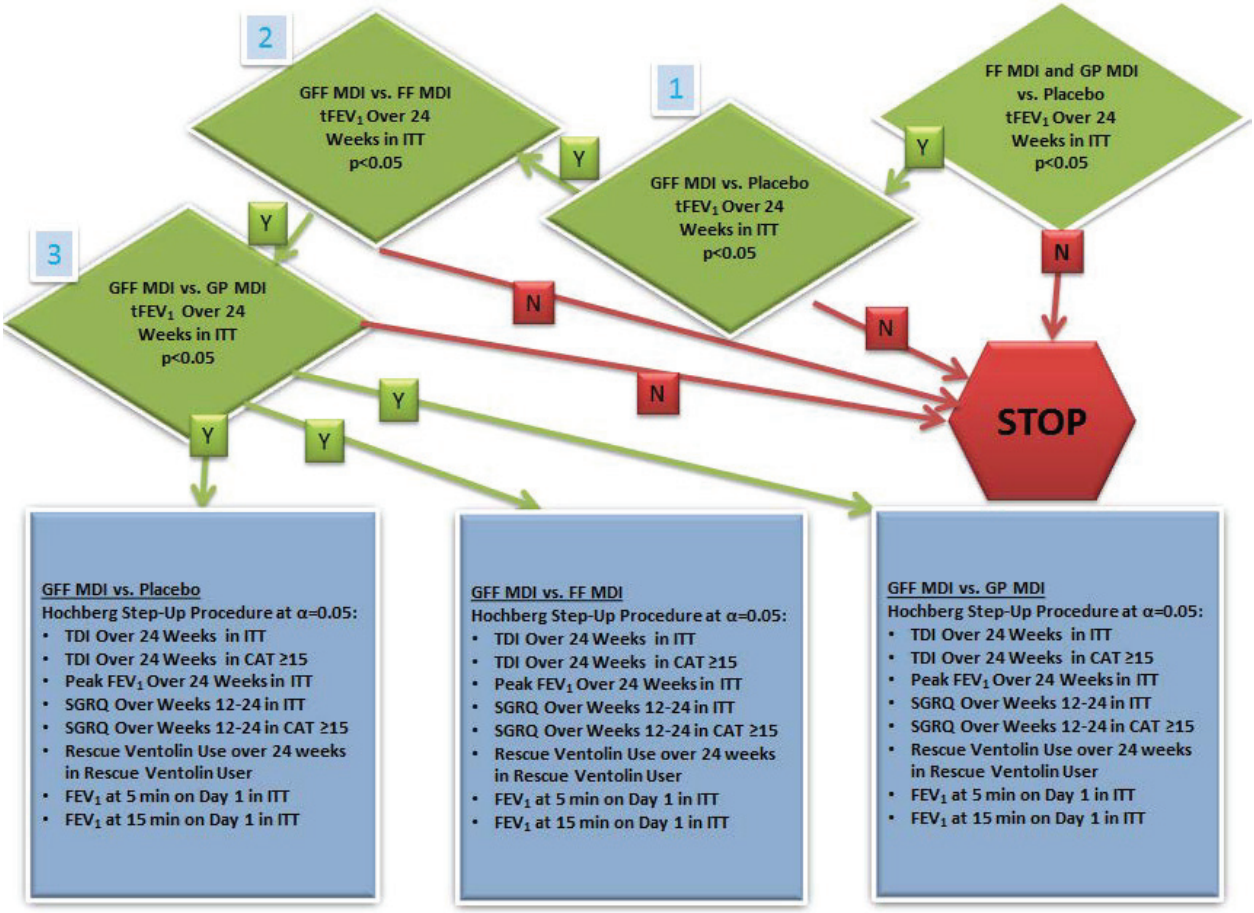


The CAT ≥15 population is the Symptomatic Population.

Control of Type I Error for GFF MDI

If the comparisons of FF MDI and GP MDI to Placebo MDI are significant for morning pre-dose trough FEV1, then GFF MDI will be sequentially compared to: 1) Placebo MDI using morning pre-dose trough FEV_1; 2) FF MDI using morning pre-dose trough FEV_1; and 3) GP MDI using morning pre-dose trough FEV_1 using a two-sided alpha level 0.05. Provided the comparisons of GFF MDI to its components are significant for morning pre-dose trough FEV_1, the secondary endpoints of TDI over 24 weeks, TDI over 24 weeks in the Symptomatic Population, peak FEV_1 over 24 weeks, SGRQ over Weeks 12-24, SGRQ over Weeks 12-24 in the Symptomatic Population, rescue Ventolin (albuterol sulfate) HFA use over 24 weeks in the Rescue Ventolin User Population, and for GFF MDI vs. Placebo MDI in order to evaluate onset of action, FEV_1 at 5 minutes post-dosing on Day 1 and FEV_1 at 15 minutes post-dosing on Day 1, will be evaluated for significance. Type I error will be controlled at the two-sided alpha of 0.05 within each comparison (GFF MDI vs. Placebo MDI, GFF MDI vs. FF MDI, and GFF MDI vs. GP MDI) using the Hochberg procedure. This strategy is illustrated in Figure 10.

Figure 10 Type I Error Control for GFF MDI (EU/South Korea/Taiwan)



The CAT ≥15 population is the Symptomatic Population.

6.5 Healthcare Resource Utilization

Data on healthcare resource utilization will be collected at all visits post-baseline.

The following variables will be calculated unadjusted (per subject) over the entire Treatment Period and also adjusted (per subject per year) and tabulated by actual treatment received for those subjects for whom they or one or more of their family members missed work:

- The number of days missed work
- The number of days that family members of subjects missed from work

The following variables will be tabulated by actual treatment received and relationship to COPD (COPD-related, not COPD-related, and combined). The means calculated across all subjects in a treatment will be calculated unadjusted (per subject) and also adjusted (per subject per year).

- The percentage of subjects with telephone calls to health care providers
- The mean number of telephone calls to health care providers
- The percentage of subjects with visits to health care providers
- The mean number of visits to health care providers
- The percentage of subjects with ER visits
- The mean number of visits to ERs
- The percentage of subjects hospitalized
- The mean number of subject hospitalizations
- The mean number of days in the hospital
- The percentage of subjects in the ICU
- The mean number of days in ICUs
- The percentage of subjects in the CCU
- The mean number of days in CCUs
- The percentage of subjects intubated of those who were hospitalized.

Analyses will be performed using the Safety Population.

Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be provided by actual treatment received for the number of days missed from work per year, the number of days that family members of subjects missed from work per year overall during the study *(Table 2.38.1 and Listing 6.2)*.

Also, descriptive statistics will be provided by actual treatment received and relationship to COPD (related, not-related, and total) overall during the entire Treatment Period for the following variables: the number of telephone calls to health care providers, the number of visits to health care providers, the number of ER visits, the number of subject hospitalizations, the

number of days in the hospital, the number of days in the ICU, and the number of days in the CCU *(Table 2.38.2 and Listing 6.2)*. The percentage of subjects intubated of those who were hospitalized will also be summarized by actual treatment received and relationship to COPD (related, non-related, and total).

The following tabulations will also be prepared for hospitalizations that were designated by the investigator as drug-related on the AE eCRF: the number and percentage of subjects hospitalized, the number of subject hospitalizations, the number of days in the hospital, the number and percentage of subjects with stays in the ICU, the number of days in the ICU, the number and percentage of subjects with stays in the CCU, and the number of days in the CCU *(Table 2.38.2 and Listing 6.2)*. The percentage of subjects intubated of those who were hospitalized will also be summarized by actual treatment received.

HCRU data will be combined with economic data collected independently of the study to construct comparative health economic analyses between treatment groups. This analysis will be reported separate from the main study report.

6.6 Safety Analysis

All safety analyses are based on the Safety Population. Hypothesis testing will not be performed for any safety analyses.

6.6.1 Adverse Events

Adverse events will be collected. Coding of adverse events for database lock will be done using Version 20.0 of the Medical Dictionary for Regulatory Activities (MedDRA). A glossary of MedDRA preferred terms used for adverse events reported in the study along with the associated Investigator's verbatim text will be provided in Listing 7.2. During the study coded terms will be updated as later versions of MedDRA become available, but updates will not occur after Version 20.0 of MedDRA.

Adverse events that occur between the time the subject signs the informed consent form for the study and the time when that subject is randomized were to be recorded as medical history and not as a study adverse event unless the event meets the definition of a serious adverse event (SAE).

An adverse event is considered treatment-emergent if the date of onset is on or after the date of first dose of study medication in the study. An adverse event would be considered attributable to a treatment if the onset of the AE was during the Treatment Period or occurred in the follow-up period afterwards. Adverse events after the Follow-up Telephone Call scheduled at least 14 days after Visit 11 or a discontinuation visit will not be considered treatment-emergent, but will be listed in adverse event data listings.

Analysis endpoints for adverse events include both the numbers of treatment-emergent adverse events as observed by the investigational team or reported by the subject, and the incidence rates

of treatment-emergent adverse events. The incidence of a treatment-emergent adverse event will be defined as the number and percentage of subjects experiencing an event.

Events with Irregular Onset Dates: All treatment-emergent adverse events will be included in the data listings regardless of the completeness of the onset dates. Partial dates will be imputed in order to determine if an AE is treatment-emergent using the imputation rules in Appendix 1; however, imputed dates will not be provided in the data listings.

All adverse events, whether treatment-emergent or not, will be included in the listings. Reported adverse events by system organ class, preferred term, treatment, country, center, subject and onset day will be provided *(Listing 7.1)*. Reported adverse events by treatment, country, center, subject, and onset date will be presented in Listing 7.3.

The listing of adverse events will provide the severity, maximum severity, relationship to study drug, action taken and outcome for each adverse event. Any SAEs reported will be listed (*Tables 3.8.1 and 3.8.2, by treatment and region subgroup and country).* Adverse events leading to discontinuation of study medication will be listed *(Table 3.6, by region subgroup and country)*. A listing of any reported deaths during the study (prior to randomization, during treatment, within 14 days post-treatment, or after 14 days post-treatment) will be provided (*Table 3.13, by treatment and region subgroup and country*); study treatment taken prior to the death and the number of days since the last dose of this study treatment at the time of the death will be included in the listing. An overview table will be prepared with the incidences of subjects, for all subjects and for each treatment, with the following: at least one treatment-emergent adverse event, at least one treatment-emergent related adverse event, at least one treatment-emergent serious adverse event, at least one treatment-emergent serious related adverse event, at least one treatment-emergent adverse event leading to early withdrawal, at least one treatment-emergent serious adverse event leading to withdrawal, and a report of death *(Tables 3.1.2.x, overall and by China and Japan regional subgroups and for the regional subgroups of non-Japan, Asia, as well as by country).*

For the purpose of determining if a death occurred during a Treatment Period (for Tables 3.13 and 3.1.2.x), the end of the Treatment Period is defined as the date of the last visit in the Treatment Period, the date of the Discontinuation Visit in the Treatment Period, or if these dates were missing, the date of the last data collection for the Treatment Period (i.e., date of death).

The incidence of an adverse event (AE) will be defined as the number and percentage of subjects experiencing an event. Summary tabulations of the following will be prepared for all subjects, for each treatment, for each primary system organ class, and for each preferred term within a system organ class:

4. The incidence of all treatment-emergent adverse events *(Table 3.2.1.1.1)*
5. The incidence of treatment-emergent adverse events with onset after the last date on treatment *(Table 3.2.1.2.1)*

6. The incidence of non-serious treatment-emergent adverse events occurring in ≥5% of subjects in a treatment *(Table 3.2.4.1)*
7. The incidence of all treatment-related treatment-emergent adverse events *(Table 3.4.1)*
8. The incidence of discontinuation from the study due to a treatment-emergent adverse event *(Table 3.5.1.1)*
9. The incidence of treatment-emergent serious adverse events overall and by region subgroup/country *(Table 3.7.1.1)*
10. The incidence of treatment-emergent serious adverse events with onset after the last date on treatment *(Table 3.7.2.1)*
11. The incidence of treatment-emergent serious related adverse events *(Table 3.10.1)*
12. The incidence of all treatment-emergent adverse events by highest severity to treatment *(Table 3.11.1.1)*
13. A summary tabulation will also be prepared for the incidence of treatment-emergent adverse events occurring in at least 2% of subjects in any treatment *(Table 3.2.2.1, sorted by descending frequency of events in a preferred term).*
14. In addition, to control for possible differences in exposure between the treatments, the following AE and SAE summaries will be presented with the frequency and rate of occurrence (total number of events per 1000 person-years of exposure) by treatment, primary system organ class, and preferred term:
    a) Frequency and rate of AEs *(Table 3.3.1)*
    b) Frequency and rate of SAEs *(Table 3.9.1).*

6.6.1.1 Adverse Events of Special Interest

Adverse events of special interest have been defined based on known effects of LAMAs and LABAs; these include cardiovascular effects, ocular disorders, urinary retention, gastrointestinal disorders, and anticholinergic effects for LAMAs and cardiovascular and tremor effects for LABAs (Table 9). Standard MedDRA queries (SMQs) will be utilized when possible and a selection of preferred terms in other situations (Appendix 5).

Table 9 Adverse Events of Special Interest

AE Group	Selection of Terms
Cardiovascular	Cardiac Arrhythmias SMQ Cardiac Failure SMQ Myocardial Infarction SMQ Other Ischaemic Heart Disease SMQ CNS Haemorrhages and Cerebrovascular Conditions SMQ Sudden Death (collection of PTs) Torsade de Pointes/QT Prolongation SMQ

AE Group	Selection of Terms
Tremor	Collection of PTs
Urinary Retention	Urinary Tract Signs and Symptoms High Level Group Term (HLGT)
Ocular Effects	Visual Disorders High Level Term (HLT) Glaucoma SMQ
Gastrointestinal	Gastrointestinal Obstruction SMQ
Anticholinergic Effects	Anticholinergic Syndrome SMQ

Appendix 5 is currently based on Version 19.1 of MedDRA and provides detail on selection of terms (narrow/wide designations for preferred terms are provided). The selection of terms may change when Appendix 5 is updated using Version 20.0 of MedDRA prior to database lock of PT003014.

A summary tabulation of the incidence of treatment-emergent adverse events occurring in SMQs/groupings of interest will be prepared for all subjects, for each treatment, for each primary system organ class, and for each preferred term within a system organ class *(Table 3.2.3.1)*.

6.6.1.2 Cause of Death Determined by Adjudication Committees

Causes of death will be listed (*Table 3.13*) by subject and summarized by treatment for (1) all-cause mortality, (2) mortality of probable cardiovascular cause, (3) mortality of probable respiratory cause and (4) mortality of probable other causes using the Safety Population based on (A) cases reported during the active Treatment Period and (B) cases reported during the active Treatment Period plus the following 14 days *(Table 3.1.1)*. The percentage of subjects with a death event will be tabulated by primary system organ class, preferred term and treatment *(Table 3.12.1)*.

6.6.2 Clinical Laboratory Measurements

Lab parameters collected include the following:

Table 10 Lab Parameters

Hematology	
Hemoglobin	Mean corpuscular hemoglobin (MCH)
Hematocrit	Mean corpuscular hemoglobin concentration (MCHC)
White Blood Cell count with differential (including eosinophils)	Mean corpuscular volume (MCV)
Red Blood Cell count	
Platelet count	
Clinical Blood Chemistry	
Liver Enzyme and Other Function Tests	**Other Clinical Blood Chemistry**
Alanine aminotransferase (ALT)	Albumin
Aspartate aminotransferase (AST)	Calcium[a]
Alkaline phosphatase	Chloride[a]
Bilirubin, total	Cholesterol
Gamma-glutamyl transferase	Bicarbonate
	Creatinine[a]
	Glucose[a]
	Magnesium
	Potassium[a]
	Phosphate
	Protein, total
	Sodium[a]
	Triglycerides
Other Tests:	
Pregnancy test (women of child-bearing potential only): serum [human chorionic gonadotropin (HCG)] at Screening and Final Visit (Visit 11) only and Urine HCG at Visit 8 (Week 12) **Glomerular filtration rate** will be estimated by the central laboratory using the CKD EPI equation.	

[a] Parameters included in the Basic Metabolic Panel (BMP).

A Clinically Significant Laboratory Abnormality as identified by the investigator after the start of study treatment will be recorded as an Adverse Event and tabulated as an AE in the AE analysis. Abnormalities occurring prior to the start of treatment will be noted in medical history and presented in a data listing. Per protocol, the criteria for a "clinically significant" laboratory abnormality are:

- A laboratory abnormality that leads to a dose-limiting toxicity (e.g., an abnormality that results in study drug dose reduction, suspension or discontinuation)
- A laboratory abnormality that results in any therapeutic intervention (i.e., concomitant medication or therapy)
- Other laboratory abnormality judged by the Investigator to be of any particular clinical concern (e.g., significant fall in hemoglobin not requiring transfusion)

All laboratory data will be stored in the database with the units in which they were originally reported. Laboratory data not reported in International System of Units (SI units; Système International d'Unités) will be converted to SI units before data analysis.

Individual clinical laboratory variables for hematology and clinical chemistry and kidney function, including creatinine clearance, will be provided in listings *(Listing 8.1 for hematology, Listing 8.2 for morphology, Listing 8.3 for blood chemistry and kidney function, Listing 8.4 for urinalysis, and Listing 9.3 for pregnancy test results after the start of treatment)*. Data will be listed in SI units where available. Comments for laboratory testing will be listed *(Listing 8.5)*. For listings, laboratory values will be flagged as Low or High based on the reference ranges provided by the central laboratory, LabCorp Laboratories (Appendix 4).

The baseline measurement for a laboratory parameter will be the last available measurement prior to the start of dosing at Day 1 (Visit 4).

If there are multiple laboratory values for the same parameter at pre-dose of a visit, the last value will be chosen for analysis.

Summary statistics (n, mean, median, standard deviation, minimum, and maximum) for the baseline assessment and for the pre-dose value and change from baseline at each post-baseline visit and end of treatment for scheduled lab assessments of continuous laboratory variables including serum potassium and glucose will be tabulated. "End of Treatment" is defined as the last non-missing assessment during the treatment period. Data from unscheduled visits will not be used for this analysis, unless a prior or subsequent visit is missing where a laboratory value was scheduled to be collected. That is, laboratory data obtained during unscheduled visits will be allocated to the scheduled visit prior to the unscheduled visit if it was missed or to the next missing scheduled visit (not more than 4 weeks subsequent) if the previous scheduled visit was not missing. If there is not an adjacent missing visit, then the data will not be used in analyses, but will be listed. This implies that laboratory data obtained during a premature discontinuation visit will generally be assigned to the next missing scheduled visit. The summaries will be

provided by treatment *(Table 3.14.1, Table 3.14.2, 3.14.3, and Table 3.14.4, for hematology, blood chemistry, kidney function, and urinalysis pH and specific gravity, respectively)*.

Other than for the change from baseline analyses mentioned above, all available data post-baseline including data from unscheduled visits will be used for laboratory analyses.

Shift tables will be produced using the categories defined by the CTCAE Version 4.03 grades *(Tables 3.14.5, Table 3.14.6, and Table 3.14.7 for hematology, chemistry, and kidney function, respectively)*. For these shift tables, for each treatment, the subject's pre-dose grade will be cross-tabulated by the subject's maximum post-baseline grade during the treatment; also, the subject's maximum post-baseline grade during treatment will be tabulated for all baseline grades combined. Percentages of subjects in each maximum post-baseline grade for a treatment will be calculated for each pre-dose grade for the treatment and also for all baseline grades combined. Laboratory abnormal values on-treatment will be flagged as High or Low values based on laboratory reference ranges provided by LabCorp Laboratories as per Pearl. These flags along with the reference ranges will be provided in the laboratory data listings.

Potentially Clinically Significant Laboratory Values Above/Below a Clinically Relevant Threshold on-treatment, based on CTCAE 4.03 and other criteria, will be identified based on the following thresholds:

Table 11 Potentially Clinically Significant (PCS) Laboratory Parameter Criteria

Parameter	Post-Baseline Criteria
Hematology	
Hemoglobin	<8.0 g/dL (<80 g/L)
	Increase of >40 g/L to a value above the ULN
White Blood Cell Count	<2000/mm^3 (<2 x 10^9/L)
	>100,000/mm^3 (>100 x 10^9/L)
Platelet Count	<50,000/mm^3 (<50 x 10^9/L)
	>700,000/mm^3 (>700 x 10^9/L)
Chemistry	
eGFR-EPI	<30 mL/min/1.73 m^2
GGT	>2.5 x ULN
AST	>3 x ULN
ALT	>3 x ULN
Alkaline Phosphatase	>5 x ULN
Total Bilirubin	>1.5 x ULN
Triglycerides	>500 mg/dL (>5.65 mmol/L)
Cholesterol	>400 mg/dL (>10.34 mmol/L)
Albumin	<2 g/dL (<20 g/L)

Parameter	Post-Baseline Criteria
Blood Glucose* (random values)	<2.2 mmol/L
	>13.9 mmol/L
Serum Potassium	<3.0 mmol/L
	>6.0 mmol/L

*CTCAE 4.03 criteria are based on fasting glucose values. However, subjects were not required to fast prior to obtaining blood glucose values.

The number and percentage of subjects with newly occurring or worsening potentially clinically significant laboratory values above or below a clinically relevant threshold value on-treatment will be summarized *(Table 3.14.8 except for the PCS high Hemoglobin criteria)*. The number and percentage of subjects with a potentially clinically significant hemoglobin increase post-baseline of >40 g/L to a value above the ULN will be tabulated similarly *(Table 3.14.8).*

Since a reduction in potassium and an increase in blood glucose are known class effects of beta-agonists, all potassium or glucose assessments for subjects who experienced newly occurring or worsening potentially clinically significant values after start of the study treatment will be provided in separate listings *(Tables 3.14.9 and 3.14.10).* For all laboratory parameters other than glucose and potassium noted in Table 11, all laboratory data for the parameter identified as potentially clinically significant for a subject will be listed *(Table 3.14.11).*

6.6.3 Vital Signs

Changes from Baseline in on-treatment supine systolic blood pressure, supine diastolic blood pressure, heart rate, and body temperature will be evaluated, where baseline is defined as the average of all available pre-dose measurements taken prior to the start of dosing for the Treatment Period (two measurements are scheduled pre-dose within 5 minutes apart for all parameters except body temperature where only one measurement is planned).

A **Clinically Significant Abnormality** in vital signs identified by the investigator will be recorded as an Adverse Event if it occurs after the start of treatment. These adverse events will be included in the AE summaries; abnormalities prior to the start of treatment will be noted in medical history and listed.

Potentially clinically significant changes in systolic and diastolic blood pressure will be defined based on the following criteria provided by Pearl:

Table 12 Potentially Clinically Significant (PCS) Criteria for Systolic and Diastolic Blood Pressure Parameters

Parameter (mmHg)	Post-Baseline Criteria
Systolic Blood Pressure, increase	≥180 mmHg and increase from baseline ≥20 mmHg
Systolic Blood Pressure, decrease	≤90 mmHg and decrease from baseline ≥20 mmHg
Diastolic Blood Pressure, increase	≥105 mmHg and increase from baseline ≥15 mmHg
Diastolic Blood Pressure, decrease	≤50 mmHg and decrease from baseline ≥15 mmHg

Potentially clinically significant (PCS) changes in heart rate will be assessed as follows:

Table 13 Potentially Clinically Significant Criteria for Heart Rate Parameters

Parameter	Post-Baseline Criteria
Tachycardia Event	≥110 bpm and increase ≥15% from baseline
Bradycardia Event	≤50 bpm and decrease ≥15% from baseline

Vital sign measurements (heart rate, systolic blood pressure, diastolic blood pressure, body temperature, weight, and height) during the study will be displayed in a vital signs listing *(Listing 9.1)*.

A summary of baseline weight, height, and BMI will be presented by treatment *(Tables 1.4.1, 1.4.2, and 1.4.4 for the ITT, PP, and Safety Populations, respectively)*.

Baseline will be defined as the average of the values prior to dosing at Visit 4 (Day 1). Summary statistics (n, mean, median, standard deviation and range) of the measured value and change from baseline for heart rate, systolic blood pressure, diastolic blood pressure, and body temperature will be tabulated by treatment, visit, and timepoint. These summaries will be prepared for baseline and each scheduled post-baseline nominal timepoint at each scheduled post-baseline visit and end of treatment. "End of Treatment" will be summarized for each scheduled post-baseline timepoint (pre-dose, post-dose 30 minutes, and post-dose 2 hours). End of Treatment for each of these assessment points is defined as the last non-missing on-treatment assessment available for the timepoint. Data from unscheduled visits will not be used for this analysis, unless a prior or subsequent visit is missing where a vital sign value was scheduled to be collected. That is, vital sign data obtained during unscheduled visits will be allocated to the scheduled visit prior to the unscheduled visit if it was missed or to the next missing scheduled visit (not more than 4 weeks subsequent) if the previous scheduled visit was not missing. If there is not an adjacent missing visit, then the data will not be used in analyses, but will be listed. This implies that vital sign data obtained during a premature discontinuation visit will generally be assigned to the next missing scheduled visit. Time windows will be derived for each post-baseline visit using the time intervals for the study time windows detailed below in Table 14 (*Table 3.15.1*).

Table 14 Analysis Study Time Windows for Vital Signs Assessments

Calculated Study Time Window	Time Interval for the Study Time Window
Pre-dose	≥0 min Prior to dose
Post-dose 30 min	>0 to <75 min Post-dose
Post-dose 2 hrs	≥75 min to <4 hrs post-dose

Note that minutes are rounded to the nearest whole number before applying time windows.

If there are multiple vital sign values for the same parameter at pre-dose assessments after Visit 4 or within the same post-dose study time window at a visit, the last value will be chosen for analysis.

The percentage of subjects with potentially clinically significant values for vital signs at any time post-dose at a visit will be summarized by treatment based on the criteria in Table 12 and Table 13 *(Table 3.15.2)*; the percentage of visits where a post-baseline value was PCS will also be provided for each treatment group in Table 3.15.2. For this analysis, all available data post-baseline including data from unscheduled visits will be used.

All vital sign assessments for subjects with potentially clinically significant values will be listed *(Tables 3.15.3 and 3.15.4)*.

6.6.4 12-Lead Electrocardiogram Measurements

Changes from baseline in Heart Rate, PR Interval, QRS Axis, QRS Interval, QT Interval and QTcF interval will be calculated where baseline is defined as the average of all available pre-dose measurements taken prior to the start of dosing for the treatment (two measurements are scheduled pre-dose within 5 minutes apart). The QTcF (Fridericia Corrected QT) is defined as $[QT/(RR^{1/3})]$.

A **Clinically Significant Abnormality** for a 12-Lead ECG measurement identified by the investigator as a clinically significant abnormality will be recorded as an Adverse Event if it occurred after the start of study treatment. These adverse events will be included in the AE summaries.

All 12-Lead ECG measurements for the Safety Population will be listed *(Listing 9.2)*. Summary statistics (mean, median, standard deviation and range) for raw values and change from baseline values in Heart Rate, PR Interval, QRS Axis, QRS Interval, QT Interval and QTcF interval will be calculated, where baseline is defined as the average of the pre-dose measurements taken prior to the start of treatment at Visit 4 (Day 1). These assessments will be tabulated for each treatment and each scheduled post-dose nominal timepoint (derived using the time intervals for the study time windows detailed below in Table 15) at each visit and at end of treatment *(Table 3.16.1)*. "End of Treatment" will be summarized for each scheduled post-baseline timepoint (pre-dose, post-dose 30 minutes, and post-dose 2 hours). End of Treatment for each of these assessment points is defined as the last non-missing on-treatment assessment available for

the timepoint. Data from unscheduled visits will not be used for this analysis, unless a prior or subsequent visit is missing where an ECG parameter value was scheduled to be collected. That is, an ECG parameter value obtained during unscheduled visits will be allocated to the scheduled visit prior to the unscheduled visit if it was missed or to the next missing scheduled visit (not more than 4 weeks subsequent) if the previous scheduled visit was not missing. If there is not an adjacent missing visit, then the data will not be used in analyses, but will be listed. This implies that an ECG parameter value obtained during a premature discontinuation visit will generally be assigned to the next missing scheduled visit. Mean pre-dose change from baseline for QTcF and heart rate will be plotted across post-baseline visits by treatment *(Figure 3.16.1a and Figure 3.16.1c)*. Mean change from baseline for QTcF and heart rate across the 2-hour post-dose interval will be plotted by treatment *(Figures 3.16.1b and 3.16.1d, respectively).*

ECG data from subjects with pacemakers will not be included in analyses, but will be listed.

Table 15 Analysis Study Time Windows for ECG Assessments

Calculated Study Time Window	Time Interval for the Study Time Window
Pre-dose	≥0 min Prior to dose
Post-dose 30 min	>0 to <75 min Post-dose
Post-dose 2 hrs	≥75 min to <4 hrs Post-dose

Note: The minutes are rounded to the nearest whole number before applying time windows.

If there are multiple ECG values for the same parameter at pre-dose of a visit date (other than for Visit 4) or within the same post-dose study time window on a visit date, the last value will be chosen for analysis.

Other than for the change from baseline analyses mentioned above, all available data post-baseline including data from unscheduled visits will be used for ECG parameter analyses.

Table 16 Criteria for Potentially Clinically Significant (PCS) ECG Values

Parameter	Post-Baseline Criteria
QTcF Prolongation	• Post-baseline value is >450 msec for male subjects or >470 msec for female subjects • Post-baseline value is >500 msec • Increase from baseline is >30 msec • Increase from baseline is >60 msec • Post-baseline value is >500 msec and increase from baseline >30 msec • Post-baseline value is >500 msec and increase from baseline >60 msec
PR Interval Increase	Increase from baseline of >50 msec
QRS Prolongation	Prolongation of >40 msec from baseline

Potentially clinically significant ECG parameter values will be identified based on criteria listed in Table 16 (provided by Pearl). The number and percentage of subjects who had such values observed any time post-dose will be tabulated for each treatment *(Table 3.16.2)* and listed *(Tables 3.16.3, 3.16.4, and 3.16.5, for QTcF prolongation, PR interval increase, and QRS prolongation, respectively).* No hypothesis tests will be performed.

6.6.5 Physical Examination

Any physical examination abnormality reported after the start of treatment for a subject is to be reported as an adverse event. Thus, these will be included in listings of adverse events and summarized in adverse event summaries. Abnormalities seen at the Screening physical examinations will be recorded as Medical History and listed.

6.7 Subgroup Analyses

Subgroup analyses will be conducted to support local registration requirements including by-country and by-region assessments of consistency. Subgroups are defined as Asia (defined by country and not by race), non-Japan, Europe, and each individual country. Asia includes Japan, China, South Korea, and Taiwan.

By country/region subgroup analyses of efficacy endpoints will implement the same methodology as described for the overall ITT population. Forest plots will be provided for each endpoint. In addition, Galbraith plots, and Q-Q plots will aid in the consistency assessment of treatment effects across countries/regional subgroups. Safety assessments will include by-country/region tabulations of adverse events.

In addition, subgroup analyses for the lung function endpoints, change from baseline in morning pre-dose trough FEV_1 and peak change from baseline in FEV_1, will also be conducted based on

GOLD 2017 categories (A, B, C, and D) and GOLD 2, 3, and 4 subgroups. Forest plots will be provided by subgroup.

Disposition, Demography, Baseline Characteristics, and Efficacy Summaries

Tabulations will be provided for subgroups of the ITT Population unless otherwise noted. The following tables will be provided for both region/country, GOLD A, B, C, and D category, and GOLD 2, 3, and 4 (unless it is specified below that subgroup tables will only be provided for region/country):

- Subject disposition by region/country *(Tables 2.20.x)*
- Reason for early discontinuation by region/country *(Tables 2.21.x)*
- Demographics and baseline characteristics (*Tables 2.22.1.x through Table 2.22.3*)
- Screening pre- and post-bronchodilator and baseline spirometry parameters by region/country *(Tables 2.23.x)*
- Severity and duration of COPD *(Tables 2.24.1.x through Table 2.24.3*)
- Reversibility to Ventolin HFA *(Tables 2.25.1.x through Table 2.25.3*)
- Reversibility to Atrovent HFA *(Tables 2.26.1.x through Table 2.26.3*)
- Exposure and compliance *(Tables 2.27.1.x through Table 2.27.3 for the Safety Population)*
- Change from baseline in trough FEV_1 *(Tables 2.28.1.x through Table 2.28.3;Forest, Galbraith, and Q-Q Plots for region subgroup/ country will be provided in Figures 2.28.1.1 through 2.28.1.3.3; Forest plots for GOLD category and severity subgroups will be provided in Figures 2.28.2.1 through 2.28.3.3)*
- TDI focal score by region/country *(Tables 2.29.x; Forest, Galbraith, and Q-Q Plots: Figures 2.29.1 through 2.29.3.2)*
- Peak change from baseline in FEV_1 (L) Within 2 Hours Post-Dose *(Tables 2.30.1.1.x, through 2.30.3; Forest Plots for all subgroups, and Galbraith and Q-Q Plots for region subgroup/country only: Figures 2.30.1.1 through 2.30.3.3)*
- Change from baseline in SGRQ total score by region/country *(Tables 2.31.1.x; Forest, Galbraith, and Q-Q Plots: Figures 2.31.1.1 through 2.31.3.2)* (these will be descriptive analyses only)
- Response in SGRQ total score (achievement of an MCID threshold of ≥4 units on average in SGRQ total score) over Weeks 12-24 and separately at Week 24 by Region/Country *(Tables 2.32.x; Forest Plot: Figure 2.32)*
- Change from baseline in mean daily number of puffs of rescue Ventolin HFA by region/country *(Table 2.33.1.x for the ITT Population and Table 2.33.2.x in the Rescue Ventolin User Population; Forest, Galbraith, and Q-Q Plots in the ITT Population: Figures 2.33.1.1through 2.33.1.3.2; Forest, Galbraith and Q-Q Plots in the Rescue Ventolin User Population: Figures 2.33.2.1through 2.33.2.3.2)*; this analysis will be repeated in the Rescue Ventolin User Population if sample sizes permit (Modelling will be performed for countries

with a sample size of ≥30, for which the sample size is no lower than 6 for any one treatment (Bell et al, 2010)

- Change from baseline in FEV_1 at 5 min post-dose on Day 1 by region/country *(Table 2.34; Forest, Galbraith, and Q-Q Plots: Figures 2.34.1 through 2.34.3).*
- Change from baseline in FEV_1 at 15 min post-dose on Day 1 by region/country (*Table 2.35; Forest , Galbraith, and Q-Q Plots: Figures 2.35.1 through 2.35.3*)

Subgroup analyses by CAT Score Subpopulation (CAT scores of ≥10, ≥15, and ≥20) have been covered above (Section 6.4) for the following symptom endpoints:

- TDI endpoints *(Tables 2.2.1 for TDI focal score, Table 2.2.2.1 for individual components, and Table 2.2.3 for TDI responder rates)*
- SGRQ endpoints *(Tables 2.4.1 for SGRQ total score, Table 2.4.2 for individual domains, and Table 2.4.3 for SGRQ responder rates)*
- COPD exacerbation endpoints *(Tables 2.13.1 for rate of COPD exacerbations of any severity and rate of moderate and severe COPD exacerbations, Table 2.13.2 for rate of COPD exacerbations of any severity and rate of moderate and severe COPD exacerbations with imputation, Table 2.14 for time to COPD exacerbation of any severity and time to moderate and severe COPD exacerbation, and Table 2.15 for time treatment failure).*

For the efficacy endpoints (except for change from baseline in FEV_1 at 5 and 15 mins post-dose on Day 1), a separate model will be fit for each subgroup category including terms for baseline for the specific endpoint, percent reversibility to Ventolin HFA, visit, treatment, and the treatment-by-visit interaction. The unstructured matrix will be used to model the variance-covariance structure within subject. If this model fails to converge, the heterogeneous Toeplitz (TOEPH) will be fit. As sample sizes will be relatively small in some countries, a compound symmetric structure will be used in the event that neither the unstructured nor the heterogeneous Toeplitz models converge. Modelling will be performed for countries with a sample size of ≥30, for which the sample size is no lower than 6 for any one treatment (Bell et al, 2010).

The subgroup analyses for change from baseline in FEV_1 at 5 and 15 mins post-dose on Day 1 will be analyzed using a model including terms for baseline FEV_1 and percent reversibility to Ventolin HFA and treatment. Estimates for the treatment effect and for the treatment difference for all pairwise comparison of treatments will be displayed in the efficacy endpoint tables for each subgroup.

For each subgroup analysis (excluding CAT Score Subpopulations), a test for the treatment-by-subgroup interaction will be performed using a model containing the following terms: baseline for the specific endpoint (baseline FEV_1 or BDI), percent reversibility to Ventolin HFA, visit, treatment, treatment-by-visit interaction, subgroup, and the treatment-by-subgroup interaction. A table will be provided with the p-value for the test of the treatment-by subgroup interaction and with the p-value for the subgroup main effect *(Table 2.37)*. Should any country/region

subgroup effects be identified, shrinkage estimates may be generated in order to further understand the impact of these effects (Carroll and Fleming, 2013).

Safety Summaries:

An overview table will be prepared with the incidences of subjects, for all subjects in the safety population and for each treatment, with the following: at least one treatment-emergent adverse event, at least one treatment-emergent related adverse event, at least one treatment-emergent serious adverse event, at least one treatment-emergent serious related adverse event, at least one treatment-emergent adverse event leading to early withdrawal, at least one treatment-emergent serious adverse event leading to withdrawal, and a report of death *(Tables 3.1.2.x, by China and Japan regional subgroups and for the regional subgroups of non-Japan, Asia, as well as by country).*

Summary tabulations of the following will be prepared for all subjects, for each treatment, for each primary system organ class, and for each preferred term within a system organ class, by region subgroup/country:

1. The incidence of all treatment-emergent adverse events by region subgroup/country *(Tables 3.2.1.1.x)*
2. The incidence of treatment-emergent adverse events with onset after the last date on treatment by region subgroup/country *(Tables 3.2.1.2.x)*
3. The incidence of treatment-emergent adverse events occurring in SMQs (Standard MedDRA Queries)/groupings of interest by region subgroup/country *(Tables 3.2.3.x)*
4. The incidence of non-serious treatment-emergent adverse events occurring in ≥5% of subjects in a treatment by region subgroup/country *(Tables 3.2.4.x)*
5. The incidence of all treatment-related treatment-emergent adverse events by region subgroup/country *(Tables 3.4.x)*
6. The incidence of discontinuation from the study due to a treatment-emergent adverse event by region subgroup/country *(Tables 3.5.1.x)*
7. The incidence of treatment-emergent serious adverse events by region subgroup/country *(Tables 3.7.1.x)*
8. The incidence of treatment-emergent serious adverse events with onset after the last date on treatment by region subgroup/country *(Tables 3.7.2.x)*
9. The incidence of treatment-emergent serious related adverse events by region subgroup/country (*Tables 3.10.x)*
10. The incidence of all treatment-emergent adverse events by highest severity to treatment by region subgroup/country *(Table 3.11.1.2 through 3.11.4.x)*
11. A summary tabulation will also be prepared for the incidence of treatment-emergent adverse events occurring in at least 2% of subjects in any treatment by region subgroup/country *(Tables 3.2.2.x, sorted by descending frequency of events in a preferred term).*

12. In addition, to control for possible differences in exposure between the treatments, the following AE and SAE summaries will be presented with the frequency and rate of occurrence (total number of events per 1000 person-years of exposure) by treatment, primary system organ class, and preferred term, by region subgroup/country:
    a) Frequency and rate of AEs *(Tables 3.3.x)*
    b) Frequency and rate of SAEs *(Tables 3.9.x).*
13. The percentage of subjects with a death event will be tabulated by primary system organ class, preferred term, and treatment by region subgroup/country (*Tables 3.12.x*).

6.7.1 China and Asia

To support registration in China, a separate Clinical Study Report will be written to present the study results in the China and Asia Populations with the objective of demonstrating consistency with the overall Study PT003014 population. Select subject disposition, demographic and baseline characteristics and extent of exposure, efficacy, and safety analyses will be repeated for the China and Asia Populations using the analysis sets described in Section 5.4, including relevant subgroup and sensitivity analyses; healthcare resource utilization analyses will be provided in the China Population. Appendix 7 and Appendix 8 contain the table of contents for Post-Text TFLs in the China and Asia Populations, respectively.

Efficacy analyses in the China and Asia Populations will proceed as described in Section 6.7. All statistical analyses based on the China and Asia Populations will be considered exploratory. No adjustment for multiplicity will be made and so the hierarchical testing detailed in Section 6.4.4 to control the Type I error will not be employed directly to the China Population results.

Safety analyses will include tabulations of adverse events, laboratory parameters, vital signs, and ECGs.

7. ANALYSES PERFORMED BEFORE DATABASE CLOSURE

Interim analyses for the purpose of evaluation of efficacy are not planned for this study. However, as planned, the Data Monitoring committee will be provided with pre-specified safety analyses at pre-determined intervals which will be provided using semi-blinded treatment codes (A, B, C, and Placebo MDI) and may require the code to fully unblind analyses if they feel that these are necessary to evaluate the safety of study subjects.

The DMC Charter specifies the analyses and output that will be performed and provided approximately every six months until the completion of the Phase III trials. These reports will be provided in an appendix to the clinical study report.

8. CHANGES FROM METHODS PLANNED IN THE PROTOCOL

The Protocol incorrectly characterized the other efficacy endpoints for total and individual symptoms scores as “morning” and “evening” which would imply a shorter duration of

assessment than what was intended. These other efficacy endpoints should actually be referred to as "daytime" and "nighttime" total and individual symptoms scores to better reflect the 12-hour assessment period.

As planned per protocol, analyses of the rate of all COPD exacerbations of any severity will be performed using negative binomial regression. The model has been revised to include an additional covariate of baseline continuous eosinophil count. Adjusted rates of exacerbations will be estimated using data-based weights from the study population for the categorical covariates of baseline COPD Exacerbation history, smoking status at baseline, and ICS use at baseline, and the arithmetic mean level of the continuous covariate, baseline percent predicted FEV_1 and baseline continuous eosinophil count.

As planned per protocol, analyses of the time to first COPD exacerbation of any severity will be performed using a Cox regression model. The model has been revised to include an additional covariate of baseline continuous eosinophil count. Hazard ratios will be estimated using the categorical covariates of baseline COPD Exacerbation history, smoking status at baseline, and ICS use at baseline, and the arithmetic mean level of the continuous covariates, baseline percent predicted FEV_1 and baseline continuous eosinophil count.

All analyses of the rate of moderate and severe COPD exacerbations and the time to first moderate or severe COPD exacerbation will be performed similarly to the rate of COPD exacerbations of any severity and the time to first COPD exacerbation of any severity (described above).

As planned in the protocol, additional analyses of the rate of COPD exacerbations will be performed with imputation of a moderate exacerbation at the time of dropout for subjects withdrawing prematurely from the trial, unless an exacerbation has already been recorded at that time. The model has been revised to include an additional covariate of baseline continuous eosinophil count.

As planned in the protocol, the time to treatment failure will be analyzed using a Cox regression model. The model has been revised to include an additional covariate of baseline continuous eosinophil count.

Any changes to methods planned in this statistical analysis plan will be documented in a revision to this statistical plan prior to database lock, or identified in the clinical study report.

9. STATISTICAL SOFTWARE

Data processing, statistical screening, descriptive reporting and analysis of the efficacy and safety data will be performed using SAS (Version 9.4 or higher). Graphs may also be produced using R (R Development Core Team, 2003).

10. REFERENCES

Anzures-Cabrera J, Higgens PT. Graphical displays for meta-analysis: An overview with suggestions for practice. Research Synthesis Methods, Published online on 23 Mar 2010 (Wiley Interscience).

Bell B, Morgan GB, Schoeneberger JA, Loudermilk BL, Kromrey JD, and Ferron JM. Dancing the Sample Size Limo with Mixed Models: How Low Can You Go? SAS Global Forum 2010: Paper 197-2010.

Calverley P, Lee A, Towse L, et al. Effect of tiotropium bromide on circadian variation in airflow limitation in chronic obstructive pulmonary disease. Br Medical J. 2003; 58(10): 855-860.

Carroll KJ, Fleming TR. Statistical Evaluation and Analysis of Regional Interactions: The PLATO Trial Case Study. Statistics in Biopharmaceutical Research 2013; 5:2, 91-101. DOI: 10.1080/19466315.2013.783878

COPD Assessment Test (CAT) (http://www.catestonline.org/)

Farrar JT, Dworkin RH, Max MB. Use of the cumulative proportion of responders analysis graph to present pain data over a range of cut-off points: Making clinical trial data more understandable. J Pain Symptom Manage 2006; 31:369-377

GOLD (Global Initiative for Chronic Obstructive Lung Disease). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. National Institutes of Health, updated 2014 Available at: www.goldcopd.com. Accessed April 11, 2014.

Hochberg Y, A sharper Bonferroni procedure for multiple tests of significance. Biometrika 1988; 75, 4, pp. 800-2.

Jones P. Creating scenarios of the impact of COPD and their relationship to CAT scores. BMC Pulmonary Medicine 2011; 11:42.

JRS Japanese Respiratory Society. Guidelines for the Diagnosis and Treatment of COPD, 4th edition, 2013.

Little RJA, Rubin DB. Statistical analysis with missing data, (2nd edn). John Wiley and Sons, Inc.: New York, 2002.

Maesen FP, Smeets JJ, Sledsens TJ, Wald FD, Cornelissen PJ. Tiotropium bromide, a new long-acting antimuscarinic bronchodilator: a pharmacodynamics study in subjects with chronic obstructive pulmonary disease (COPD). Dutch Study Group. Eur Respir J. 1995; 8(9): 1506-13.

Mahler DA, MD, Waterman LA, Ward J, McCusker C, ZuWallack R, and Baird JC. Validity and Responsiveness of the Self-Administered Computerized Versions of the Baseline and Transition Dyspnea Indexes Chest 2007:132 (4):1283-1290.

Mahler DA, Ward J, Waterman LA, McCusker C, ZuWallack R, and Baird JC. Patient-Reported Dyspnea in COPD Reliability and Association With Stage of Disease. Chest 2009;136: 1473-1473.

Miller et al, Standardisation of spirometry. Eur Respir J 2005; 26: 319–338).

Molenberghs G, Kenward MG. Missing data in clinical studies. John Wiley and Sons, Inc.: New York, 2007.

National Center for Health Statistics. 1996. NHANES III Reference Manuals and Reports. Data Dissemination Branch, Hyattsville, MD. CD-ROM No. 6-0178 (1096).

National Research Council. Panel on Handling Missing Data in Clinical Trials. Committee on National Statistics, Division of Behavioral and Social Sciences and Education. The prevention and treatment of missing data in clinical trials. The National Academies Press: Washington, DC, 2010.

R Development Core Team. R: A language and environment for statistical computing, 2003. R Foundation for Statistical Computing, Vienna, Austria.

Ratitch B, O'Kelley M, and Tosiello R. Missing data in clinical trials: from clinical assumptions to statistical analysis using pattern mixture models. Pharmaceutical Statistics, 2013 (wileyonlinelibrary.com) DOI: 10.1002/pst. 1549

Rubin DB. M. Multiple imputation for nonresponse in surveys. John Wiley and Sons, Inc.: New York, 1987.

Sarkar SK. On the Simes inequality and its generalization. Institute of Mathematical Statistics. 2008; 231–242.

Sarkar SK and Chang CK. The Simes method for multiple hypothesis testing with positively dependent test statistics. Journal of the American Statistical Association, 1997; 92 1601–1608.

van Noord JA. Comparison of tiotropium once daily, formoterol twice daily and both combined once daily in subjects with COPD. European Respiratory Journal. 2005; 26(2): 214–222.

APPENDIX 1: DATA HANDLING RULES

Programming of the tables, listings and figures will be performed using SAS Version 9.4 or a more recent version. This appendix will be provided as a separate document.

APPENDIX 2: ANALYSIS DATASET SPECIFICATIONS

Analysis datasets will be built to gain efficiency and ensure consistency in data analyses and presentation for this trial. The specifications for each analysis data set will be prepared separately and will not be a part of this SAP.

APPENDIX 3: SAS CODE FOR STATISTICAL ANALYSES

Test	**Template SAS Code for Modeling** (SAS Version 9.4)
Linear Repeated Measures (RM) Analysis of Covariance for primary and applicable secondary or other efficacy analyses (not for analyses of time to onset of action and percent response variables)	ODS GRAPHICS ON; PROC MIXED PLOTS =ALL; TITLE2 ‘UNSTRUCTURED COVARIANCE MATRIX'; TITLE3 'Y IS CHANGE FROM BASELINE IN MORNING PRE-DOSE TROUGH’; CLASS SUBJECT TRT VISIT; MODEL Y= BASEFEV1 REVVEN VISIT TRT TRT*VISIT /DDFM=KR INFLUENCE OUTP=PREDICT; REPEATED VISIT / TYPE = UN SUBJECT=SUBJECT; LSMEANS TRT | VISIT/PDIFF CL; *SAS default: LSMEANS will be provided at the average level of the continuous baseline covariates where the average was defined as the average taken across all observations used in the analysis; LSMEANS TRT/PDIFF CL; /*over 12-24 weeks*/ ODS GRAPHICS OFF; Where BASEFEV1 is baseline FEV_1, TRT is treatment, and REVVEN is percent reversibility to Ventolin HFA at Visit 2.

Test	**Template SAS Code for Modeling** (SAS Version 9.4)
	THE PLOTS=ALL OPTION FOR PROC MIXED WILL BE USED TO GET PLOTS TO PERFORM MODEL DIAGNOSTICS. Influence statistics will be requested using the "influence (<options>)" option on the model statement. LSMEANS TRT | VISIT/PDIFF; /* This lsmeans statement shown in the model above will automatically compute the lsmeans at the mean values of the two covariates in the data being analyzed, BASEREV1 and REVVEN (V1 and V2, respectively). *The following code could be used to compute and compare means that will be averaged across the last four visit values (weeks 12, 16, 20, and 24) where v1 and v2 are the values of the two covariates, then the means were obtained from; ESTIMATE 'TRT 1 LAST 4' INTERCEPT 1 BASEFEV1 v1 REVVEN v2 VISIT 0 0 0 .25 .25 .25 .25 TRT 1 0 0 0 TRT*VISIT 0 0 0 .25 .25 .25 .25 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0/ CL; ESTIMATE 'TRT 2 LAST 4' INTERCEPT 1 BASEFEV1 v1 REVVEN v2 VISIT 0 0 0 .25 .25 .25 .25 TRT 0 1 0 0 TRT*VISIT 0 0 0 0 0 0 0 0 0 0 .25 .25 .25 .25 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0/ CL; ESTIMATE 'TRT 3 LAST 4' INTERCEPT 1 BASEFEV1 v1 REVVEN v2 VISIT 0 0 0 .25 .25 .25 .25 TRT 0 0 1 0 TRT*VISIT 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 .25 .25 .25 .25 0 0 0 0 0 0 0 0/ CL; ESTIMATE 'TRT 4 LAST 4' INTERCEPT 1 BASEFEV1 v1 REVVEN v2 VISIT 0 0 0 .25 .25 .25 .25 TRT 0 0 0 1 TRT*VISIT 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 .25 .25 .25 .25/ CL; /* PAIRWISE DIFFERENCES AMONG THE TRTS WHEN AVERAGING OVER THE LAST FOUR

Test	**Template SAS Code for Modeling** (SAS Version 9.4)
	VISITS WERE GIVEN BY: */ ESTIMATE 'TRT 1 VS 2 LAST 4' TRT 1 -1 0 0 TRT*VISIT 0 0 0 .25 .25 .25 .25 0 0 0 -.25 -.25 -.25 -.25 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0/ CL; ESTIMATE 'TRT 1 VS 3 LAST 4' TRT 1 0 -1 0 TRT*VISIT 0 0 0 .25 .25 .25 .25 0 0 0 0 0 0 0 0 0 0 -.25 -.25 -.25 -.25 0 0 0 0 0 0 0 0/ CL; ESTIMATE 'TRT 1 VS 4 LAST 4' TRT 1 0 0 -1 TRT*VISIT 0 0 0 .25 .25 .25 .25 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 -.25 -.25 -.25 -.25/ CL; ESTIMATE 'TRT 2 VS 3 LAST 4' TRT 0 1 -1 0 TRT*VISIT 0 0 0 0 0 0 0 0 0 0 .25 .25 .25 .25 0 0 0 -.25 -.25 -.25 -.25 0 0 0 0 0 0 0 0/ CL; ESTIMATE 'TRT 2 VS 4 LAST 4' TRT 0 1 0 -1 TRT*VISIT 0 0 0 0 0 0 0 0 0 0 .25 .25 .25 .25 0 0 0 0 0 0 0 0 0 0 0 -.25 -.25 -.25 -.25/ CL; ESTIMATE 'TRT 3 VS 4 LAST 4' TRT 0 0 1 -1 TRT*VISIT 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 .25 .25 .25 .25 0 0 0 -.25 -.25 -.25 -.25/ CL; ESTIMATE "Treatment 1 at 4 Weeks" INTERCEPT 1 BASEFEV1 v1 REVVEN v2 VISIT 1 0 0 0 0 0 0 TRT 1 0 0 0 TRT*VISIT 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0/ cl;

Test	**Template SAS Code for Modeling** (SAS Version 9.4)

	Etc... To estimate the treatment effect for a treatment at a specific visit.
	
	FOR DIAGNOSTIC PLOTS, THE FOLLOWING SAS CODE WILL BE USED:
	proc sort data=predict;
	by resid;
	
	proc plot data=predict;
	plot resid*pred
	resid*TRT;
	
	proc sort data=predict;
	by TRT;
	
	proc univariate normal plot data=predict;
	id usubjid;
	var resid;
	by TRT;

Negative binomial using PROC GENMOD	PROC GENMOD; CLASS SMKSTAT ICSUSE COPDEXFL TRT STUDY; MODEL Y=PPFEV1 CATSCR EOS COPDEXFL TRT SMKSTAT ICSUSE; LINK=LOG DIST=NEGBIN OFFSET=LYRS; LSMEANS TRT / DIFF CL; ODS OUTPUT LSMEANDIFFS = LSDIFS ESTIMATES=EST LSMEANS=LSMEANS PARAMETERESTIMATES=PE; *LYRS is the logarithm of the amount of time in years (since first dose) over which the subject was observed for the count variable Y. PPFEV1 is screening continuous percent predicted FEV1. EOS is baseline continuous eosinophil count. CATSCR is screening continuous CAT Score. COPDEXFL is COPD exacerbation history (1 for yes and 0 for no) where no will be the reference group. ICSUSE is ICS use at baseline (1 for yes and 2 for no) where no will be the reference group. Smoking status is 1 for current smoker and 2 for former smoker, where current smoker will be the reference group. Treatment will be coded: 1=GFF 2=GP 3=FF and 4=Placebo where Placebo will be the reference group.

Test	**Template SAS Code for Modeling** (SAS Version 9.4)

	/* verify lsmeans*/ ****macro variables specified below are the weights/arithmetic means for the covariates;
	ESTIMATE '1' INT **1** PPFEV1 &MP CATSCR &MC EOS &MEOS COPDEXFL &COPDEXFL1 &COPDEXFL2
	TRT01PN **1 0 0 0**;
	ESTIMATE '2' INT **1** PPFEV1 &MP CATSCR &MC EOS &MEOS COPDEXFL &COPDEXFL1 &COPDEXFL2
	TRT01PN **0 1 0 0**;
	ESTIMATE '3' INT **1** PPFEV1 &MP CATSCR &MC EOS &MEOS COPDEXFL &COPDEXFL1 &COPDEXFL2
	TRT01PN **0 0 1 0**;
	ESTIMATE '4' INT **1** PPFEV1 &MP CATSCR &MC EOS &MEOS COPDEXFL &COPDEXFL1 &COPDEXFL2
	TRT01PN **0 0 0 1**;
	
	data lsdifs;
	set lsdifs;
	rateratio=exp(estimate);
	lcl_rateratio=exp(lowercl);
	ucl_rateratio=exp(uppercl);
	
	The following NLMIXED model will be used to get the estimates of the treatment differences based on rates.
	
	PROC NLMIXED;
	PARMS /DATA=PE1; *note that parameter estimates from PROC GENMOD are fed into proc nlmixed as starting values; PE1 is based on PE and has B0 to B9 variables;
	*b0 is the intercept. K is the dispersion parameter.
	LINP=LYRS+
	B0+B1*(TRT01PN=**1**)+B2*(TRT01PN=**2**)+B3*(TRT01PN=**3**)+B4*EOS
	+B5*CATSCR+B6*(ICSUSE='Y')+B7*(SMKSTAT=**2**)+B8*PPFEV1
	+B9*COPDEXFL;
	
	MU = EXP(LINP);
	P = **1**/(**1**+MU*K);
	MODEL Y ~ NEGBIN(**1**/K,P);
	
	ESTIMATE '1'

Test	**Template SAS Code for Modeling** (SAS Version 9.4)
	EXP(B0+B1+B4*&MEOS+B5*&MCATSCR+B6*&MICSUSE+B7*&MSMK STAT +B8*&MPPFEV1+B9*&MCOPDEXFL)***365.25**; *ESTIMATE IN DAYS; ESTIMATE '2' EXP(B0+B2 +B4*&MEOS+B5*&MCATSCR+B6*&MICSUSE+B7*&MSMKSTAT +B8*&MPPFEV1+B9*&MCOPDEXFL)***365.25**; ESTIMATE '3' EXP(B0+B3 +B4*&MEOS+B5*&MCATSCR+B6*&MICSUSE+B7*&MSMKSTAT +B8*&MPPFEV1+B9*&MCOPDEXFL)***365.25**; ESTIMATE '4' EXP(B0+B4 +B4*&MEOS+B5*&MCATSCR+B6*&MICSUSE+B7*&MSMKSTAT +B8*&MPPFEV1+B9*&MCOPDEXFL)***365.25**; /* A CHECK TO MATCH GENMOD RESULT */ ESTIMATE '12' EXP(B0+B1 +B4*&MEOS+B5*&MCATSCR+B6*&MICSUSE+B7*&MSMKSTAT +B8*&MPPFEV1)***365.25-** EXP(B0+B2 +B4*&MEOS+B5*&MCATSCR+B6*&MICSUSE+B7*&MSMKSTAT +B8*&MPPFEV1+B9*&MCOPDEXFL)***365.25**; ESTIMATE '13' EXP(B0+B1 +B4*&MEOS+B5*&MCATSCR+B6*&MICSUSE+B7*&MSMKSTAT +B8*&MPPFEV1+B9*&MCOPDEXF)***365.25-** EXP(B0+B3 +B4*&MEOS+B5*&MCATSCR+B6*&MICSUSE+B7*&MSMKSTAT +B8*&MPPFEV1+B9*&MCOPDEXFL)***365.25**; ESTIMATE '14' EXP(B0+B1 +B4*&MEOS+B5*&MCATSCR+B6*&MICSUSE+B7*&MSMKSTAT +B8*&MPPFEV1+B9*&MCOPDEXFL)***365.25-** EXP(B0+B4 +B4*&MEOS+B5*&MCATSCR+B6*&MICSUSE+B7*&MSMKSTAT

Test	**Template SAS Code for Modeling** (SAS Version 9.4)
	+B8*&MPPFEV1+B9*&MCOPDEXFL)***365.25**; ESTIMATE '23' EXP(B0+B2 +B4*&MEOS+B5*&MCATSCR+B6*&MICSUSE+B7*&MSMKSTAT +B8*&MPPFEV1+B9*&MCOPDEXFL)***365.25**- EXP(B0+B3 +B4*&MEOS+B5*&MCATSCR+B6*&MICSUSE+B7*&MSMKSTAT +B8*&MPPFEV1+B9*&MCOPDEXFL)***365.25**; ESTIMATE '24' EXP(B0+B2 +B4*&MEOS+B5*&MCATSCR+B6*&MICSUSE+B7*&MSMKSTAT +B8*&MPPFEV1+B9*&MCOPDEXFL)***365.25**- EXP(B0+B4 +B4*&MEOS+B5*&MCATSCR+B6*&MICSUSE+B7*&MSMKSTAT +B8*&MPPFEV1+B9*&MCOPDEXFL)***365.25**; ESTIMATE '34' EXP(B0+B3 +B4*&MEOS+B5*&MCATSCR+B6*&MICSUSE+B7*&MSMKSTAT +B8*&MPPFEV1 +B9*&MCOPDEXFL)*3**65.25**- EXP(B0+B4 +B4*&MEOS+B5*&MCATSCR+B6*&MICSUSE+B7*&MSMKSTAT +B8*&MPPFEV1+B9*&MCOPDEXFL)***365.25**; &MEOS is a macro variable with the value of the mean EOS value. &MCATSCR is a macro variable with the value of the mean CATSCR value. &MPPFEV1 is a macro variable with the value of mean PPFEV1 value. &MCOPDEXFL is a macro variable with the weight for COPDEXFL='Y'. &MICSUSE is macro value with the weight for ICSUSE='Y'. &MSMKSTAT is a macro value with weight for SMKSTAT=2 which is former smoker.

Logistic regression using PROC GENMOD	ods output Estimates = est;
	ods output lsmeans=lsmeans;
	ods output LSMeanDiffs=diffs;
	proc genmod data=<dataset> descending;
	by &by;
	class usubjid trt (ref='4');
	model respn = trt base revven / dist=bin;
	lsmeans trt / diff;

Test	**Template SAS Code for Modeling** (SAS Version 9.4)

	*to verify the lsmeans;
	estimate '1' int **1** trt **1 0 0 0** base &mbase revven &mrevven; *verify lsmeans;
	estimate '2' int **1** trt **0 1 0 0** base &mbase revven &mrevven; *verify lsmeans;
	estimate '3' int **1** trt **0 0 1 0** base &mbase revven &mrevven; *verify lsmeans;
	estimate '4' int **1** trt **0 0 0 1** base &mbase revven &mrevven; *verify lsmeans;
	
	*estimate treatment differences;
	estimate '12' trt **1 -1 0 0**/* not using /exp option as it will not provide
	p-values in those rows */
	estimate '13' trt **1 0 -1 0**;
	estimate '14' trt **1 0 0 -1**;
	estimate '23' trt **0 1 -1 0**;
	estimate '24' trt **0 1 0 -1**;
	estimate '34' trt **0 0 1 -1**;
	
	Where:
	
	RESPN is a binary response variable with values of either 1 (responder) or 0 (not a responder).
	BASE is baseline continuous value and is the baseline for RESPN.
	REVVEN is screening continuous percent reversibility.
	TRT will be coded: '1'=GFF '2'=GP '3'=FF and '4'=Placebo where Placebo will be the reference group.
	
	&mbase macro variable is average level of covariate base, where average is calculated over non-missing base and percent reversibility to Ventolin HFA; *study cannot be missing.
	&mrevven macro variable is the average level of covariate percent reversibility to Ventolin HFA, where average is calculated over non-missing base and percent reversibility to Ventolin HFA;
	
	data lsm; /* proportions */
	set est where length(label)=**1**;
	trt=input(label,**1.**);
	keep &by trt mean:;
	
	data or; /* odds ratios */
	set est;
	where length(label)=**2**;
	trt=input(substr(label,**1**,**1**),**1.**);
	trt=input(substr(label,**2**,**1**),**1.**);

Test	**Template SAS Code for Modeling** (SAS Version 9.4)

	lbetaestimate=exp(lbetaestimate);
	lbetalowercl=exp(lbetalowercl);
	lbetauppercl=exp(lbetauppercl);
	keep &by trt _trt lbetaestimate lbetalowercl lbetauppercl probchisq;
	ods output additionalestimates=diff; /* differences in proportions */
	
	proc nlmixed data=&dsin;
	by &by;
	parms /data=pe1;*b0 is the intercept;
	eta=b0+b1*(trt=**1**)+b2*(trt=**2**)+b3*(trt=**3**)+b4*base+b5*revven;
	p=exp(eta)/(**1**+exp(eta));
	model respn ~ binomial(**1**,p);
	
	estimate "d12"
	1/(**1**+exp(b0+b1+b4*&mbase+b5*&mrevven))-
	1/(**1**+exp(b0+b2+b4*&mbase+b5*&mrevven));
	
	estimate "d13"
	1/(**1**+exp(b0+b1+b4*&mbase+b5*&mrevven))-
	1/(**1**+exp(b0+b3+b4*&mbase+b5*&mrevven));
	
	estimate "d14"
	1/(**1**+exp(b0+b1+b4*&mbase+b5*&mrevven))-
	1/(**1**+exp(b0+b4+b4*&mbase+b5*&mrevven));
	
	estimate "d23"
	1/(**1**+exp(b0+b2+b4*&mbase+b5*&mrevven))-
	1/(**1**+exp(b0+b3+b4*&mbase+b5*&mrevven));
	
	estimate "d24"
	1/(**1**+exp(b0+b2+b4*&mbase+b5*&mrevven))-
	1/(**1**+exp(b0+b4+b4*&mbase+b5*&mrevven));
	
	estimate "d34"
	1/(**1**+exp(b0+b3+b4*&mbase+b5*&mrevven))-
	1/(**1**+exp(b0+b4+b4*&mbase+b5*&mrevven));

Cox regression model for time to COPD	ODS GRAPHICS ON; PROC PHREG PLOTS (OVERLAY)=(SURVIVAL CUMHAZ); STRATA TREATMENT; MODEL TIME*CENSOR(0)=COVARIATE1 COVARIATE2 ….; OUT=PRED1 SURVIVAL=_ALL_ / ROWID=SUBJECT;

Test	**Template SAS Code for Modeling** (SAS Version 9.4)
exacerbation and time to first moderate or severe COPD exacerbation	ODS GRAPHICS OFF; Hazard ratios with Wald two-sided 95% confidence limits for these ratios will also be provided for all treatment comparisons. The time to first COPD exacerbation of any severity will be analyzed up through Day 183 (Week 26).
Kaplan-Meier Survival method for time to COPD exacerbation and time to first moderate or severe COPD exacerbation --95% two-sided confidence interval (CI) for cumulative response rate	PROC LIFETEST METHOD=KM PLOTS = (S) OUTSURV=OUT1; TIME TIME*CENSOR(0); STRATA TREATMENT; Get 95% CI from dataset 'out1'. ** event=1; censored=0; Subjects who do not experience a COPD exacerbation will be censored at the Week 24 visit or Day 183, whichever is earlier. Subjects who withdraw from the study without experiencing a COPD exacerbation will be censored at the date of last contact, the date of the last visit, or the last date of treatment, whichever is latest but on Day 183 or earlier.

APPENDIX 4: CTCAE LABORATORY TEST CRITERIA FOR SHIFT TABLES

This appendix is provided as a separate document.

APPENDIX 5: STANDARD MEDDRA QUERIES (SMQ)

This appendix is provided as a separate document.

APPENDIX 6: MOCK-UP TABLES, LISTINGS, AND FIGURES

Mock-up tables, listings, and figures are presented in a separate document.

APPENDIX 7: TABLE OF CONTENTS FOR POST-TEXT TLFs IN THE CHINA POPULATION

The table of contents for Post-Text TFLs in the China Population is presented in a separate document.

APPENDIX 8: TABLE OF CONTENTS FOR POST-TEXT TLFs IN THE ASIA POPULATION

The table of contents for Post-Text TFLs in the Asia Population is presented in a separate document.

APPENDIX 1: DATA HANDLING RULES

Study Number:	PT003014
Investigational Drug and Drug Number:	Glycopyrronium and Formoterol Fumarate Inhalation Aerosol (GFF MDI); PT003 Glycopyrronium Inhalation Aerosol (GP MDI); PT005 Formoterol Fumarate Inhalation Aerosol (FF MDI); PT001
Indication:	COPD
Dosage Form/Strength:	GFF MDI 14.4/9.6 μg ex-actuator BID GP MDI 14.4 μg ex-actuator BID FF MDI 9.6 μg ex-actuator BID

PT003014 Protocol Title: A Randomized, Double-Blind, Chronic Dosing (24 Weeks), Placebo-Controlled, Parallel Group, Multi-Center Study to Assess the Efficacy and Safety of PT003, PT005, and PT001 in Subjects with Moderate to Very Severe COPD, Compared with Placebo

Programming of the tables, listings and figures will be performed using SAS Version 9.4 or a more recent version.

The following table presents the algorithms to be used in SAS to calculate the derived variables, including rules for handling other missing data or partial dates, or irregular/unexpected data issues. Additional variables and rules may be found in the ADaM specification document.

Category	Description	Data Handling Rule
1. Pulmonary Function Testing data	iCardiac Technologies, Inc. (nSpire Health) data transferred	• Only data of rank =1 (best effort) will be transferred; data transferred will be grade 1 = acceptable, grade 2 = borderline, or grade = 3 (unacceptable). Only data of grade = 1 or grade = 2 will be included in baseline or on-treatment spirometry calculations. • All data transferred from iCardiac Technologies, Inc. (grade = 1, 2, or 3) will be listed in data listings with the grade.
2. Age (years)	Age (years)	Age = integer part of (Visit 1 date – Birth date +1)/365.25.
3. Smoking History	Number of pack years smoked	Number of pack years smoked = (number of cigarettes per day/20) x number of years smoked.
	Former smoker	Former smokers are defined as those who have stopped smoking for at least 6 weeks prior to Screening (Visit 1).
	Weeks Since a Former Smoker Quit	(Date of Screening Visit 1 – Date Former Smoker Quit)/7.
4. Severity of COPD	Severity of COPD: GOLD 2, 3, and 4	Based on post-bronchodilator FEV_1, severity of COPD at Screening is defined as follows, where % predicted values are values derived by iCardiac Technologies, Inc. (formerly nSpire Health for PT003006 and PT003007) using NHANES III reference equations: • Moderate = 50% ≤ FEV_1 <80% predicted • Severe = 30% ≤ FEV_1 <50% predicted • Very Severe = FEV_1 <30% predicted
	GOLD 2017 COPD Assessment Categories: A, B, C, and D	A (low exacerbation risk [0 or 1 exacerbation not leading to hospitalization], less symptoms [CAT <10] B (low exacerbation risk [0 or 1 exacerbation

Category	Description	Data Handling Rule
		not leading to hospitalization], more symptoms[CAT ≥10]) C (high exacerbation risk [≥2 exacerbations or ≥1 exacerbation leading to hospitalization], less symptoms [CAT <10]) D (high exacerbation risk [≥2 exacerbations or ≥1 exacerbation leading to hospitalization] , more symptoms [CAT ≥10])
5. COPD Diagnosis	Missing Date COPD First Diagnosed	Day of Diagnosis will be imputed for all subjects as the 1st of the month. Missing month of Diagnosis will be imputed as June, or the month in which 1st will be the latest before informed consent date, whichever is earliest.
	Years Prior to First Dose in the Study When COPD First Diagnosed	(Date of First Dose of Study Treatment in the study – Date COPD First Diagnosed)/365.25.
6. Medical History	Medical History Begin Date of Condition	Missing month of Condition will be imputed as June, or the month in which 1st will be the latest before informed consent date, whichever is earliest. Begin date of Condition will be imputed for all subjects as the 1st of the month.
	Medical History End Date of Condition	Other than for 'Ongoing' conditions, missing month of End Date of Condition will be imputed as June, or the month in which 1st will be the latest before informed consent date, whichever is earliest. End date of Condition will be imputed for all subjects as the 1st of the month.
7. Surgical History	Surgical History Date of Surgery	Missing month of Surgery will be imputed as June, or the month in which 1st will be the latest before informed consent date, whichever is earliest. Begin date of Surgery will be imputed for all subjects as the 1st of the month.
8. First and Last Treatment Dates	date/time of first and last dose of a study treatment	The date and time (24 hr. clock) of the first dose of study treatment will be taken from the Dosing eCRF. The date of the last dose of study treatment will be the later of the last date of dosing from the eDiary or the last date of dosing from the Dosing eCRF for the

Category	Description	Data Handling Rule
		treatment.
9. Last Visit Date	Date of Last Visit	Date of last visit according to the Visit eCRF.
10. Last Study Participation Date (STDM variable, RFPENDTC)	Last Study Participation Date (STDM variable, RFPENDTC)	Last study participation date is defined as last known date of contact which would be the later of the following dates: last visit date, date of the last dose, date of last contact if lost-to-follow-up, date of telephone follow-up, or death date.
11. Study Day Definitions	**Study Day** for assessment/event which occurs on or after the start of study treatment	Study Day = Date of assessment/event – date of the first dose of study treatment + 1.
	Study Day for assessments/events on days prior to the first dose of study treatment in the study	Study Day = date of assessment/event – first dose date of treatment in the study.
	Study Day Post-Treatment of Assessment or event which occurs after study treatment	Study Day = 'P' concatenated with the number of days post-treatment that the assessment or event occurred which is defined as Date of assessment/event – date of last dose of study treatment.
	Study Day of Randomization	Study Day of Randomization = date of randomization – date of the first dose of study treatment in the study + 1. Study Day is 1 if baseline day is on the day of randomization.
	First Dose Day	**First Dose Day** in the study is defined as the study day of the first dose of study treatment in the study (Study Day 1).

Category	Description	Data Handling Rule
	Last Study Day	**For subjects who did not receive study treatment in the study (e.g., Non-Randomized subjects)**, Last Study Day is defined as (the later of the last visit date and the date of last contact for subjects lost-to-follow-up from the Study Completion/Early Discontinuation eCRF) – Date of Screening Visit + 1. **For subjects who received study treatment in the study,** Last Study Day is defined as (the later of the last visit date and the date of last contact for subjects lost-to-follow-up from the Study Completion/Early Discontinuation eCRF) – first dose date in the study + 1.
	Days Since Last Dose for event (e.g., Death)	**Days Since Last Dose** is defined as date of event – date of last dose of study treatment.
12. Duration of event	The duration of any event	The duration of any event is defined as (stop date – start date + 1).
13. Multiple assessments for the same visit	Vital Sign, ECG, and Laboratory assessments	• All data will be listed in data listings. • The last of multiple valid assessments within a post-baseline study time window will be used for summaries and statistical testing. • If there are multiple laboratory values for the same parameter at pre-dose of a visit, the last value will be chosen for analysis. • If there are multiple ECG values for the same parameter at pre-dose of a visit date, the last value will be chosen for analysis. • The average of all available pre-dose vital sign measurements for a vital sign parameter taken prior to the start of dosing for the Treatment Period will be used for calculation of baseline for a parameter.
	Spirometry assessments	• The last of multiple valid assessments within a post-baseline study time window will be used for summaries and statistical testing.
14. Special Lab Value	Lab values with a prefix such as: '>', '<',	• '>': use the available original value +0.001 in the analyses.

Category	Description	Data Handling Rule
Handling (not including PK values)	'+' and 'Less than' etc…	• '<': use the available original value –0.001 in the analyses. • '+': use the available original value without the prefix in the analyses. • '>=': use the available original value in the analyses. • '<=': use the available original value in the analyses.
15. Prior. concomitant, and post-treatment medication / treatment	Prior, concomitant, and post-treatment medication/treatment	1. Prior medication/treatment: is any medication/treatment taken prior to the first dose of study medication in the study (or the date of the randomization visit, Visit 4, if the date of the start of study medication is missing), even if this medication/treatment continued into the study medication treatment period. A medication/treatment will be considered prior if the start and end date of the medication/treatment are missing OR the start date is missing and the end date is on or after the first dose date of study medication in the study, or either the medication/treatment start date or end date or both are before first dose date of study medication in the study (or the date of the randomization visit, Visit 4, if the date of the start of study medication is missing). 2. A medication/treatment will be identified as a concomitant medication/treatment if any of the following are true: o The start date is on or after the date of the start of study treatment (or the date of randomization, Visit 4, if missing), but prior to the date of Visit 11a, the date of the Discontinuation Visit, or the date of the last in-clinic or diary data collection. o The end date is prior to the date of Visit 11a, the date of the Discontinuation Visit, or the date of the last in-clinic or diary data, but the end date is on or after

Category	Description	Data Handling Rule
		the start of study medication in the study (or the date of the randomization visit, Visit 4, if missing). The medication/treatment is checked as 'Ongoing', and the start date of the medication/treatment is prior to the date of Visit 11a, the date of the Discontinuation Visit, or the date of the last in-clinic or diary data collection. 3. A medication with an onset date of the date of Visit 11a, the date of the Discontinuation Visit, or the date of the last in-clinic or diary data collection or after will not be considered concomitant, but will be considered a **Post-Treatment medication/treatment**. 4. Note that for Completers, the Visit 11a date used for the rules above was the later of the Visit 11a date and the last date of treatment. For those who discontinued, and with a discontinuation visit, the date of the Discontinuation Visit used for the rules above is the later of the Discontinuation Visit date or the last diary date. The date of the last in-clinic or diary data collection date used for the rules above was the death date or the date of the last treatment when these dates were later than the last in-clinic visit or the last diary date. 5. Any medication/treatment which cannot be identified as Prior, Concomitant, or Post-Treatment will be considered as being in each of the possible categories depending on available information
16. Adverse event	Missing severity	For the AE summary by severity, an AE with missing severity will be deemed as Severe. Imputed values will not be listed in data listings.
	Missing relationship to study drug	For AE summary by relationship, an AE with a missing relationship to study drug will be deemed as Definitely related. Imputed values will not be listed in data listings.

Category	Description	Data Handling Rule
	Treatment-emergent adverse event	An adverse event is considered treatment-emergent if the date of onset is on or after the date of first dose of study medication. Adverse events after the Follow-up Telephone Call scheduled at least 14 days after Visit 11a or a discontinuation visit will not be considered treatment-emergent, but will be listed in adverse event data listings.
		If the AE start date is partial/missing, then • If AE start date is completely missing, then the AE is considered as treatment emergent. • If both AE start month and day are missing and AE start year is the same or after the first dose year, then the AE is considered as treatment emergent. • If AE start day is missing and AE start year and month are the same or after the first dose year and month, then the AE is considered as treatment emergent. Missing/incomplete (partial) AE start and end dates will not be imputed for data listings.
17. AE rate adjusted for exposure	Rate of AEs per 1000 person-years	Adjusted rate per 1000 person-years = 1000 x (Total number of AEs/Total years of exposure across all subjects for the treatment).
18. Time to death	Time to death in weeks	Time to death (weeks) = (date of death – first treatment administration date +1)/7.
19. Treatment Duration	Treatment Duration	Treatment duration is defined as Date of last dose of a study treatment - Date of first dose of a study treatment +1.
20. Total Years of Exposure	Total years of exposure to study treatment	Total exposure (years) for a treatment as a whole is defined as the sum of all days of exposure for a treatment /365.25.
21. Exposure (days)	Exposure (days)	Exposure (days) is defined as (Date of the last dose of the study treatment – Date of first dose of the study treatment + 1).
22. Total Expected Puffs of Study Medication	Total expected number of puffs taken of a study treatment	The expected number of puffs for a test day which is the last date of treatment will be 2, the expected number of puffs for the last date of treatment which is not a test day will be 4 when a PM dose has been taken and then 2

Category	Description	Data Handling Rule
		otherwise, and the expected number of puffs on dates prior to the last date of treatment will be 4.
23. Treatment Compliance (%)	Treatment Compliance (%) for a treatment	Percent compliance is defined as (total number of puffs of study treatment taken on a study day/total expected puffs taken on a study day) averaged across all days of a subject's dosing between start of study treatment and last day on study treatment) x 100. The expected number of puffs for a test day which was the last date of treatment will be 2, the expected number of puffs for the last date of treatment which was not a test day will be 4 when a PM dose was taken and then 2 otherwise; the expected number of puffs on dates prior to the last date of treatment will be 4.
24. Hard coding	Hard coding for data analysis	Hard Coding is not allowed during data analysis unless agreed to in writing by Pearl.
25. AUC calculation for spirometry endpoints	AUC_{0-2}	AUC_{0-2} will be calculated using the trapezoidal rule and actual time of assessment when available and nominal time of assessment otherwise.
26. HCRU	Number of days in CCU and ICU	Unknown ICU stay (and CCU) responses will be included as zero days in the ICU/CCU for the summary stats. If the response was yes that there was a stay in the ICU/CCU, but the number of days is missing, then the average value for ICU/CCU stays in the treatment group should be used.

APPENDIX 4 CTCAE LABORATORY TEST CRITERIA FOR SHIFT TABLES

Study Number:	PT003014
Investigational Drug and Drug Number:	Glycopyrronium and Formoterol Fumarate Inhalation Aerosol (GFF MDI); PT003 Glycopyrronium Inhalation Aerosol (GP MDI); PT005 Formoterol Fumarate Inhalation Aerosol (FF MDI); PT001
Indication:	COPD
Dosage Form/Strength:	GFF MDI 14.4/9.6 µg ex-actuator BID GP MDI 14.4 µg ex-actuator BID FF MDI 9.6 µg ex-actuator BID

PT003014 Protocol Title: A Randomized, Double-Blind, Chronic Dosing (24 Weeks), Placebo-Controlled, Parallel Group, Multi-Center Study to Assess the Efficacy and Safety of PT003, PT005, and PT001 in Subjects with Moderate to Very Severe COPD, Compared with Placebo

CTCAE LABORATORY TEST CRITERIA

Investigations				
	Grade			
Adverse Event	1	2	3	4
Alanine aminotransferase increased	>ULN – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
Alkaline phosphatase increased	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
Aspartate aminotransferase increased	>ULN – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
Blood bilirubin increased	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN
Cholesterol high	>ULN – 300 mg/dL; >ULN -7.75 mmol/L	>300 – 400 mg/dL; >7.75 -10.34 mmol/L	>400 – 500 mg/dL; >10.34 -12.92 mmol/L	>500 mg/dL; >12.92 mmol/L
Creatinine increased	>1 – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 x ULN	>6.0 x ULN
GGT increased	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
Hemoglobin increased	Increase in >0 – 2 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >2 – 4 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >4 gm/dL above ULN or above baseline if baseline is above ULN	n/a

Investigations				
	Grade			
Adverse Event	1	2	3	4
Anemia (hemoglobin decreased)	LLN- 10g/dL; <LLN – 6.2 mmol/L; <LLN – 100 g/L	<10.0 – 8.0 g/dL; <6.2 – 4.9 mmol/L; <100 – 80g/L	<8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated
Leukocytosis (White blood cell increased) (a)	>ULN – 40,000/mm^3	>40,000 – 100,000/mm^3	>100,000/mm^3	Clinical manifestations of leucostasis; urgent intervention indicated
White blood cell decreased	<LLN – 3000/mm^3; <LLN – 3.0 x 10^9/L	<3000 – 2000/mm^3; <3.0 – 2.0 x 10^9 /L	<2000 – 1000/mm^3; <2.0 – 1.0 x 10^9 /L	<1000/mm^3; <1.0 x 10^9 /L
Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10^9/L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10^9/L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10^9/L	<25,000/mm3; <25.0 x 10^9/L

Metabolism and Nutrition Disorders				
	Grade			
Adverse Event	1	2	3	4
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life-threatening consequences
Hyperglycemia	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 - 500 mg/dL; >13.9 - 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences
Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	n/a	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L; life-threatening consequences
Hypernatremia (Sodium Increased)	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences

Metabolism and Nutrition Disorders				
	Grade			
Adverse Event	1	2	3	4
Hypoalbuminemia (Albumin Decreased)	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated
Hypocalcemia (Calcium Decreased)	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium<LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0- 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L; hospitalizationindicated	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L;Ionized calcium <0.8 mmol/L;life-threatening consequences
Hypoglycemia (Glucose Decreased)	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; life-threatening consequences; seizures
Hypokalemia (Potassium Decreased)	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences
Hypomagnesemia (Magnesium Decreased)	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L; life-threatening consequences

Metabolism and Nutrition Disorders				
	Grade			
Adverse Event	1	2	3	4
Hyponatremia (Sodium Decreased)	<LLN - 130 mmol/L	n/a	<130 - 120 mmol/L	<120 mmol/L; life-threatening consequences
Hypophosphatemia (Phosphate Decreased)	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 - 1.0 mg/dL; <0.6 - 0.3 mmol/L	<1.0 mg/dL; <0.3 mmol/L; life-threatening consequences

Renal and Urinary Disorders				
	Grade			
Adverse Event	1	2	3	4
Chronic kidney disease	eGFR (estimated Glomerular Filtration Rate) or CrCl (creatinine clearance) <LLN -60 ml/min/1.73 m^2 or proteinuria 2+ present; urine protein/creatinine >0.5	eGFR or CrCl 59 - 30 ml/min/1.73 m^2	eGFR or CrCl 29 - 15 ml/min/1.73 m^2	eGFR or CrCl <15 ml/min/1.73 m^2; dialysis or renal transplant indicated
(a) Grade 1 and Grade 2 not categorized in CTCAE4; Grade 1 and 2 based on reference laboratory alert criteria of 40,000 /mm^3 (LabCorp)				

APPENDIX 5 STANDARD MEDDRA VERSION 19.1 QUERIES (SMQs)

Study Number:	PT003014
Investigational Drug and Drug Number:	Glycopyrronium and Formoterol Fumarate Inhalation Aerosol (GFF MDI); PT003 Glycopyrronium Inhalation Aerosol (GP MDI); PT005 Formoterol Fumarate Inhalation Aerosol (FF MDI); PT001
Indication:	COPD
Dosage Form/Strength:	GFF MDI 14.4/9.6 µg ex-actuator BID GP MDI 14.4 µg ex-actuator BID FF MDI 9.6 µg ex-actuator BID

PT003014 Protocol Title: A Randomized, Double-Blind, Chronic Dosing (24 Weeks), Placebo-Controlled, Parallel Group, Multi-Center Study to Assess the Efficacy and Safety of PT003, PT005, and PT001 in Subjects with Moderate to Very Severe COPD, Compared with Placebo

Standard MedDRA Query (SMQ)	
Cerebrovascular disorders	
Central nervous system haemorrhages and cerebrovascular conditions (SMQ)	
Haemorrhagic central nervous system vascular conditions (SMQ)	
Narrow	Basal ganglia haemorrhage
	Basal ganglia stroke
	Brain stem haematoma
	Brain stem haemorrhage
	Brain stem microhaemorrhage
	Brain stem stroke
	Carotid aneurysm rupture
	Central nervous system haemorrhage
	Cerebellar haematoma
	Cerebellar haemorrhage
	Cerebellar microhaemorrhage
	Cerebral aneurysm perforation
	Cerebral aneurysm ruptured syphilitic
	Cerebral arteriovenous malformation haemorrhagic
	Cerebral haematoma
	Cerebral haemorrhage
	Cerebral haemorrhage foetal
	Cerebral haemorrhage neonatal
	Cerebral microhaemorrhage
	Cerebrovascular accident
	Cerebrovascular disorder
	Epidural haemorrhage
	Extradural haematoma
	Haemorrhage intracranial
	Haemorrhagic cerebral infarction
	Haemorrhagic stroke
	Haemorrhagic transformation stroke
	Intracerebral haematoma evacuation
	Intracranial haematoma
	Intracranial tumour haemorrhage
	Intraventricular haemorrhage
	Intraventricular haemorrhage neonatal
	Meningorrhagia
	Perinatal stroke
	Pituitary haemorrhage
	Putamen haemorrhage
	Ruptured cerebral aneurysm
	Spinal cord haemorrhage
	Spinal epidural haematoma
	Spinal epidural haemorrhage
	Spinal haematoma

	Spinal subarachnoid haemorrhage
	Spinal subdural haematoma
	Spinal subdural haemorrhage
	Stroke in evolution
	Subarachnoid haemorrhage
	Subarachnoid haemorrhage neonatal
	Subdural haematoma
	Subdural haematoma evacuation
	Subdural haemorrhage
	Subdural haemorrhage neonatal
	Thalamus haemorrhage
	Basal ganglia haematoma
	Basilar artery perforation
	Carotid artery perforation
	Cerebral artery perforation
	Extra-axial haemorrhage
	Periventricular haemorrhage neonatal
	Spinal cord haematoma
	Subarachnoid haematoma
	Vertebral artery perforation
Ischaemic central nervous system vascular conditions (SMQ)	
Narrow	Amaurosis fugax
	Basal ganglia infarction
	Basal ganglia stroke
	Basilar artery occlusion
	Basilar artery stenosis
	Basilar artery thrombosis
	Brachiocephalic arteriosclerosis
	Brachiocephalic artery occlusion
	Brachiocephalic artery stenosis
	Brain hypoxia
	Brain stem embolism
	Brain stem infarction
	Brain stem ischaemia
	Brain stem stroke
	Brain stem thrombosis
	Capsular warning syndrome
	Carotid angioplasty
	Carotid arterial embolus
	Carotid arteriosclerosis
	Carotid artery bypass
	Carotid artery disease
	Carotid artery insufficiency
	Carotid artery occlusion

	Carotid artery restenosis
	Carotid artery stenosis
	Carotid artery stent insertion
	Carotid artery stent removal
	Carotid artery thrombosis
	Carotid endarterectomy
	Carotid revascularisation
	Cerebellar artery occlusion
	Cerebellar artery thrombosis
	Cerebellar embolism
	Cerebellar infarction
	Cerebellar ischaemia
	Cerebral arteriosclerosis
	Cerebral artery embolism
	Cerebral artery occlusion
	Cerebral artery restenosis
	Cerebral artery stenosis
	Cerebral artery thrombosis
	Cerebral gas embolism
	Cerebral infarction
	Cerebral infarction foetal
	Cerebral ischaemia
	Cerebral revascularisation
	Cerebral septic infarct
	Cerebral small vessel ischaemic disease
	Cerebral thrombosis
	Cerebral vasoconstriction
	Cerebral venous thrombosis
	Cerebrovascular accident
	Cerebrovascular disorder
	Cerebrovascular insufficiency
	Cerebrovascular stenosis
	Embolic cerebral infarction
	Embolic stroke
	Hypoxic-ischaemic encephalopathy
	Inner ear infarction
	Ischaemic cerebral infarction
	Ischaemic stroke
	Lacunar infarction
	Lateral medullary syndrome
	Migrainous infarction
	Millard-Gubler syndrome
	Moyamoya disease
	Perinatal stroke
	Post procedural stroke

	Precerebral artery occlusion
	Reversible ischaemic neurological deficit
	Spinal artery embolism
	Spinal artery thrombosis
	Stroke in evolution
	Subclavian steal syndrome
	Thalamic infarction
	Thrombotic cerebral infarction
	Thrombotic stroke
	Transient ischaemic attack
	Vascular encephalopathy
	Vertebral artery occlusion
	Vertebral artery stenosis
	Vertebral artery thrombosis
	Vertebrobasilar insufficiency
	Carotid artery calcification
	Cerebral microembolism
	Cerebral vascular occlusion
	Delayed ischaemic neurological deficit
	Lacunar stroke
	Post cardiac arrest syndrome
	Precerebral arteriosclerosis
	Reversible cerebral vasoconstriction syndrome
	Vascular stent occlusion
	Vascular stent restenosis
	Vascular stent stenosis

Cardiac failure (SMQ)	
Narrow	Acute left ventricular failure
	Acute pulmonary oedema
	Acute right ventricular failure
	Cardiac asthma
	Cardiac failure
	Cardiac failure acute
	Cardiac failure chronic
	Cardiac failure congestive
	Cardiac failure high output
	Cardiogenic shock
	Cardiopulmonary failure
	Cardiorenal syndrome
	Chronic left ventricular failure
	Chronic right ventricular failure
	Cor pulmonale
	Cor pulmonale acute
	Cor pulmonale chronic

	Ejection fraction decreased
	Hepatic congestion
	Hepatojugular reflux
	Left ventricular failure
	Low cardiac output syndrome
	Neonatal cardiac failure
	Obstructive shock
	Pulmonary oedema
	Pulmonary oedema neonatal
	Right ventricular failure
	Ventricular failure
	Radiation associated cardiac failure
	Right ventricular ejection fraction decreased

Ischaemic Heart Disease (SMQ)	
Myocardial infarction (SMQ)	
Narrow	Acute coronary syndrome
	Acute myocardial infarction
	Angina unstable
	Blood creatine phosphokinase MB abnormal
	Blood creatine phosphokinase MB increased
	Coronary artery embolism
	Coronary artery occlusion
	Coronary artery reocclusion
	Coronary artery thrombosis
	Coronary bypass thrombosis
	Kounis syndrome
	Myocardial infarction
	Myocardial necrosis
	Myocardial reperfusion injury
	Myocardial stunning
	Papillary muscle infarction
	Post procedural myocardial infarction
	Postinfarction angina
	Silent myocardial infarction
	Troponin I increased
	Troponin increased
	Troponin T increased
	Coronary vascular graft occlusion
Other ischaemic heart disease (SMQ)	
Narrow	Angina pectoris
	Angina unstable
	Arteriosclerosis coronary artery
	Arteriospasm coronary

	Coronary angioplasty
	Coronary arterial stent insertion
	Coronary artery bypass
	Coronary artery disease
	Coronary artery dissection
	Coronary artery insufficiency
	Coronary artery restenosis
	Coronary artery stenosis
	Coronary endarterectomy
	Coronary no-reflow phenomenon
	Coronary ostial stenosis
	Coronary revascularisation
	Dissecting coronary artery aneurysm
	ECG signs of myocardial ischaemia
	External counterpulsation
	Haemorrhage coronary artery
	Ischaemic cardiomyopathy
	Microvascular coronary artery disease
	Myocardial ischaemia
	Percutaneous coronary intervention
	Prinzmetal angina
	Stress cardiomyopathy
	Subclavian coronary steal syndrome
	Subendocardial ischaemia
	Coronary brachytherapy
	Coronary bypass stenosis
	Coronary vascular graft stenosis
	Ischaemic mitral regurgitation

Cardiac arrhythmias (SMQ)	
Cardiac Arrhythmia Terms (incl bradyarrhythmias and tachyarrhythmias) (SMQ)	
Bradyarrhythmias (including conduction defects and disorders of sinus node function) (SMQ)	
Bradyarrhythmia terms, nonspecific (SMQ)	
Narrow	Bradyarrhythmia
	Ventricular asystole
Conduction defects (SMQ)	
Narrow	Accessory cardiac pathway
	Adams-Stokes syndrome
	Agonal rhythm
	Atrial conduction time prolongation
	Atrioventricular block
	Atrioventricular block complete
	Atrioventricular block first degree
	Atrioventricular block second degree

	Atrioventricular conduction time shortened
	Atrioventricular dissociation
	Bifascicular block
	Brugada syndrome
	Bundle branch block
	Bundle branch block bilateral
	Bundle branch block left
	Bundle branch block right
	Conduction disorder
	Defect conduction intraventricular
	Electrocardiogram delta waves abnormal
	Electrocardiogram PQ interval prolonged
	Electrocardiogram PQ interval shortened
	Electrocardiogram PR prolongation
	Electrocardiogram PR shortened
	Electrocardiogram QRS complex prolonged
	Electrocardiogram QT prolonged
	Electrocardiogram repolarisation abnormality
	Lenegre's disease
	Long QT syndrome
	Sinoatrial block
	Trifascicular block
	Ventricular dyssynchrony
	Wolff-Parkinson-White syndrome
	Paroxysmal atrioventricular block
Disorders of sinus node function (SMQ)	
Narrow	Nodal arrhythmia
	Nodal rhythm
	Sick sinus syndrome
	Sinus arrest
	Sinus arrhythmia
	Sinus bradycardia
	Wandering pacemaker
Cardiac arrhythmia terms, nonspecific (SMQ)	
Narrow	Arrhythmia
	Heart alternation
	Heart rate irregular
	Pacemaker generated arrhythmia
	Pacemaker syndrome
	Paroxysmal arrhythmia
	Pulseless electrical activity
	Reperfusion arrhythmia
	Withdrawal arrhythmia

Tachyarrhythmias (including supraventricular and ventricular tachyarrhythmias) (SMQ)	
Supraventricular tachyarrhythmias (SMQ)	
Narrow	Arrhythmia supraventricular
	Atrial fibrillation
	Atrial flutter
	Atrial parasystole
	Atrial tachycardia
	Junctional ectopic tachycardia
	Sinus tachycardia
	Supraventricular extrasystoles
	Supraventricular tachyarrhythmia
	Supraventricular tachycardia
Tachyarrhythmia terms, nonspecific (SMQ)	
Narrow	Anomalous atrioventricular excitation
	Cardiac flutter
	Extrasystoles
	Tachyarrhythmia
	Cardiac fibrillation
Ventricular tachyarrhythmias (SMQ)	
Narrow	Accelerated idioventricular rhythm
	Cardiac fibrillation
	Parasystole
	Rhythm idioventricular
	Torsade de pointes
	Ventricular arrhythmia
	Ventricular extrasystoles
	Ventricular fibrillation
	Ventricular flutter
	Ventricular parasystole
	Ventricular pre-excitation
	Ventricular tachyarrhythmia
	Ventricular tachycardia
Arrhythmia related investigations, signs and symptoms (SMQ) [selected PTs]	
	Bradycardia
	Central bradycardia
	Heart rate abnormal
	Heart rate decreased
	Heart rate increased
	Rebound tachycardia
	Tachycardia
	Tachycardia paroxysmal

Torsade de pointes/QT prolongation (SMQ)	
Narrow	Electrocardiogram QT interval abnormal
	Electrocardiogram QT prolonged
	Long QT syndrome
	Long QT syndrome congenital
	Torsade de pointes
	Ventricular tachycardia
	Ventricular flutter
	Ventricular tachyarrhythmia

Death	
	Suddent Death
	Brain death
	Death
	Sudden cardiac death
	cardiac arrest
	Cardio-respiratory arrest
	cardiac death
	Sudden Death
	Sudden unexplained death in epilepsy
	Accidental death
	Apparent death
	Maternal death during child birth
	Cardio-respiratory arrest

Anticholinergic syndrome (SMQ)	
Narrow	Anticholinergic syndrome
	Dry mouth
Broad	Ataxia
	Autonomic nervous system imbalance
	Balance disorder
	Coordination abnormal
	Depressed level of consciousness
	Dizziness
	Hyporesponsive to stimuli
	Loss of consciousness
	Presyncope
	Sedation
	Slow response to stimuli
	Somnolence
	Stupor
	Agitation
	Confusional state
	Delirium
	Disorientation

	Hallucination
	Hallucination, auditory
	Hallucination, gustatory
	Hallucination, olfactory
	Hallucination, synaesthetic
	Hallucination, tactile
	Hallucination, visual
	Hallucinations, mixed
	Restlessness
	Thinking abnormal
	Abasia
	Accommodation disorder
	Anhidrosis
	Blindness transient
	Cycloplegia
	Dry eye
	Dysphagia
	Gait disturbance
	Hyperaemia
	Hyperpyrexia
	Hypohidrosis
	Mydriasis
	Pyrexia
	Tachycardia
	Thirst
	Toxicity to various agents
	Urinary retention
	Vision blurred
	Visual acuity reduced
	Visual acuity reduced transiently
	Hemifacial anhidrosis

Gastrointestinal perforation, ulceration, haemorrhage or obstruction (SMQ)	
Gastrointestinal obstruction (SMQ)	
Narrow	Anal dilation procedure
	Anal stenosis
	Anastomotic stenosis
	Anastomotic ulcer, obstructive
	Anorectal stenosis
	Appendicolith
	Barium impaction
	Distal intestinal obstruction syndrome
	Duodenal obstruction
	Duodenal stenosis
	Duodenal ulcer perforation, obstructive

	Duodenal ulcer, obstructive
	Fibrosing colonopathy
	Fixed bowel loop
	Gallstone ileus
	Gastric ileus
	Gastric stenosis
	Gastric ulcer haemorrhage, obstructive
	Gastric ulcer perforation, obstructive
	Gastric ulcer, obstructive
	Gastric volvulus
	Gastrointestinal anastomotic leak
	Gastrointestinal dilation procedure
	Gastrointestinal motility disorder
	Gastrointestinal obstruction
	Gastrointestinal stenosis
	Ileal stenosis
	Ileus
	Ileus paralytic
	Ileus spastic
	Impaired gastric emptying
	Intestinal fibrosis
	Intestinal malrotation repair
	Intestinal obstruction
	Intestinal scarring
	Intestinal stenosis
	Intussusception
	Jejunal stenosis
	Large intestinal obstruction
	Large intestinal obstruction reduction
	Large intestinal stenosis
	Mechanical ileus
	Necrotising colitis
	Necrotising gastritis
	Necrotising oesophagitis
	Neonatal intestinal obstruction
	Obstruction gastric
	Oesophageal compression
	Oesophageal dilation procedure
	Oesophageal obstruction
	Oesophageal stenosis
	Peptic ulcer perforation, obstructive
	Peptic ulcer, obstructive
	Postoperative ileus
	Prepyloric stenosis
	Pylorus dilation procedure

	Rectal obstruction
	Rectal stenosis
	Small intestinal bacterial overgrowth
	Small intestinal obstruction
	Small intestinal stenosis
	Stomach dilation procedure
	Stricturoplasty
	Subileus
	Volvulus
HLGT Urinary Tract signs and symptoms	
HLT Bladder and Urethral symptoms	
	Bladder discomfort
	Bladder irritation
	Bladder pain
	Bladder spasm
	Bladder tamponade
	Dysuria
	Enuresis
	Fowler's syndrome
	Incontinence
	Lower urinary tract symptoms
	Micturition disorder
	Micturition frequency decreased
	Micturition urgency
	Mixed incontinence
	Paruresis
	Pollakiuria
	Psychogenic dysuria
	Strangury
	Stress urinary incontinence
	Terminal dribbling
	Urethral pain
	Urethral syndrome
	Urge incontinence
	Urinary hesitation
	Urinary incontinence
	Urinary retention
	Urinary retention postoperative
	Urinary straining
	Urine flow decreased
HLT Urinary Abnormalities	
	Acquired aminoaciduria
	Albuminuria
	Alkaptonuria

	Aminoaciduria
	Ammoniuria
	Aspartylglucosaminuria
	Asymptomatic bacteriuria
	Bacteriuria
	Bacteriuria in pregnancy
	Bence Jones proteinuria
	Bilirubinuria
	Candiduria
	Choluria
	Chromaturia
	Chyluria
	Cryoglobulinuria
	Crystalluria
	Cylindruria
	Cystinuria
	Essential fructosuria
	Faecaluria
	Globulinuria
	Glycosuria
	Glycosuria during pregnancy
	Haematinuria
	Haematuria
	Haematuria traumatic
	Haemoglobinuria
	Haemosiderinuria
	Homocystinuria
	Hydroxyprolinuria
	Hypercalciuria
	Hyperchloruria
	Hyperkaliuria
	Hypermagnesuria
	Hypermethioniuria
	Hyperoxaluria
	Hyperphosphaturia
	Hypersthenuria
	Hyperuricosuria
	Hypocalciuria
	Hypocitraturia
	Hyposthenuria
	Isosthenuria
	Ketonuria
	Leukocyturia
	Lipiduria
	Loin pain haematuria syndrome

	March haemoglobinuria
	Methaemoglobinuria
	Methylmalonic aciduria
	Microalbuminuria
	Myoglobinuria
	Nitrituria
	Oroticaciduria
	Oroticaciduria congenital
	Orthostatic proteinuria
	Paroxysmal nocturnal haemoglobinuria
	Pentosuria
	Phenylketonuria
	Pneumaturia
	Porphyrinuria
	Post procedural haematuria
	Proteinuria
	Pyuria
	Semenuria
	Sterile pyuria
	Urine abnormality
	Urine odour abnormal
	Urobilinuria
	Funguria
	Hypernatriuria
	Hyponatriuria
HLT Urinary tract signs and symptoms NEC	
	Costovertebral angle tenderness
	Cystitis-like symptom
	Extravasation of urine
	Flank pain
	Haemorrhage urinary tract
	Nocturia
	Pelvic discomfort
	Pelvic pain
	Perinephric collection
	Periureteral collection
	Polyuria
	Prostatism
	Renal colic
	Renal lymphocele
	Renal pain
	Transurethral resection syndrome
	Urinary tract pain
	Bladder hyperaemia

	Kidney congestion
	Postoperative pathological diuresis
	Urinary tract discomfort
	Urothelium erosion

HLT Tremor (excl congenital)	
	Action tremor
	Asterixis
	Essential tremor
	Head titubation
	Holmes tremor
	Intention tremor
	Orthostatic tremor
	Postural tremor
	Psychogenic tremor
	Resting tremor
	Tremor
	Tremor neonatal
HLT Visual Disorders NEC	
	Charles Bonnet syndrome
	Computer vision syndrome
	Diplopia
	Dysmetropsia
	Eccentric fixation
	Glare
	Halo vision
	Irlen syndrome
	Loss of visual contrast sensitivity
	Metamorphopsia
	Oscillopsia
	Photopsia
	Retinal migraine
	Scintillating scotoma
	Subacute myelo-opticoneuropathy
	Vision abnormal neonatal
	Vision blurred
	Visual brightness
	Visual impairment
	Visual perseveration
	Cortical visual impairment
	Delayed dark adaptation
	Delayed visual maturation
	Heteronymous diplopia

	Homonymous diplopia
	Neurologic neglect syndrome
	Psychogenic visual disorder

Glaucoma (SMQ)	
Narrow	Angle closure glaucoma
	Borderline glaucoma
	Developmental glaucoma
	Diabetic glaucoma
	Exfoliation glaucoma
	Fundoscopy abnormal
	Glaucoma
	Glaucoma drug therapy
	Glaucoma surgery
	Glaucoma traumatic
	Glaucomatocyclitic crises
	Glaucomatous optic disc atrophy
	Gonioscopy abnormal
	Halo vision
	Intraocular pressure fluctuation
	Intraocular pressure increased
	Intraocular pressure test abnormal
	Iridotomy
	Loss of visual contrast sensitivity
	Normal tension glaucoma
	Ocular hypertension
	Open angle glaucoma
	Ophthalmic fluid drainage
	Optic discs blurred
	Optic nerve cup/disc ratio increased
	Optic nerve cupping
	Phacolytic glaucoma
	Phacotrabeculectomy
	Pigmentary glaucoma
	Pupillary light reflex tests abnormal
	Slit-lamp tests abnormal
	Trabeculectomy
	Trabeculoplasty
	Uveitic glaucoma
	Uveitis-glaucoma-hyphaema syndrome
	Visual field tests abnormal
	Ocular stent placement
	Pseudophakic glaucoma
	Viscocanalostomy

APPENDIX 6 MOCK-UP TABLES, LISTINGS, AND FIGURES

Study Number:	PT003014
Investigational Drug and Drug Number:	Glycopyrronium and Formoterol Fumarate Inhalation Aerosol (GFF MDI); PT003 Glycopyrronium Inhalation Aerosol (GP MDI); PT005 Formoterol Fumarate Inhalation Aerosol (FF MDI); PT001
Indication:	COPD
Dosage Form/Strength:	GFF MDI 14.4/9.6 µg ex-actuator BID GP MDI 14.4 µg ex-actuator BID FF MDI 9.6 µg ex-actuator BID

PT003014 Protocol Title: A Randomized, Double-Blind, Chronic Dosing (24 Weeks), Placebo-Controlled, Parallel Group, Multi-Center Study to Assess the Efficacy and Safety of PT003, PT005, and PT001 in Subjects with Moderate to Very Severe COPD, Compared with Placebo

General Instructions for End-of-Text TFLs

Following are the specifications for end of text standard tables, listings, and figures (TFLs).

Header

The following header should appear at the very top of each page of a table, a listing, or a figure (TLF):

```
Protocol PT003014                                                    GFF MDI/GP MDI/FF MDI
```

Footer

The following footer should appear at the bottom of each page of a TLF generated in SAS:

```
Report generated by program:/sasdir/PGNAME.sas  Version YYYY-mm-dd hh:mm (Page n of N)
```

where: PGNAME = SAS program name. Version will be replaced by "Draft" or "Final". Page number will be right-justified.

Title

At least two (2) lines should be reserved for the whole title. The first line of the title is for the TLF number (i.e., title index #) and the actual title (title); a longer title may continue onto subsequent lines. The analysis population descriptor (Population) will be specified on the line following the title line(s). All titles should be centered, as shown in the following example:

```
                    Table 1.5.3 Demographics
                Analysis Set: Safety Population
```

Footnotes

- In general, a footnote serves as a brief explanation/clarification/definition/concept of a flag symbol or a character, an abbreviation, a terminology, etc., that appears in or related directly to the displayed content of a TLF. Detailed/technical elaboration of, for example, a mathematical/statistical formula, a statistical term/test, or an algorithm for deriving a parameter value, should be addressed in the text of the statistical analysis plan (SAP).
- All footnotes should follow immediately after a horizontal solid line. There should be one and only one space between the last footnote and the footer.
- Each line of a complete footnote should end with a period. When a footnote needs more than 1 line, one (1) period is needed.
- Footnotes should be in the format shown in the following example:

Row Labels/Column Labels: The mockups will reflect the preferred style of capitalization.

Page Layout

- All output should be in landscape orientation. A margin of 1.5, 1, 1, and 1 inch should be on the top, right, left, and bottom, respectively.
- All efforts should be made to present all Treatment groups in one page.
- When 3 or more Treatment groups are designed for a study and if it is not possible to fit all of them in one page, the 4th and 5th treatment groups should be displayed on the 2nd page, etc. The Study Biostatistician will pre-determine the order for the display of the treatment groups.

Page Format

- There should be a solid line at the top of the tables and listings just below the title.
- There should be a solid line just below the column headings that runs completely across the width of the tables and listings.
- There should be a solid line at the bottom of the tables and listings just above the footnote(s) on every page.

Font

- The default font to be used in the actual study tables/listings should be Courier New 8 point which is approximately equivalent to the acceptable font size of Times New Roman 9-10 in accordance with the FDA's guidance on Electronic Common Technical Document Specification.
- The use of Courier New 7 point is optional for some tables/listings and will be determined at the study level by the Study Biostatistician and Study Programmer. However, it is recommended that this option be used primarily for data listings.

Descriptive Statistics

By default, descriptive statistics in this template covers: n, Mean, Median, Standard Deviation (SD), Minimum (Min), and Maximum (Max). Unless otherwise specified in the actual table shells, the mean, standard deviation, standard error of the mean, and median should be displayed to one more decimal place than the original data. The standard error of the mean will be displayed with at least 2 significant digits for efficacy tables.

Rounding for Percentage

Unless specified in the actual table shells for a study, all percentages will be rounded to 1 decimal place in all TLFs.

Unless specified in the actual table shells for a study, p-values will be presented with 4 decimal places.

Alignment of Decimals

- It is recommended that all the decimal places be aligned in summary tables, as shown in the following example:

	Decimal Align
n	xxx
Mean	xx.xx
SD	xx.xx xx.xxx
Median	xx.xx
Minimum, Maximum	xx.x, xx.x

- When numbers with decimal points are included in brackets (e.g., percentages), have the brackets aligned to the right and then padded to allow for all possible percentages and then the left brackets will also be aligned. For example:

Brackets Align	
(99.9)	(xx.x)
(9.9)	(x.x)

- It is recommended that all column entries in a summary tables and listings are aligned to the center.
- Columns for text fields are all left justified. Columns with whole numbers are all right justified.
- For graphs, the lines are distinguishable and that the symbols for each line are appropriate. Legend is consistent across output for Treatment names and abbreviations.

Use of N Versus n

- N = total number of subjects in the defined analysis set.
- n = total number of subjects in the specific category.
- If N is specified in the column heading then any reference to the number of subjects in the body should be small n, as shown in the following example:

Demographic Parameter	Treatment Group A (N=XXX)	Treatment Group B (N=XXX)	Total (N=XXX)
Age (years)			
n	xxx	xxx	xxx
Mean	xx.x	xx.x	xx.x
SD	x.xx	x.xx	x.xx
Median	xx.x	xx.x	xx.x
Minimum, Maximum	xx, xx	xx, xx	xx, xx

A Note for Subject Data Listings

- Observed Dates/AE Severity/Relationship to investigational product are used in subject data listings.
- Observed values or raw assessment scores are used in data listings along with their derived values used in analyses, e.g., raw assessment scores and derived total scores.

TABLE OF CONTENTS FOR END-OF-TEXT TLFs

SHELLS FOR END-OF-TEXT TLFS

1. Subject Disposition, Demographic, Baseline, and Other Summary Tables

Table 1.1.1 Subject Disposition
Analysis Set: All Subjects Randomized

	GFF MDI 14.4/9.6 µg (N=xxx)	FF MDI 9.6 µg (N=xxx)	GP MDI 14.4 µg (N=xxx)	Placebo MDI (N=xxx)	All Subjects (N=xxxx)
	n (%)	n (%)	n (%)	n (%)	n (%)
Not Treated	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Treated	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Completed Week 12	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Completed Week 24	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Completed Follow-up Telephone Call	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Early Discontinuation [a]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
ITT Population [b]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PP Population [c]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Symptomatic Population [d]					
Rescue Ventolin User Population [e]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Safety Population [f]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

[a] Early discontinuation was defined as failure to complete both the final visit and the Follow-up Telephone Call.
[b] The Intent-To-Treat (ITT) Population was defined as all subjects who were randomized to treatment and received at least one dose of study treatment.
[c] The Per Protocol (PP) Population was a subset of the ITT Population defined as all subjects with post-randomization data obtained prior to a major protocol deviation. Data obtained after any major protocol deviation were excluded. Since receiving the wrong treatment is a major protocol deviation, subjects in the PP Population were analyzed according to the treatment they received. Post-randomization visits will be excluded from the per protocol set if there is no evidence in the diary that study medication was used the evening prior to the scheduled visit.
[d] The Symptomatic Population was defined as all subjects in the ITT Population with CAT scores of >=15 at Visit 4.
[e] The Rescue Ventolin User Population was defined as all subjects in the ITT Population with average baseline rescue Ventolin use of ≥1 puff/day.
[f] The Safety Population was defined as all subjects who were randomized to treatment and received at least one dose of the study treatment.

Table 1.1.2 Distribution of Subjects by Country/Region and Treatment
Analysis Set: All Subjects Randomized

Country/Region Subgroup	GFF MDI 14.4/9.6 µg (N=xxx) n (%)	FF MDI 9.6 µg (N=xxx) n (%)	GP MDI 14.4 µg (N=xxx) n (%)	Placebo MDI (N=xxx) n (%)	All Subjects (N=xxxx) n (%)
Country					
<Country 1>	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<Country 2>	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<Country 3>	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<Country 4>	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Regional Subgroup					
Non-Japan	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Asia	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Europe	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
North America	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Asia includes subjects from China, Japan, South Korea and Taiwan; Asian subjects from other regions/countries are excluded.

Report generated by program: pt003014/sasdir/statout/t010102.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Repeat for each country and center within country.

Table 1.1.3 Distribution of Subjects in Analysis Populations, by Country, Center, and Treatment
Analysis Set: All Subjects Randomized

Country / Center # (Investigator)	Analysis Population	GFF MDI 14.4/9.6 µg (N=xxx)	FF MDI 9.6 µg (N=xxx)	GP MDI 14.4 µg (N=xxx)	Placebo MDI (N=xxx)	All Subjects (N=xxxx)
<Country>	Total Randomized	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	ITT Population	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	PP Population	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Symptomatic Population	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Rescue Ventolin User Population	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Safety Population	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<Center 1 (Investigator)>	Total Randomized	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	ITT Population	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	PP Population	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Symptomatic Population	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Rescue Ventolin User Population	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Safety Population	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Notes to Programmer: Repeat for each country and center within country.

Table 1.1.4 Reasons for Subjects Not Randomized
Analysis Set: Non-Randomized Analysis Set

Reason Not Randomized	All Subjects Not Randomized (N=xxx) n (%)
Any Inclusion/Exclusion Criterion	xxx (xx.x)
Exclusion Criterion #x: xxxx xxxx xx xxxxx xxxxx xxxx	xxx (xx.x)
Exclusion Criterion 3h(c): Not Reproducible at Visit 4	xxx (xx.x)
Inclusion Criterion #x: xx x x xxx xxxx xxxx xxxxxxxxxxx	xxx (xx.x)
Inclusion Criterion #x: xxxx xxxx xx xxxxx xxxxx xxxx	xxx (xx.x)
	xxx (xx.x)
Administrative Reasons	
Additional Protocol-Specified Criteria	xxx (xx.x)
Heart Rate Increase	xxx (xx.x)
SBP Increase	xxx (xx.x)
Prescription of Any Prohibited Medications	xxx (xx.x)
Decrease in Creatinine Clearance	xxx (xx.x)
Hepatic Impairment	xxx (xx.x)
QTcF Increase	xxx (xx.x)
COPD Exacerbations	xxx (xx.x)
eDiary Non-Compliance	xxx (xx.x)
Other	xxx (xx.x)

Note: Reasons of Other are listed by subject in Listing 1.2.

Report generated by program: pt003014/sasdir/programs/statout/t010104.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Order by frequency within each category (Screen Failure and Protocol-Specified Criteria).

Table 1.1.5 Subjects Excluded From ITT, PP, Symptomatic, Rescue Ventolin User, and Safety Populations
Analysis Set: All Subjects Randomized

	Analysis Population								
Subject ID	Randomized	ITT	PP	Symptomatic	Rescue Ventolin User	Safety	Population Excluded	Visit Excluded	Reason for Exclusion
Treatment: GFF MDI 14.4/9.6 µg, FF MDI 9.6 µg, GP MDI 14.4 µg, or Placebo MDI									
Country Center # (Investigator): xxxxxxxxxxxxxxxxx Center ### (xxxxxxxxxx)									
xxxxxx	Yes	No	No	No	No	No	ITT	All	Did not receive at least one dose of the study treatment.
							PP	All	Did not receive at least one dose of the study treatment.
							Symptomatic	All	Screening CAT Score was not >=15.
							Rescue Ventolin User	All	Did not have an average baseline rescue Ventolin use of ≥1 puff/day.
							Safety	All	Did not receive at least one dose of the study treatment.
xxxxxx	Yes	No	No	Yes	Yes	No	ITT	All	Did not receive at least one dose of the study treatment
							PP	All	xxxxxxxxxxxxxxxxxxxxxxxxx
							Safety	ALL	Did not receive at least one dose of the study treatment
xxxxxx	Yes	No	No	Yes	Yes	No	PP	Week xx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxx

Note: A subject may be included in an analysis population as a whole, but may have period or timepoint data excluded.

Report generated by program: pt003014/sasdir/programs/statout/ t010105.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort by Actual Treatment, Country, Center, and Subject ID within Center. List records per subject, population excluded, and visits excluded.

Table 1.2.1 Reason for Early Discontinuation
Analysis Set: All Subjects Randomized

	GFF MDI 14.4/9.6 µg (N=xxx)	FF MDI 9.6 µg (N=xxx)	GP MDI 14.4 µg (N=xxx)	Placebo MDI (N=xxx)	All Subjects (N=xxxx)
	n (%)	n (%)	n (%)	n (%)	n (%)
Early Discontinuation	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reason for Early Discontinuation					
Adverse Event(s)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Administrative Reasons	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lack of Efficacy	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject Discretion	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Withdrawal of Consent	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
COPD	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Investigator Considers It to Be in the Best Interest of Subject	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<Specified Reason>	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject Lost to Follow-up	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
On or Before Week 24	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
After Week 24	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Major Protocol Violation	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<Specified Reason>	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Protocol-specified Discontinuation Criteria [a]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Heart Rate Increase	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Systolic Blood Pressure Increase	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Prescription of Any Prohibited Medications	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Decrease in Creatinine Clearance	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Hepatic Impairment	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
QTcF Increase	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
COPD Exacerbations	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
eDiary Non-Compliance	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Screen Failure (subject randomized in error)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: Reasons of Other are listed by subject in Listing 1.2.
[a] As per Protocol Section 5.7, except for eDiary non-compliance which is per Protocol Section 7.1.3.

Report generated by program: pt003014/sasdir/programs/statout/t010201.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmers; Sort by descending frequency of major category using All Subjects column. Within major category, sort by descending frequency of subcategory using All Subjects column.

Table 1.2.2 Reason for Early Discontinuation Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Notes to Programmer:
Display the following at top of summary as follows:
<CAT Score Subpopulation>

Note to Programmer: Do for category "CAT Score Overall" and then repeat tabulation below for CAT Score ≥10, Symptomatic Population (CAT Score ≥15), and CAT Score ≥20.

Table 1.2.3 Reason for Early Discontinuation
Analysis Set: PP Population

Table 1.2.4 Reason for Early Discontinuation
Analysis Set: Safety Population

Table 1.3 Reason for Exclusion From the PP Population
Analysis Set: ITT Population

Reason for	GFF MDI 14.4/9.6 µg (N=xxx) n (%)	FF MDI 9.6 µg (N=xxx) n (%)	GP MDI 14.4 µg (N=xxx) n (%)	Placebo MDI (N=xxx) n (%)	All Subjects (N=xxxx) n (%)
Exclusion from PP Population	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reason 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reason 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
…	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Subjects may have multiple reasons for exclusion; therefore, counts for individual reasons may not add up to the total number of subjects excluded from the population.

Report generated by program: pt003014/sasdir/programs/statout/t0103.sas Version YYYY-MM-DD xx:xx (Page n of N)

Table 1.4.1 Demographics and Baseline Characteristics Overall and by CAT Subpopulation
Analysis Set: ITT Population

<CAT Score Subpopulation>

Note to Programmer: Do for category "CAT Score Overall" and then repeat tabulation below for CAT Score ≥10, Symptomatic Population (CAT Score ≥15), and CAT Score ≥20.

Parameter	GFF MDI 14.4/9.6 µg (N=xxx)	FF MDI 9.6 µg (N=xxx)	GP MDI 14.4 µg (N=xxx)	Placebo MDI (N=xxx)	All Subjects (N=xxxx)
Age (Years)[a]					
n	xxx	xxx	xxx	xxx	xxxx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum	xx	xx	xx	xx	xx
Maximum	xx	xx	xx	xx	xx
Age Group, n (%)					
Age < 65 years	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Age >= 65 years	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Missing	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)
Gender, n (%)					
Male	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Female	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Missing	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)
Race, n (%)					
American Indian or Alaska Native	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Asian	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Australia or New Zealand (Indigenous)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Black or African American	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Native Hawaiian or Other Pacific	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

<CAT Score Subpopulation>

Note to Programmer: Do for category "CAT Score Overall" and then repeat tabulation below for CAT Score ≥10, Symptomatic Population (CAT Score ≥15), and CAT Score ≥20.

Parameter	GFF MDI 14.4/9.6 µg (N=xxx)	FF MDI 9.6 µg (N=xxx)	GP MDI 14.4 µg (N=xxx)	Placebo MDI (N=xxx)	All Subjects (N=xxxx)
Islander					
White	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Other	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Missing	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Ethnicity, n (%)					
Hispanic	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Non-Hispanic	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Missing	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)
Total CAT Score [b]					
n	xxx	xxx	xxx	xxx	xxxx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum	xx.x	xx.x	xx.x	xx.x	xx.x
Maximum	xx.x	xx.x	xx.x	xx.x	xx.x
< 10, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
>=10, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
< 15, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
>=15, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
< 20, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
>=20, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
MMRC Grade [c]					
n	xxx	xxx	xxx	xxx	xxx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum	xx.x	xx.x	xx.x	xx.x	xx.x
Maximum	xx.x	xx.x	xx.x	xx.x	xx.x

<CAT Score Subpopulation>

Note to Programmer: Do for category "CAT Score Overall" and then repeat tabulation below for CAT Score ≥10, Symptomatic Population (CAT Score ≥15), and CAT Score ≥20.

Parameter	GFF MDI 14.4/9.6 µg (N=xxx)	FF MDI 9.6 µg (N=xxx)	GP MDI 14.4 µg (N=xxx)	Placebo MDI (N=xxx)	All Subjects (N=xxxx)
< 2, n (%)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
>=2, n (%)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Missing, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Used Inhaled Corticosteroids at Baseline [d], n (%)					
Yes	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
No	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Missing	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Smoking Status [e], n (%)					
Current Smoker	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Former Smoker	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Missing	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of Years Smoked					
n	xxx	xxx	xxx	xxx	xxx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum	xx.x	xx.x	xx.x	xx.x	xx.x
Maximum	xx.x	xx.x	xx.x	xx.x	xx.x
Average Number of Cigarettes Smoked Per Day					
n	xxx	xxx	xxx	xxx	xxx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum	xx.x	xx.x	xx.x	xx.x	xx.x
Maximum	xx.x	xx.x	xx.x	xx.x	xx.x

Number of Pack Years Smoked [f]

<CAT Score Subpopulation>

Note to Programmer: Do for category "CAT Score Overall" and then repeat tabulation below for CAT Score ≥10, Symptomatic Population (CAT Score ≥15), and CAT Score ≥20.

Parameter	GFF MDI 14.4/9.6 µg (N=xxx)	FF MDI 9.6 µg (N=xxx)	GP MDI 14.4 µg (N=xxx)	Placebo MDI (N=xxx)	All Subjects (N=xxxx)
n	xxx	xxx	xxx	xxx	xxx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum	xx.x	xx.x	xx.x	xx.x	xx.x
Maximum	xx.x	xx.x	xx.x	xx.x	xx.x
Weight (kg)					
n	xxx	xxx	xxx	xxx	xxx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum	xx.x	xx.x	xx.x	xx.x	xx.x
Maximum	xx.x	xx.x	xx.x	xx.x	xx.x
Height (cm)					
n	Xxx	xxx	xxx	xxx	xxx
Mean	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
SD	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
Median	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
Minimum	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
Maximum	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
BMI (kg/m2)					
n	Xxx	xxx	xxx	xxx	xxx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum	xx.x	xx.x	xx.x	xx.x	xx.x
Maximum	xx.x	xx.x	xx.x	xx.x	xx.x

[a] Age is age at Visit 1. The remaining characteristics were based on data from Screening visits prior to the start of the study.
[b] CAT = COPD Assessment Test. The total score is the sum of eight CAT item scores (Range: 0-40)
[c] MMRC = Modified Medical Research Council Scale, grades range between 0 and 4, where 4 represents the highest level of

<CAT Score Subpopulation>

Note to Programmer: Do for category "CAT Score Overall" and then repeat tabulation below for CAT Score ≥10, Symptomatic Population (CAT Score ≥15), and CAT Score ≥20.

Parameter	GFF MDI 14.4/9.6 µg (N=xxx)	FF MDI 9.6 µg (N=xxx)	GP MDI 14.4 µg (N=xxx)	Placebo MDI (N=xxx)	All Subjects (N=xxxx)

breathlessness.
[d] 'At baseline' means that the medication was taken on the day of the first dose of study medication.
[e] Former Smoker was defined as those who have stopped smoking for at least 6 weeks prior to first Screening Visit.
[f] Number of pack years smoked = (number of cigarettes per day / 20) x number of years smoked.

Report generated by program: pt003014/sasdir/programs/statout/t010401.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Calculate BMI using Height at Visit 1. BMI = weight (kg)/height (m)^2.
Keep the summary for a parameter in the same page when breaking the table into multiple pages. Repeat titles, column headers and footnotes on each page. The race/ethnicities of Native Hawaiian or other Pacific Islander OR American Indian or Alaska Native OR Australia or New Zealand (indigenous) can be removed from this table if they do not exist in the database.
Please delete Missing row when there are no missing values.

Table 1.4.2 Demographics and Baseline Characteristics
Analysis Set: PP Population

Table 1.4.3 Demographics and Baseline Characteristics
Analysis Set: Rescue Ventolin User Population

Table 1.4.4 Demographics and Baseline Characteristics
Analysis Set: Safety Population

Table 1.4.5 Demographics and Baseline Characteristics
Analysis Set: Non-Randomized Analysis Set

Table 1.5.1 Severity and Duration of COPD Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

<CAT Score Subpopulation>

Note to Programmer: Do for category "CAT Score Overall" and then repeat tabulation below for CAT Score ≥10, Symptomatic Population (CAT Score ≥15), and CAT Score ≥20.

	GFF MDI 14.4/9.6 µg (N=xxx)	FF MDI 9.6 µg (N=xxx)	GP MDI 14.4 µg (N=xxx)	Placebo MDI (N=xxx)	
COPD Severity [a], n (%)					
Moderate (GOLD 2)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Severe (GOLD 3)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Very Severe (GOLD 4)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx(xx.x)
Duration of COPD (yrs) [b]					
n	xxx	xxx	xxx	xxx	xxxx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.x	xx.x	xx.x	xx.x	xx.x
25th Percentile	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x	xx.x
75th Percentile	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum	xx.x	xx.x	xx.x	xx.x	xx.x
Maximum	xx.x	xx.x	xx.x	xx.x	xx.x
GOLD Category, n (%)					
A	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
B	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
C	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx(xx.x)
D	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

[a] Severity of COPD defined in Appendix 3 of the protocol was based on the non-missing post-Ventolin HFA assessment at Screening Visit 2 (or if the assessment was missing, the non-missing post-Atrovent assessment at Screening Visit 3).
[b] The duration of COPD is calculated relative to the start of study treatment Day 1 (Visit 4).

Report generated by program: pt003014/sasdir/programs/statout/t010501.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Duration of COPD = (First Dose date of Study Treatment - Date COPD First Diagnosed)/365.25, where day of COPD diagnosed is assumed to be the 1st of the month. Add a footnote noting how many missing values there are for severity if this is true for the final data.

Table 1.5.2 Severity and Duration of COPD
Analysis Set: PP Population

Table 1.5.3 Severity and Duration of COPD
Analysis Set: Rescue Ventolin User Population

Table 1.5.4 Severity and Duration of COPD
Analysis Set: Safety Population

Table 1.6.1 Screening Pre- and Post-Bronchodilator and Baseline Spirometry Parameters Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

<CAT Score Subpopulation>

Note to Programmer: Do for category "CAT Score Overall" and then repeat tabulation below for CAT Score ≥10, Symptomatic Population (CAT Score ≥15), and CAT Score ≥20.

	GFF MDI 14.4/9.6 µg (N=xxx)	FF MDI 9.6 µg (N=xxx)	GP MDI 14.4 µg (N=xxx)	Placebo MDI (N=xxx)	All Subjects (N=xxxx)
Screening FEV1 (% predicted)					
Pre-Ventolin HFA:					
n	xx	xx	xx	xx	xx
Mean	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
SD	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
25th Percentile	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Median	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
75th Percentile	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Minimum	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Maximum	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Post-Ventolin HFA:					
n	xx	xx	xx	xx	xx
Mean	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
SD	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
25th Percentile	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Median	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
75th Percentile	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Minimum	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Maximum	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Pre-Atrovent HFA:					
n	xx	xx	xx	xx	xx
Mean	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
SD	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
25th Percentile	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Median	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
75th Percentile	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Minimum	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Maximum	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx

Post-Atrovent HFA:					
n	xx	xx	xx	xx	xx
Mean	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
SD	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
25th Percentile	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Median	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
75th Percentile	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Minimum	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Maximum	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx

Notes to Programmer:

Repeat above for these Screening parameters:
Screening FEV1 (L) Pre-Bronchodilator
Screening FEV1 (L) Post-Bronchodilator
Screening FVC (% predicted) Pre-Bronchodilator
Screening FVC (% predicted) Post-Bronchodilator
Screening FVC (L) Pre-Bronchodilator
Screening FVC (L) Post-Bronchodilator

Also, provide for the following Baseline parameters:
Baseline FEV1 (% predicted)
Baseline FEV1 (L)
Baseline FVC (% predicted)
Baseline FVC (L)

Show only 2 significant digits for the % predicted statistics.

Baseline is defined as the mean of all evaluable 60 and 30 minute pre-dose values on Day 1 (Visit 4).

Report generated by program: pt003014/sasdir/programs/statout/t010601.sas Version YYYY-MM-DD xx:xx (Page n of N)

Table 1.6.2 Screening Pre- and Post-Bronchodilator and Baseline Spirometry Parameters
Analysis Set: PP Population

Table 1.6.3 Screening Pre- and Post-Bronchodilator and Baseline Spirometry Parameters
Analysis Set: Rescue Ventolin User Population

Table 1.7.1 Reversibility to Ventolin HFA Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

<CAT Score Subpopulation>

Note to Programmer: Do for category "CAT Score Overall" and then repeat tabulation below for CAT Score ≥10, Symptomatic Population (CAT Score ≥15), and CAT Score ≥20.

	GFF MDI 14.4/9.6 µg (N=xxx)	FF MDI 9.6 µg (N=xxx)	GP MDI 14.4 µg (N=xxx)	Placebo MDI (N=xxx)	All Subjects (N=xxxx)
Post-Ventolin HFA FEV1 - Pre-Ventolin HFA FEV1 (mL)					
n	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum	xx.x	xx.x	xx.x	xx.x	xx.x
Maximum	xx.x	xx.x	xx.x	xx.x	xx.x
Reversibility (%) Post-Ventolin HFA for FEV1 [a]					
n	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum	xx.x	xx.x	xx.x	xx.x	xx.x
Maximum	xx.x	xx.x	xx.x	xx.x	xx.x
Reversible [b], n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
≥12% Improvement in FEV1 from Pre-Ventolin HFA at Post-Ventolin HFA, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
≥ 150 mL Improvement in FEV1 from Pre-Ventolin HFA at Post-Ventolin HFA, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
≥ 200 mL Improvement in FEV1 from Pre-Ventolin HFA at Post-Ventolin HFA, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

If a subject was missing a Post-Ventolin or Pre-Ventolin FEV1 value at Screening Visit 2, these values were replaced by the Pre-Atrovent and Post-Atrovent values from Screening Visit 3

[a] Reversibility (%) is defined as 100 x (the change from pre-Ventolin HFA to post for FEV1)/pre-Ventolin HFA FEV1.
[b] Reversible is defined as Improvement in FEV1 post-Ventolin HFA administration compared to pre-Ventolin HFA of >=12% and >=200 mL.

Report generated by program: pt003014/sasdir/programs/statout/t010701.sas Version YYYY-MM-DD xx:xx (Page n of N)

Table 1.7.2 Reversibility to Ventolin HFA
Analysis Set: PP Population

Table 1.7.3 Reversibility to Ventolin HFA
Analysis Set: Rescue Ventolin User Population

Table 1.8.1 Reversibility to Atrovent HFA Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Table 1.8.2 Reversibility to Atrovent HFA
Analysis Set: PP Population

Table 1.8.3 Reversibility to Atrovent HFA
Analysis Set: Rescue Ventolin User Population

Table 1.8.4 Reversibility to Ventolin HFA and/or Atrovent HFA
Analysis Set: ITT Population

	GFF MDI 14.4/9.6 µg (N=xxx)	FF MDI 9.6 µg (N=xxx)	GP MDI 14.4 µg (N=xxx)	Placebo MDI (N=xxx)	All Subjects (N=xxxx)
	n (%)	n (%)	n (%)	n (%)	n (%)
Reversible to neither Ventolin HFA nor Atrovent HFA	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Reversible to Ventolin HFA only	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Reversible to Atrovent HFA only	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Reversible to Both Ventolin HFA and Atrovent HFA	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Reversible to Atrovent HFA, Reversibility to Ventolin HFA is missing	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Reversible to Ventolin HFA, Reversibility to Atrovent HFA is missing	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Reversibility to Ventolin HFA and Atrovent HFA are missing	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Reversibility to Ventolin HFA missing, Not Reversible to Atrovent HFA	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Not Reversible to Ventolin HFA, Reversibility to Atrovent HFA is missing	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

Report generated by program: pt003014/sasdir/programs/statout/t0108004.sas Version YYYY-MM-DD xx:xx (Page n of N)

Note to Programmer: add last 2 rows into the table if there is at least one subject in the study included in these rows, ie, n greater than 0 for at least one treatment.

Table 1.9.1 Medical/Surgical History
Analysis Set: Safety Population

	GFF MDI 14.4/9.6 µg (N=xxx)	FF MDI 9.6 µg (N=xxx)	GP MDI 14.4 µg (N=xxx)	Placebo MDI (N=xxx)	All Subjects (N=xxxx)
	n (%)	n (%)	n (%)	n (%)	n (%)
Subject Had Medical /Surgical History					
No	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Yes	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Cardiovascular	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
CNS/Neurological	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Dermatologic	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Drug Allergy	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
EENT	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Endocrine/Metabolic	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
High Total Cholesterol	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Diabetes	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Type I	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Type II	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Gastrointestinal	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Genitourinary	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Hepatic	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Hematologic	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Immunological	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Malignancy	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Musculoskeletal	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Psychiatric	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Respiratory	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Renal	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Other	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

Note to Programmer: Please sort by descending frequency of occurrence in All Subjects. Denominator should be N from the column header for a treatment.

Table 1.9.2 Cardiovascular Risk Factors of Interest
Analysis Set: Safety Population

	GFF MDI 14.4/9.6 µg (N=xxx)	FF MDI 9.6 µg (N=xxx)	GP MDI 14.4 µg (N=xxx)	Placebo MDI (N=xxx)	All Subjects (N=xxxx)
	n (%)	n (%)	n (%)	n (%)	n (%)
Subject Had Cardiovascular Risk Factor of Interest					
No	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Yes	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Hypertension	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
High Total Cholesterol	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Transient Ischemic Attack	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Stroke	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Atrial Fibrillation	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Peripheral Vascular Disease	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Diabetes	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Type I	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Type II	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Angina	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Angioplasty	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Stents	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
CABG	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
No Surgery	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Myocardial Infarction	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Angioplasty	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Stents	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
CABG	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
No Surgery	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

Report generated by program: pt003014/sasdir/programs/statout/t010902.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Please sort risk factors in descending frequency of occurrence in All Subjects, then within diabetes, angina, and myocardial infarction subcategories, sort by descending frequency.

Table 1.9.3 History of Moderate or Severe COPD Exacerbations Within Past 12 Months
Analysis Set: ITT Population

	GFF MDI 14.4/9.6 µg (N=xxx)	FF MDI 9.6 µg (N=xxx)	GP MDI 14.4 µg (N=xxx)	Placebo MDI (N=xxx)	All Subjects (N=xxxx)
Subject treated for an exacerbation with systemic (oral or IV) corticosteroids and/or antibiotics, n(%) [Events]	xxx (xx.x) [xx]	xxx (xx.x) [xx]	xxx (xx.x) [xx]	xxx (xx.x) [xx]	xxx (xx.x) [xx]
Number of exacerbations per subject					
Mean	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
SD	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Median	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Minimum	xx	xx	xx	xx	xx
Maximum	xx	xx	xx	xx	xx
Subject admitted to hospital or received emergency room (urgent care center) treatment, n(%) [Events}	xxx (xx.x) [xx]	xxx (xx.x) [xx]	xxx (xx.x) [xx]	xxx (xx.x) [xx]	xxx (xx.x) [xx]
Number of hospitalizations/ emergency room (urgent care center) visits per subject					
Mean	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
SD	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Median	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx

	GFF MDI 14.4/9.6 µg (N=xxx)	FF MDI 9.6 µg (N=xxx)	GP MDI 14.4 µg (N=xxx)	Placebo MDI (N=xxx)	All Subjects (N=xxxx)
Minimum	xx	xx	xx	xx	xx
Maximum	xx	xx	xx	xx	xx

The number of exacerbations and number of hospitalizations/emergency room (urgent care center) visits for subjects without an exacerbation, hospitalization, or emergency room (urgent care center) visit was 0.

Table 1.10.1 Prior Medications - COPD-Related
Analysis Set: Safety Population

Preferred Term/Active Ingredients (COPD Medications only)	GFF MDI 14.4/9.6 µg (N=xxx) n (%)	FF MDI 9.6 µg (N=xxx) n (%)	GP MDI 14.4 µg (N=xxx) n (%)	Placebo MDI (N=xxx) n (%)	All Subjects (N=xxxx) n (%)
Any Prior COPD Medication	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Medication 1	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Medication 2	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

Report generated by program: pt003014/sasdir/programs/statout/t011001.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort Medications by descending frequency of use in All Subjects

Table 1.10.2 Prior Medications - Non-COPD-Related
Analysis Set: Safety Population

Notes to Programmer: Sort Medications by descending frequency of use in All Subjects
Add a row for "Any Prior Non-COPD Medication".

Table 1.11.1 Concomitant Medications - COPD Related
Analysis Set: Safety Population

Preferred Term/Active Ingredients	GFF MDI 14.4/9.6 µg (N=xxx) n(%)	FF MDI 9.6 µg (N=xxx) n(%)	GP MDI 14.4 µg (N=xxx) n(%)	Placebo MDI (N=xxx) n(%)	All Subjects (N=xxxx) n(%)
Any Concomitant COPD Medication	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Medication 1	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Medication 2	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

All subjects were allowed sponsor provided Ventolin HFA which was reported on the Concomitant Medications CRF.
See Listing 6.1.1 for any subject(s) who took Ventolin HFA within 6 hours of pre-dose assessments during the treatment. See Listing 6.1.3 for any subjects who took Ventolin HFA for rescue pre-dose or post-dose during the course of the test day measurements. Table 2.8.1 summarizes the mean number of puffs of rescue Ventolin during treatment.

Report generated by program: pt003014/sasdir/programs/statout/t011101.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort Medications by descending frequency of use in All Subjects

Table 1.11.2 Concomitant Medications - Non-COPD Related
Analysis Set: Safety Population

*Notes to Programmer: Sort Medications by descending frequency of use in All Subjects
Add a row for "Any Non-COPD Medication".*

Table 1.12 Study Treatment Exposure and Compliance
Analysis Set: Safety Population

		GFF MDI 14.4/9.6 µg (N=xxx)	FF MDI 9.6 µg (N=xxx)	GP MDI 14.4 µg (N=xxx)	Placebo MDI (N=xxx)	All Subjects (N=xxxx)
Exposure [a]	n	xxx	xxx	xxx	xxx	xxx
	Mean	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
	SD	xx.x	xx.x	xx.x	xx.x	xx.x
	Median	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
	Minimum	xxx	xxx	xxx	xxx	xxx
	Maximum	xxx	xxx	xxx	xxx	xxx
Total Person-Years of Exposure [b]		xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Total Number of Puffs of Study Medication	n	xxx	xxx	xxx	xxx	xxx
	Mean	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
	SD	xx.x	xx.x	xx.x	xx.x	xx.x
	Median	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
	Minimum	xxx	xxx	xxx	xxx	xxx
	Maximum	xxx	xxx	xxx	xxx	xxx
Percent Compliance [c], n (%)	0 - < 20%	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)
	20 - < 40%	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)
	40 - < 60%	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)
	60 - < 80%	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)
	80 - 100%	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)
	>100 - 120%	x(xx.x)	x(xx.x)	x(xx.x)	x(xx.x)	x(xx.x)
	>120%	x(xx.x)	x(xx.x)	x(xx.x)	x(xx.x)	x(xx.x)
	Missing	xx	xx	xx	xx	xx
	n	xxx	xxx	xxx	xxx	xxx
	Mean	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
	SD	xx.x	xx.x	xx.x	xx.x	xx.x
	Median	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
	Minimum	xxx	xxx	xxx	xxx	xxx
	Maximum	xxx	xxx	xxx	xxx	xxx

[a] Exposure (days) = (End date of treatment – Date of first dose of treatment) + 1.
[b] Total person-years of exposure for a treatment group is the total exposure in the study across all subjects in the treatment.
[c] Percent compliance is defined as (total number of puffs of study treatment taken on a study day/total expected puffs taken on a study day) averaged across all days of a subject's dosing between start of study treatment and last day on study treatment x 100.
The expected number of puffs on dates prior to the last date of treatment was 4.
The expected number of puffs for a test day which was the last date of treatment was 2.
The expected number of puffs for the last date of treatment which was not a test day was 4 when a PM dose was taken and 2 otherwise.

Table 1.13 Changes in Smoking Status After Start of Treatment
Analysis Set: Safety Population

Change in Smoking Status Relative to Screening Smoking Status	GFF MDI 14.4/9.6 µg (N=xxx) n (%)	FF MDI 9.6 µg (N=xxx) n (%)	GP MDI 14.4 µg (N=xxx) n (%)	Placebo MDI (N=xxx) n (%)	All Subjects (N=xxxx) n (%)
Former Smoker Switched to Current Smoker at Any Point During Treatment	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Current Smoker Switched to Former Smoker at Any Point During Treatment	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

Report generated by program: pt003014/sasdir/programs/statout/t0113.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Put a row for 'Non-smoker Switched to Smoker' only if this data case is present in the data.

2. Efficacy Data Summary Tables and Figures, Including HCRU Tables

Change From Baseline in Morning Pre-dose Trough FEV_1

Table 2.1.1 Morning Pre-dose Trough FEV_1 (L)
Analysis Set: ITT Population

			LS Mean Differences Between Treatments		
				FF MDI	GP MDI
Treatment	Baseline FEV1	Change From Baseline	Placebo MDI	9.6 µg	14.4 µg
Over 24 Weeks					
GFF MDI 14.4/9.6 µg					
n	xx				
Mean	x.xxx				
SD	x.xxx				
Median	x.xxx				
Min-Max	x.xxx-x.xxx				
LS Mean (SE)		x.xxx (x.xxxx)	x.xxx (x.xxxx)	x.xxx (x.xxxx)	x.xxx (x.xxxx)
95% CI		(x.xxx, x.xxx)	(x.xxx, x.xxx)	(x.xxx, x.xxx)	(x.xxx, x.xxx)
P-value			x.xxxx	x.xxxx	x.xxxx
FF MDI 9.6 µg					
n	xx				
Mean	x.xxx				
SD	x.xxx				
Median	x.xxx				
Min-Max	x.xxx-x.xxx				
LS Mean (SE)		x.xxx (x.xxxx)	x.xxx (x.xxxx)	Not Applicable	x.xxx (x.xxxx)
95% CI		(x.xxx, x.xxx)	(x.xxx, x.xxx)		(x.xxx, x.xxx)
P-value			x.xxxx		x.xxxx
GP MDI 14.4 µg					
n	xx				
Mean	x.xxx				
SD	x.xxx				
Median	x.xxx				
Min-Max	x.xxx-x.xxx				
LS Mean (SE)		x.xxx (x.xxxx)	x.xxx (x.xxxx)	Shown Above	Not Applicable
95% CI		(x.xxx, x.xxx)	(x.xxx, x.xxx)		
P-value			x.xxxx		
Placebo					

			LS Mean Differences Between Treatments		
Treatment	Baseline FEV1	Change From Baseline	Placebo MDI	FF MDI 9.6 µg	GP MDI 14.4 µg
n	xx				
Mean	x.xxx				
SD	x.xxx				
Median	x.xxx				
Min-Max	x.xxx-x.xxx				
LS Mean (SE)		x.xxx (x.xxxx)	Not Applicable	Shown Above	Shown Above
95% CI		(x.xxx, x.xxx)			

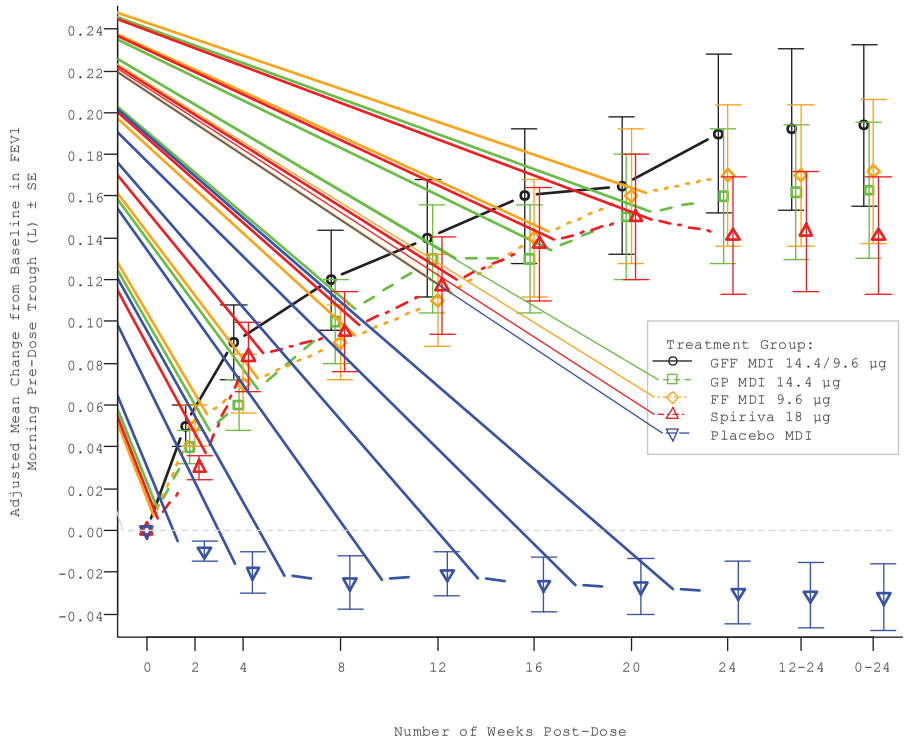
Note to Programmer: Repeat for "Over Weeks 12-24" and for each post-baseline visit from Week 2 to Week 24. The raw change from baseline will be added for each individual visit, but not for 0-24 weeks or 12-24 weeks. Do not split a treatment across a page. The baseline summary statistics are based on subjects who were included in the model used for analysis. (.e.g., subjects who had at least one data point post-baseline from Week 2 to Week 24 and had non-missing data for all covariates used for the analysis).

Baseline is defined as the mean of evaluable 60 and 30 minute pre-dose values on Day 1 (Visit 4).

LS Mean = least squares mean from the linear repeated measures model which included the following covariates: baseline FEV1, percent reversibility to Ventolin HFA, treatment, visit, and treatment by visit interaction.

Report generated by program: pt003014/sasdir/programs/statout/t020101.sas Version YYYY-MM-DD hh:mm (Page n of N)

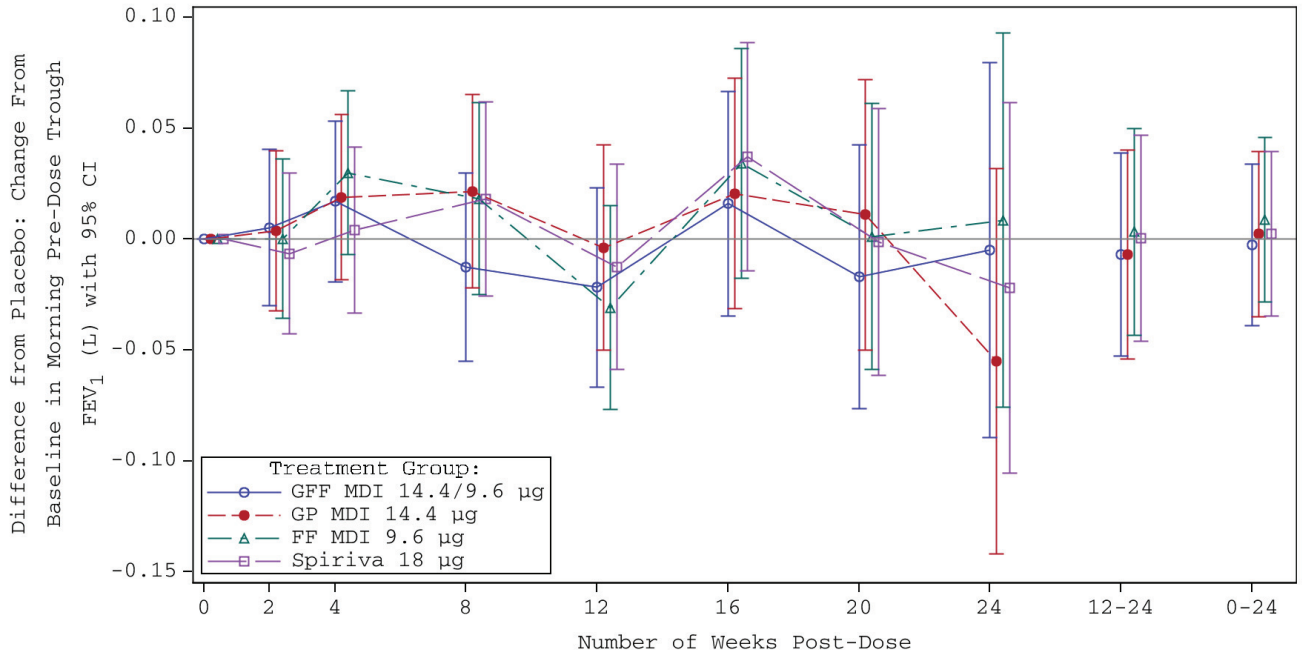
Figure 2.1.1.1 Adjusted Mean Change From Baseline in Morning Pre-dose Trough FEV_1 (L) ± SE Over Time
Analysis Set: ITT Population



Source: Table 14.2.1.1
Program: /pt003006/dryrun1/programs/graphs/f14_2_1_1.sas Draft 2013-09-13 15:16

Source: Table 2.1.1
Report generated by program: pt003014/sasdir/programs/statout/f020101.sas Version YYYY-MM-DD xx:xx (Page n of N)

Figure 2.1.1.2 Treatment Differences From Placebo MDI*: Adjusted Mean Change From Baseline (95% CI) in Morning Pre-dose Trough FEV_1 (L) Over Time
Analysis Set: ITT Population



*Superiority of test treatments vs. Placebo MDI.

Source: Table 2.1.1

Program generated by program:pt003014/dryrun1/programs/statout/f02010102.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Add "Adjusted Mean" in front of "Difference" in the y axis label. Update treatment names for treatments in this study.

Table 2.1.2 Morning Pre-dose Trough FEV_1 (L)
Analysis Set: PP Population

Figure 2.1.2 Adjusted Mean Change From Baseline in Morning Pre-dose Trough FEV_1 (L) ± SE Over Time
Analysis Set: PP Population

Table 2.1.3.1 Missing Data for Change From Baseline in Morning Pre-dose Trough FEV_1 by Visit and Reason
Analysis Set: ITT Population

	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
GFF MDI 14.4/9.6 µg:							
Total Missing	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing Baseline (Day 1)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing value due to unacceptable grade (MNAR)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing value since subject did not complete FEV_1 spirometry (MNAR)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Visit missed due to COPD?	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Yes (MNAR)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
No (MAR/MCAR)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Unknown (MNAR)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reason for early discontinuation at the visit or in the interval between visit and previous visit							

	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Adverse Event (MAR/MCAR)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Adverse Event (MNAR)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Administrative Reasons (MAR/MCAR)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lack of Efficacy (MAR/MCAR)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lack of Efficacy (MNAR)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject Discretion (MAR/MCAR)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other (MAR/MCAR)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject Discretion (MNAR)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Withdrawal of Consent (MNAR)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
COPD Related (MNAR)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other (MNAR)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Investigator's decision in the best interest of subject (MAR/MCAR)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Investigator's decision in the best interest of subject (MNAR)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject Lost to Follow-up (MNAR)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Major Protocol Violation	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<Specified Reason> (MAR/MCAR or MNAR)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<Specified Reason> (MAR/MCAR or MNAR)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Discontinuation Due to Protocol Specified Criteria	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Heart rate increase as per protocol (MAR/MCAR)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
SBP increase as per protocol (MAR/MCAR)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Prescription of any prohibited medications (MAR/MCAR or MNAR)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Decrease in creatinine clearance as per protocol (MAR/MCAR)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Hepatic impairment as per protocol (MAR/MCAR)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
QTcF increase as per protocol (MAR/MCAR)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
COPD exacerbations as per protocol (MAR/MCAR)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
COPD exacerbations as per protocol (MNAR)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
eDiary non-compliance as per protocol (MNAR)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Pregnancy as per protocol (MAR/MCAR)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other (MAR/MCAR)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other (MNAR)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Notes to Programmer: Repeat above for each remaining Treatment.

MAR = missing at random. MCAR = missing completely at random. MNAR = Missing not at random.

Notes to Programmer: When <Other Specify> OR <Specify Reason> reasons are to be collapsed and can be either MAR/MCAR or MNAR, a category was create above for MAR/MCAR and one collapsed category for MNAR. For example, this was done for "Subject Discretion" and "Investigator's Decision in the best interest of subject".
For empty cells, show a count of 0 without a percentage.

Table 2.1.3.2 Unique Patterns of Missing Visits for Change From Baseline in Morning Pre-dose Trough FEV_1
Analysis Set: ITT Population

Pattern of Missing Data	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
All Treatments (N=xxxx)							
Pattern 1 (n=xxx)	M	M	M	M	M	M	M
Pattern 2 (n=xxx)	M	M	M	M	M	M	M
Etc…							

P = Present. M = Missing.

Report generated by Program: pt003014/final/programs/statout/t02010302.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Repeat for each Treatment.

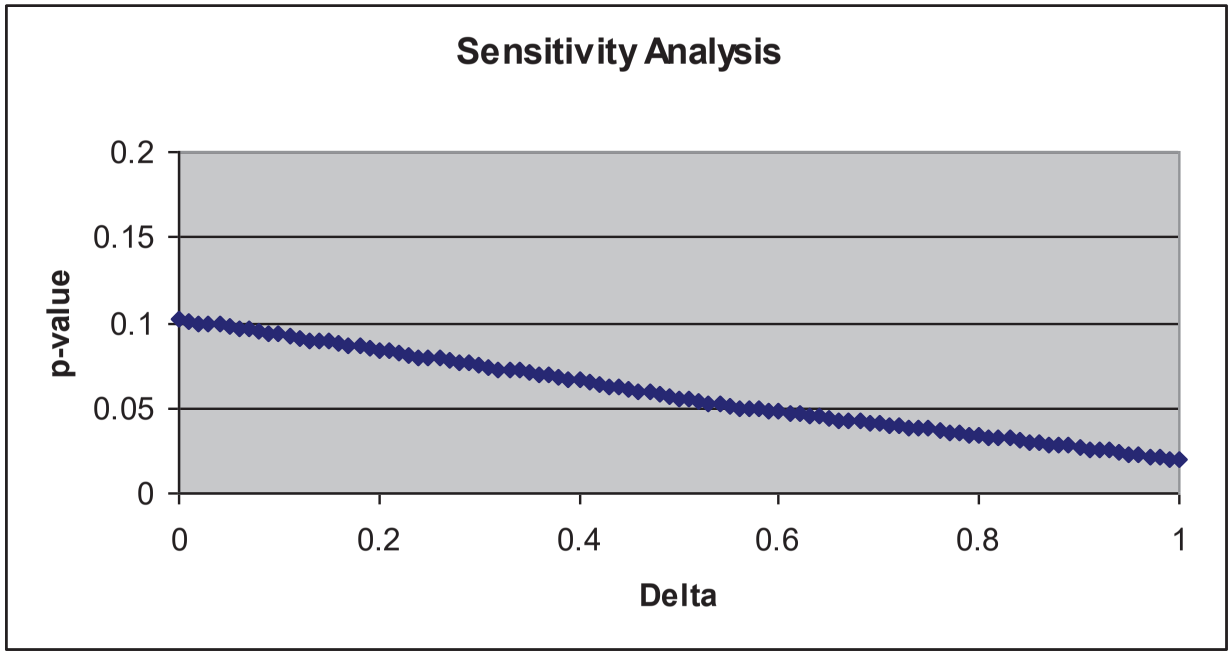
Table 2.1.4.1 Sensitivity Analysis: Treatment Comparisons for Change From Baseline in Morning Pre-dose Trough FEV_1 (L) at Week 24
Analysis Set: ITT Population

Key Pairwise Comparison	Delta [L] [a]	Estimated Difference and 95% CI [b]	P-value [b]	Relative Increase in Variance [c]	Fraction of Missing Information [d]	Relative Efficiency [e]
GFF MDI 14.4/9.6 µg vs. Placebo MDI	x.xxxx					
	x.xxxx					
	x.xxxx					
	x.xxxx					
	x.xxxx					
	x.xxxx					
	x.xxxx					
	x.xxxx					
	x.xxxx					
Repeat for Each of the 4 Remaining Key Comparisons (treatment vs. control) in the following order: FF MDI 9.6 µg vs Placebo GP MDI 14.4 µg vs Placebo GFF MDI 14.4/9.6 µg vs. FF MDI 9.6 µg GFF MDI 14.4/9.6 µg vs. GP MDI 14.4 µg						

[a] Delta is defined as the amount on average by which the first unobserved trough value at dropout in the non-control treatment is worsened compared to the observed trough value of subjects who continue in the study.
[b] The estimated difference is the least squares (LS) mean difference at Week 24. This estimated difference is from the linear repeated measures model which included the following covariates: baseline FEV1, percent reversibility to Ventolin HFA, treatment, visit, and treatment by visit interaction.
[c] Relative increase in variance is the ratio of between-imputation variance to within-imputation variance.
[d] Fraction of missing information: the relative loss of efficiency in estimation of the treatment difference due to missing data.
[e] Relative efficiency of using the finite number of imputations vs. infinite number of imputations.

Notes to Programmer: in the footnote, please replace "At Week 24" with "Over 24 Weeks" when using this mockup for the change in Morning Pre-dose Trough FEV1 Over 24 Weeks and TDI summary tables below.

Figure 2.1.4.1 Sensitivity Analysis: Comparison of GFF MDI 14.4/9.6 µg vs. Placebo MDI for Change From Baseline in Morning Pre-dose Trough FEV_1 (L) at Week 24
Analysis Set: ITT Population



Delta varies from 0 to the estimated treatment difference.

Report generated by program: pt003014/sasdir/programs/graphs/f02_01_04_01.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Remove 'Sensitivity Analysis' from the plot area. Delta values plotted will be replaced and will be specified at analysis time. Delta values will be based on the estimated treatment difference from comparator from the primary analysis in the ITT population where values will vary from 0 to the estimated difference.

THIS GRAPH WILL BE REPEATED FOR EACH OF THE 5 PRIMARY COMPARISONS (GFF, FF, and GP vs. Placebo and GFF vs. FF and GFF vs. GP) for the following 3 endpoints: change from baseline in morning pre-dose trough FEV_1 at Week 24, change from baseline in morning pre-dose trough FEV_1 over 24 weeks, and TDI over 24 weeks.

Figure 2.1.4.2 Sensitivity Analysis: Comparison of FF MDI 9.6 µg vs. Placebo MDI for Change From Baseline in Morning Pre-dose Trough FEV_1 (L) at Week 24
Analysis Set: ITT Population

Figure 2.1.4.3 Sensitivity Analysis: Comparison of GP MDI 14.4 µg vs. Placebo MDI for Change From Baseline in Morning Pre-dose Trough FEV_1 (L) at Week 24
Analysis Set: ITT Population

Figure 2.1.4.4 Sensitivity Analysis: Comparison of GFF MDI 14.4/9.6 µg vs. FF MDI 9.6 µg for Change From Baseline in Morning Pre-dose Trough FEV_1 (L) at Week 24
Analysis Set: ITT Population

Figure 2.1.4.5 Sensitivity Analysis: Comparison of GFF MDI 14.4/9.6 µg vs. GP MDI 14.4 µg for Change From Baseline in Morning Pre-dose Trough FEV_1 (L) at Week 24
Analysis Set: ITT Population

Table 2.1.4.2 Sensitivity Analysis: Treatment Comparisons for Change From Baseline in Morning Pre-dose Trough FEV_1 (L) Over 24 Weeks
Analysis Set: ITT Population

Figure 2.1.4.6 Sensitivity Analysis: Comparison of GFF MDI 14.4/9.6 µg vs. Placebo MDI for Change From Baseline in Morning Pre-dose Trough FEV_1 (L) Over 24 Weeks
Analysis Set: ITT Population

Figure 2.1.4.7 Sensitivity Analysis: Comparison of FF MDI 9.6 µg vs. Placebo MDI for Change From Baseline in Morning Pre-dose Trough FEV_1 (L) Over 24 Weeks
Analysis Set: ITT Population

Figure 2.1.4.8 Sensitivity Analysis: Comparison of GP MDI 14.4 µg vs. Placebo MDI for Change From Baseline in Morning Pre-dose Trough FEV_1 (L) Over 24 Weeks
Analysis Set: ITT Population

Figure 2.1.4.16 Comparison of GFF MDI 14.4/9.6 µg vs. Placebo MDI for Change From Baseline in Morning Pre-dose Trough FEV_1 (L) at Week 24 Using Imputed Estimates at Various Deltas
Analysis Set: ITT Population

Notes to Programmer: Plot mean adjusted estimates for all weeks post-baseline (using imputed values). 5 Groups would be plotted: Treatment Completers, Comparator Completers, Treatment Dropouts MAR/MCAR, Treatment Dropouts MNAR, and <Comparator Dropouts or Placebo Dropouts---no MAR/MCAR or MNAR for these.>. Legend symbols should match the line symbols. At the top of each page of the figure, put "Delta =xx mL (y treatment effect)" where y = 0, 1/3, 2/3, and 1 x".

Figure 2.1.4.17 Comparison of FF MDI 9.6 µg vs. Placebo MDI for Change From Baseline in Morning Pre-dose Trough FEV1 at Week 24 Using Imputed Estimates at Various Deltas
Analysis Set: ITT Population

Figure 2.1.4.18 Comparison of GP MDI 14.4 µg vs. Placebo MDI for Change From Baseline in Morning Pre-dose Trough FEV_1 at Week 24 Using Imputed Estimates at Various Deltas
Analysis Set: ITT Population

Figure 2.1.4.19 Comparison of GFF MDI 14.4/9.6 µg vs. FF MDI 9.6 µg for Change From Baseline in Morning Pre-dose Trough FEV_1 at Week 24 Using Imputed Estimates at Various Deltas
Analysis Set: ITT Population

Figure 2.1.4.20 Comparison of GFF MDI 14.4/9.6 µg vs. GP MDI 14.4 µg for Change From Baseline in Morning Pre-dose Trough FEV_1 at Week 24 Using Imputed Estimates at Various Deltas
Analysis Set: ITT Population

Figure 2.1.4.21 Comparison of GFF MDI 14.4/9.6 µg vs. Placebo MDI for Change From Baseline in Morning Pre-dose Trough FEV_1 Over 24 Weeks Using Imputed Estimates at Various Deltas
Analysis Set: ITT Population

Figure 2.1.4.22 Comparison of FF MDI 9.6 µg vs. Placebo MDI for Change From Baseline in Morning Pre-dose Trough FEV_1 Over 24 Weeks Using Imputed Estimates at Various Deltas
Analysis Set: ITT Population

Figure 2.1.4.23 Comparison of GP MDI 14.4 µg vs. Placebo MDI for Change From Baseline in Morning Pre-dose Trough FEV_1 Over 24 Weeks Using Imputed Estimates at Various Deltas
Analysis Set: ITT Population

Figure 2.1.4.24 Comparison of GFF MDI 14.4/9.6 µg vs. FF MDI 9.6 µg for Change From Baseline in Morning Pre-dose Trough FEV_1 Over 24 Weeks Using Imputed Estimates at Various Deltas
Analysis Set: ITT Population

Figure 2.1.4.25 Comparison of GFF MDI 14.4/9.6 µg vs. GP MDI 14.4 µg for Change From Baseline in Morning Pre-dose Trough FEV_1 Over 24 Weeks Using Imputed Estimates at Various Deltas
Analysis Set: ITT Population

Figure 2.1.4.26 Comparison of GFF MDI 14.4/9.6 µg vs. Placebo MDI for Change From Baseline in Morning Pre-dose Trough FEV_1 Over Weeks 12-24Using Imputed Estimates at Various Deltas
Analysis Set: ITT Population

Figure 2.1.4.27 Comparison of FF MDI 9.6 µg vs. Placebo MDI for Change From Baseline in Morning Pre-dose Trough FEV_1 Over Weeks 12-24 Using Imputed Estimates at Various Deltas
Analysis Set: ITT Population

Figure 2.1.4.28 Comparison of GP MDI 14.4 µg vs. Placebo MDI for Change From Baseline in Morning Pre-dose Trough FEV_1 Over Weeks 12-24Using Imputed Estimates at Various Deltas
Analysis Set: ITT Population

Figure 2.1.4.29 Comparison of GFF MDI 14.4/9.6 µg vs. FF MDI 9.6 µg for Change From Baseline in Morning Pre-dose Trough FEV_1 Over Weeks 12-24 Using Imputed Estimates at Various Deltas
Analysis Set: ITT Population

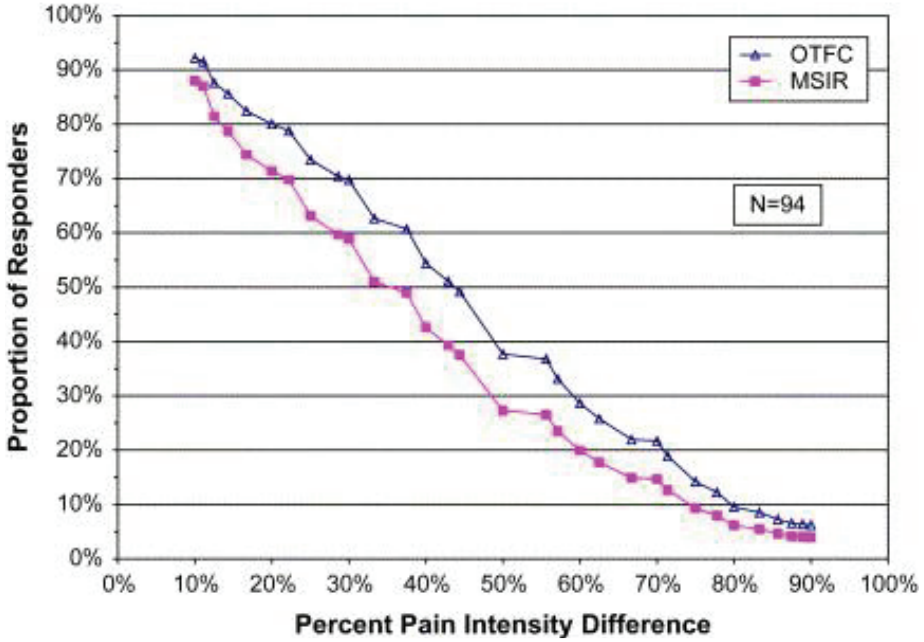
Figure 2.1.4.30 Comparison of GFF MDI 14.4/9.6 µg vs. GP MDI 14.4 µg for Change From Baseline in Morning Pre-dose Trough FEV_1 Over Weeks 12-24 Using Imputed Estimates at Various Deltas
Analysis Set: ITT Population

Table 2.1.4.4 Cumulative Proportion of Responders Based on Change From Baseline in Morning Pre-dose Trough FEV_1 at Week 24
Analysis Set: ITT Population

Response Criteria	Cumulative Response (%)				Treatment Difference vs. Placebo MDI			Treatment Difference for GFF MDI 14.4/9.6 vs. Components	
Change from Baseline in FEV1 (L) ≥	GFF MDI 14.4/9.6 µg (N=xxx)	FF MDI 9.6 µg (N=xxx)	GP MDI 14.4 µg (N=xxx)	Placebo MDI (N=xxx)	GFF MDI 14.4/9.6 µg (p-value)	FF MDI 9.6 µg (p-value)	GP MDI 14.4 µg (p-value)	FF MDI 9.6 µg (N=xxx)	GP MDI 14.4 µg (N=xxx)
P-value					x.xxxx	x.xxxx	x.xxxx	x.xxxx	x.xxxx
x.xxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
x.xxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
x.xxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
x.xxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
x.xxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
x.xxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
x.xxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
x.xxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
x.xxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
x.xxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
x.xxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
x.xxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
x.xxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
x.xxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
x.xxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
x.xxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
x.xxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
x.xxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
x.xxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
x.xxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
x.xxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
x.xxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
x.xxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x

The cumulative response is defined as the percentage of subjects with a change from baseline in FEV1 meeting or exceeding the criteria. Subjects with missing data at Week 24 were considered non-responders. The p-value shown is from a Kolmogorov-Smirnov Test comparing test treatments with Placebo MDI (or components) on the distribution of cumulative response rates across all values of the change from baseline in FEV1 at Week 24.

Figure 2.1.4.31 Cumulative Proportion of Responders Based on Change From Baseline in Morning Pre-dose Trough FEV_1 at Week 24
Analysis Set: ITT Population



This is just an example plot. "Percent Pain Intensity Difference" shown above will be replaced with values of change from baseline in morning pre-dose trough FEV_1 representing values from the 1st to the 99 percentile (irrespective of treatment order). All treatments will be plotted. Subjects with missing data will be considered non-responders for the analysis and this figure.

Transition Dyspnea Index (TDI)

Table 2.2.1 TDI Focal Score Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

<CAT Score Subpopulation>

Note to Programmer: Do for category "CAT Score Overall" which will include subjects with missing TDI score and then repeat tabulation below for CAT Score ≥10, Symptomatic Population (CAT Score ≥15), and CAT Score ≥20. The model will be run separately for each category.

			LS Mean Differences Between Treatments		
Treatment	BDI Focal Score	TDI Focal Score	Placebo MDI	FF MDI 9.6 µg	GP MDI 14.4 µg
Over 24 Weeks					
GFF MDI 14.4/9.6 µg					
n	xx				
Mean	x.x				
SD	x.x				
Median	x.x				
Min-Max	x.x-x.x				
LS Mean (SE)		x.x (x.xx)	x.xx (x.xxx)	x.xx (x.xxx)	x.xx (x.xxx)
95% CI		(x.x, x.x)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)
P-value			x.xxxx	x.xxxx	x.xxxx
FF MDI 9.6 µg					
n	xx				
Mean	x.x				
SD	x.x				
Median	x.x				
Min-Max	x.x-x.x				
LS Mean (SE)		x.x (x.xx)	x.xx (x.xxx)	Not Applicable	x.xx (x.xxx)
95% CI		(x.x, x.x)	(x.xx, x.xx)		(x.xx, x.xx)
P-value			x.xxxx		x.xxxx
GP MDI 14.4 µg					
n	xx				
Mean	x.x				

<CAT Score Subpopulation>

Note to Programmer: Do for category "CAT Score Overall" which will include subjects with missing TDI score and then repeat tabulation below for CAT Score ≥10, Symptomatic Population (CAT Score ≥15), and CAT Score ≥20. The model will be run separately for each category.

			LS Mean Differences Between Treatments		
				FF MDI	GP MDI
Treatment	BDI Focal Score	TDI Focal Score	Placebo MDI	9.6 µg	14.4 µg
SD	x.x				
Median	x.x				
Min-Max	x.x-x.x				
LS Mean (SE)		x.x (x.xx)	x.xx (x.xxx)	Shown Above	Not Applicable
95% CI		(x.x, x.x)	(x.xx, x.xx)		
P-value			x.xxxx		
Placebo					
n	xx				
Mean	x.x				
SD	x.x				
Median	x.x				
Min-Max	x.x-x.x				
LS Mean (SE)		x.x (x.xx)	Not Applicable	Shown Above	Shown Above
95% CI		(x.x, x.x)			

Note to Programmer: Repeat for Over Weeks 12-24 and for each post-baseline visit from Week 4 to Week 24. Descriptive statistics for the raw TDI focal score will be added for each individual visit, but not for 0-24 weeks or for Over Weeks 12-24. Do not split a treatment across a page.

LS Mean = least squares means are from the linear repeated measures model which included the following covariates: BDI focal score, percent reversibility to Ventolin HFA, treatment, visit, and treatment by visit interaction.

Report generated by program: pt003014/sasdir/programs/statout/t020201.sas Version YYYY-MM-DD hh:mm (Page n of N)

Figure 2.2.1.1.1 Adjusted Mean TDI Focal Score ± SE Over Time
Analysis Set: ITT Population

Note to Programmer: show by visit and also 4-24 value as a single point. Do not start x axis at 0.

Figure 2.2.1.1.2 Treatment Differences From Placebo MDI*: Adjusted Mean TDI Focal Score (95% CI) Over Time
Analysis Set: ITT Population

Figure 2.2.1.2.1 Adjusted Mean TDI Focal Score ± SE Over Time: CAT Score Subpopulation of >= 10
Analysis Set: ITT Population

Figure 2.2.1.2.2 Adjusted Mean TDI Focal Score ± SE Over Time: Symptomatic Population (CAT Score ≥15),
Analysis Set: ITT Population

Figure 2.2.1.2.3 Adjusted Mean TDI Focal Score ± SE Over Time: CAT Score Subpopulation of >= 20
Analysis Set: ITT Population

Table 2.2.2.1 TDI Component Scores for Functional Impairment, Magnitude of Task, and Magnitude of Effort Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Figure 2.2.2.1.x Adjusted Mean TDI Functional Impairment Component Score ± SE Over Time Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Figure 2.2.2.2.x Adjusted Mean TDI Magnitude of Task Component Score ± SE Over Time Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Figure 2.2.2.3.x Adjusted Mean TDI Magnitude of Effort Component Score ± SE Over Time Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Table 2.2.3 Response in TDI Focal Score (Achievment of a Minimum Clinically Important Difference Threshold of ≥1 Unit on Average) Over 24 Weeks and Over Weeks 12-24 Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

<CAT Score Subpopulation>

Note to Programmer: Do for "CAT Score Overall" population which will include subjects with missing CAT score and then repeat tabulation below for subpopulations of CAT Score ≥10, Symptomatic Population (CAT Score ≥15),and CAT Score ≥20. The model will be run separately for each category.

		Model-Based Percentages [a]		
Percentage of Subjects Achieving TDI Focal Score of at Least 1.0 Unit On Average Over 24 Weeks		Comparator		
Observed % (n/N)		Placebo MDI	FF MDI 9.6 µg	GP MDI 14.4 µg
Over 24 Weeks				
GFF MDI 14.4/9.6 µg xx.xx% (xxx/xxx)	Treatment	xx.xx	xx.xx	xx.xx
	Comparator	xx.xx	xx.xx	xx.xx
	Difference	xx.xx	xx.xx	xx.xx
	95% CI	(x.xx, xx.xx)	(x.xx, xx.xx)	(x.xx, xx.xx)
	Odds Ratio	x.xxxx	x.xxxx	x.xxxx
	95% CI	(x.xxxx, x.xxxx)	(x.xxxx, x.xxxx)	(x.xxxx, x.xxxx)
	P-value	x.xxxx	x.xxxx	x.xxxx
FF MDI 9.6 µg xx.xx% (xxx/xxx)	Treatment	xx.xx	Not Applicable	xx.xx
	Comparator	xx.xx		xx.xx
	Difference	xx.xx		xx.xx
	95% CI	(x.xx, xx.xx)		(x.xx, xx.xx)
	Odds Ratio	x.xxxx		x.xxxx
	95% CI	(x.xxxx, x.xxxx)		(x.xxxx, x.xxxx)
	P-value	x.xxxx		x.xxxx
GP MDI 14.4 µg xx.xx% (xxx/xxx)	Treatment	xx.xx	Shown Above	Not Applicable
	Comparator	xx.xx		
	Difference	xx.xx		

<CAT Score Subpopulation>

Note to Programmer: Do for "CAT Score Overall" population which will include subjects with missing CAT score and then repeat tabulation below for subpopulations of CAT Score ≥10, Symptomatic Population (CAT Score ≥15),and CAT Score ≥20. The model will be run separately for each category.

		Model-Based Percentages [a]		
		Comparator		
Percentage of Subjects Achieving TDI Focal Score of at Least 1.0 Unit On Average Over 24 Weeks				
Observed % (n/N)		Placebo MDI	FF MDI 9.6 µg	GP MDI 14.4 µg
	95% CI	(x.xx, xx.xx)		
	Odds Ratio	x.xxxx		
	95% CI	(x.xxxx, x.xxxx)		
	P-value	x.xxxx		
Placebo MDI xx.xx% (xxx/xxx)		Not Applicable	Shown Above	Shown Above
REPEAT for Over Weeks 12-24				

[a] Estimated percentages, differences between percentages and p-values are based on a logistic regression model with TDI response as a binary response and the following covariates in the model: BDI Focal Score, percent reversibility to Ventolin HFA, and treatment. The p-value is associated with the test of whether the odds ratio is equal to 1.0. A significant p-value for the test of the odds ratio indicates that the odds of a treatment effect in the treatment is not equal to that for the comparator (either significantly higher or significantly lower than 1.0).

Report generated by program: pt003014/sasdir/programs/statout/t020203.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer:

USE THIS TABLE FORMAT FOR ALL RESPONSE TABLES IN THIS DOCUMENT (SGRQ AND PERCENT RESPONSE TABLES).

Peak Change From Baseline in FEV_1

Table 2.3.1 Peak Change From Baseline in FEV1 (L) Within 2 Hours Post-dose
Analysis Set: ITT Population

Figure 2.3.1 Adjusted Mean Peak Change From Baseline in FEV_1 (L) ± SE Within 2 Hours Post-dose
Analysis Set: ITT Population

St. George Respiratory Questionnaire (SGRQ)

Table 2.4.1 SGRQ Total Score (units) Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

```
Note to Programmer: Similar to Table 2.2.1, use all ITT data and then repeat tabulation below for CAT Score ≥10, Symptomatic
Population (CAT Score ≥15), and CAT Score ≥20. The model will be run separately for each category.

The following will be the first footnote in the table:

A 1 unit change in the SGRQ total score corresponds to a change of 1% per the SGRQ scoring manual.
```

Figure 2.4.1.1 Adjusted Mean Change From Baseline in SGRQ Total Score (units) ± SE Over Time
Analysis Set: ITT Population

Note to Programmer; show by visit and also 4-24 and 12-24 value as a single point.

Figure 2.4.1.2 Adjusted Mean Change From Baseline in SGRQ Total Score (units) ± SE Over Time: CAT Score Subpopulation of >= 10
Analysis Set: ITT Population

Figure 2.4.1.3 Adjusted Mean Change From Baseline in SGRQ Total Score (units) ± SE Over Time: Symptomatic Population (CAT Score ≥15),
Analysis Set: ITT Population

Figure 2.4.1.4 Adjusted Mean Change From Baseline in SGRQ Total Score (units) ± SE Over Time: CAT Score Subpopulation of >= 20
Analysis Set: ITT Population

Table 2.4.2 Total Score (units) of Each SGRQ Domain Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Table 2.4.3 Response in SGRQ Total Score (Achievment of a Minimum Clinically Important Difference Threshold of ≥4 Units on Average) Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Notes to the Programmer: please use the format of Table 2.2.4.1. Replace the covariate of BDI with baseline SGRQ total score. Do for at Week 24 and for over Weeks 12-24.

The following will be the first footnote in the table:

A 1 unit change in the SGRQ total score corresponds to a change of 1% per the SGRQ scoring manual.

Number of Puffs of Rescue Ventolin HFA

Table 2.5.1 Mean Daily, Daytime, and Nighttime Number of Puffs of Rescue Ventolin HFA
Analysis Set: Rescue Ventolin User Population

Note to Programmer: Similar to Table 2.2.1.

Figure 2.5.1.1 Adjusted Mean Change From Baseline in Mean Daily Number of Puffs of Rescue Ventolin HFA ± SE Over Time
Analysis Set: Rescue Ventolin User Population

Notes to Programmer: Show each 4-week interval, and Over Weeks 12-24 and over 24 weeks as single points (1-24 and 12-24). Label the 4-week intervals as "1-4, 5-8, 9-12, 13-16, 17-20, and 21-24". Connect all treatment lines to 0.

Figure 2.5.1.2 Adjusted Mean Change From Baseline in Mean Daytime Number of Puffs of Rescue Ventolin HFA ± SE Over Time
Analysis Set: Rescue Ventolin User Population

Figure 2.5.1.3 Adjusted Mean Change From Baseline in Mean Nighttime Number of Puffs of Rescue Ventolin HFA± SE Over Time
Analysis Set: Rescue Ventolin User Population

Table 2.5.2 Percentage of Days With No Rescue Ventolin HFA Use Over 24 Weeks
Analysis Set: Rescue Ventolin User Population

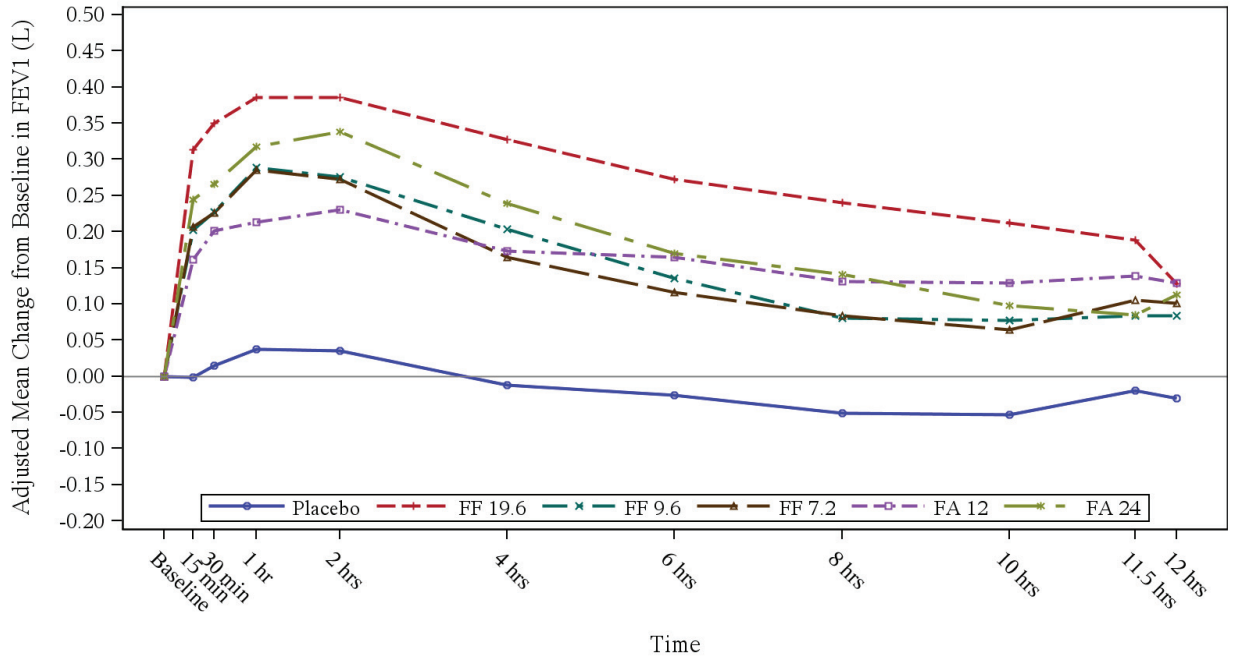
Notes to Programmer: A 'Day with no rescue use' is defined, using rescue Ventolin usage data from days where rescue Ventolin usage data is non-missing, as any day where the subject reported no puffs of rescue Ventolin. The percentage of days with 'no rescue use' will be summarized by treatment and analyzed using ANCOVA with baseline average daily rescue Ventolin use and percent reversibility to Ventolin HFA as continuous covariates.

Time to Onset of Action Assessed Using FEV_1 on Day 1

Table 2.6.1 FEV_1 (L) by Post-dose Timepoint on Day 1
Analysis Set: ITT Population

Notes to Programmer: Please use the format of Table 2.1.1 and within this table, sort by 2 hour post-dose assessment.

Figure 2.6.1 Adjusted Mean Change From Baseline in FEV_1 (L) ± SE Over the 2 Hour Post-dose Interval on Day 1
Analysis Set: ITT Population



Source: Table 2.6.1.

Report generated by program: pt003014/sasdir/programs/statout/f021801.sas Version YYYY-MM-DD hh:mm (Page n of N)

Notes to Programmer: Timepoints up to and including 2 hours post dose are shown, including the 5 min timepoint. Replace treatments shown with the 5 treatments used in this study. Replace the x axis label with "Time Post-dose". Add +/- SE to end of the y axis label.

Other Spirometry Measures Including Percent Responders Analyses for Day 1

Table 2.7 FEV_1 AUC_{0-2} (L)
Analysis Set: ITT Population

Note to Programmer: tabulate for over 24 weeks, over 12-24 weeks, and for each post-baseline visit. This variable is based on change from baseline in FEV_1.

Figure 2.7 Adjusted Mean FEV_1 AUC_{0-2} (L) ± SE Over Time
Analysis Set: ITT Population

Table 2.8 FVC AUC_{0-2} (L)
Analysis Set: ITT Population

Figure 2.8 Adjusted Mean FVC AUC_{0-2} (L) ± SE Over Time
Analysis Set: ITT Population

Table 2.9 Peak Change From Baseline in FVC (L) Within 2 Hours Post-dose
Analysis Set: ITT Population

Figure 2.9 Adjusted Mean Peak Change From Baseline in FVC (L) ± SE Within 2 Hours Post-dose
Analysis Set: ITT Population

Table 2.10 Morning Pre-dose Trough FVC (L)
Analysis Set: ITT Population

Figure 2.10 Adjusted Mean Change From Baseline in Morning Pre-dose Trough FVC (L) ± SE
Analysis Set: ITT Population

Table 2.11.1 Percentage of Subjects With ≥10% Improvement From Baseline in FEV_1 During 2 Hour Post-dose Interval and by Post-dose Timepoint on Day 1
Analysis Set: ITT Population

Notes to the Programmer: please use the format of Table 2.2.8.1. Do for Over 2 Hour Post-dose Interval and also for each Post-dose timepoint.

Footnote:
[a] Estimated percentages, differences between percentages and p-values are based on a logistic regression model with ≥10% improvement From baseline in FEV_1 during 2 hour post-dose interval as a binary response and the following covariates in the model: baseline FEV1, percent reversibility to Ventolin HFA, and treatment. The p-value is associated with the test of whether the odds ratio is equal to 1.0. A significant p-value for the test of the odds ratio indicates that the odds of a treatment effect in the treatment is not equal to that for the comparator (either significantly higher or significantly lower than 1.0).

Table 2.11.2 Percentage of Subjects With ≥12% Improvement From Baseline in FEV_1 During 2 Hour Post-dose Interval and by Post-dose Timepoint on Day 1
Analysis Set: ITT Population

Table 2.11.3 Percentage of Subjects With ≥100 mL Improvement From Baseline in FEV_1 During 2 Hour Post-dose Interval and by Post-dose Timepoint on Day 1
Analysis Set: ITT Population

Table 2.11.4 Percentage of Subjects With ≥200 mL Improvement From Baseline in FEV_1 During 2 Hour Post-dose Interval and by Post-dose Timepoint on Day 1
Analysis Set: ITT Population

Table 2.11.5 Percentage of Subjects With Improvement From Baseline in FEV_1 of Both ≥12% and ≥200 mL During 2 Hour Post-dose Interval and by Post-dose Timepoint on Day 1
Analysis Set: ITT Population

Table 2.12 FVC (L) Over the 2 Hour Post-dose Interval on Day 1
Analysis Set: ITT Population

Figure 2.12 Adjusted Mean Change From Baseline in FVC (L) ± SE Over the 2 Hour Post-dose Interval on Day 1
Analysis Set: ITT Population

Exacerbations

Table 2.13.1 Rate of COPD Exacerbations Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

<CAT Score Subpopulation>

Note to Programmer: Do for "CAT Score Overall" population which will include subjects with missing CAT score and then repeat tabulation below for subpopulations of CAT Score ≥10, Symptomatic Population (CAT Score ≥15),and CAT Score ≥20. The model will be run separately for each category.

	GFF MDI 14.4/9.6 µg (N=xxx)	FF MDI 9.6 µg (N=xxx)	GP MDI 14.4 µg (N=xxx)	Placebo MDI (N=xxx)
Subjects with COPD Exacerbations [a], n(%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
[Events]	[x]	[x]	[x]	[x]
Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	[x]	[x]	[x]	[x]
Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	[x]	[x]	[x]	[x]
Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	[x]	[x]	[x]	[x]
Moderate or Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	[x]	[x]	[x]	[x]
Any Severity	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	[x]	[x]	[x]	[x]
COPD Exacerbation of Any Severity				
Rate (per year) of COPD Exacerbation [b]	x.xx	x.xx	x.xx	x.xx
Adjusted Rate of COPD Exacerbation (c)	x.xx	x.xx	x.xx	x.xx
Treatment Incidence Rate Ratio (P-value) (95% CI) [c][e]				
GFF MDI 14.4/9.6 µg (n=xxx)	Not Applicable	x.xx (x.xxxx) (x.xx, x.xx)	x.xx (x.xxxx) (x.xx, x.xx)	x.xx (x.xxxx) (x.xx, x.xx)
FF MDI 9.6 µg (n=xxx)		Not Applicable	x.xx (x.xxxx) (x.xx, x.xx)	x.xx (x.xxxx) (x.xx, x.xx)
GP MDI 14.4 µg (n=xxx)			Not Applicable	x.xx (x.xxxx)

				(x.xx, x.xx)
Placebo MDI (n=xxx)				Not Applicable
Treatment Difference in Rates (95% CI) [c] [d]				
GFF MDI 14.4/9.6 µg (n=xxx)	Not Applicable	x.xx (x.xx, x.xxxx)	x.xx (x.xx, xxxx)	x.xx (x.xx, x.xx)
FF MDI 9.6 µg (n=xxx)		Not Applicable	xxxx (xxxx, x.xx)	xxxx (x.xx, x.xx)
GP MDI 14.4 µg (n=xxx)			Not Applicable	x.xx (x.xx, x.xx)
Placebo MDI (n=xxx)				Not Applicable

Notes to Programmer: Repeat above for Rate of Moderate or Severe COPD exacerbation except for the 1st 6 rows of the table. If n is not sufficient, only relevant statistics will be provided. Replace 'COPD Exacerbation of Any Severity' with 'Moderate or Severe COPD Exacerbation'. Repeat these labels when starting a new page and put '(Continued)' at the end of the phrase.

[a] COPD exacerbations were considered separate events provided that 7 or more days were between the recorded stop date of the earlier event and start date of the later.
[b] The rate of exacerbations per year = Total number of exacerbations / Total years of exposure across all subjects for the treatment. Time during an exacerbation or in the 7 days following an exacerbation was not included in the calculation of exposure.
[c] Treatments were compared adjusting for baseline percent predicted FEV_1, baseline CAT score, baseline COPD exacerbation history (yes/no), smoking status at baseline (former smoker/current smoker), baseline continuous eosinophil count, and inhaled corticosteroid use at baseline (yes/no) using negative binomial regression. Treatment exposure was used as an offset variable.
[d] Row Treatment minus Column Treatment.
[e] Row Treatment / Column Treatment.

Report generated by program: pt003014/sasdir/programs/statout/t021301.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmers: put a blank line after each treatment row.

Table 2.13.2 Rate of COPD Exacerbations With Imputation Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Notes to Programmer: Repeat above for Rate of Moderate or Severe COPD exacerbation except for the 1st 6 rows of the table. Add a footnote: Analyses include the imputation of a moderate exacerbation at the time of dropout for subjects withdrawing prematurely from the trial, unless an exacerbation has already been recorded at that time.

Table 2.14 Time to First COPD Exacerbation of Any Severity and Time to First Moderate or Severe COPD Exacerbation Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

<CAT Score Subpopulation>

Note to Programmer: Do for "CAT Score Overall" population which will include subjects with missing CAT score and then repeat tabulation below for subpopulations of CAT Score ≥10, Symptomatic Population (CAT Score ≥15),and CAT Score ≥20. The model will be run separately for each category.

	GFF MDI 14.4/9.6 µg (N=xxx)	FF MDI 9.6 µg (N=xxx)	GP MDI 14.4 µg (N=xxx)	Placebo MDI (N=xxx)
Subjects with COPD Exacerbation of Any Severity, n(%)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Time to First COPD Exacerbation of Any Severity				
Hazard Ratio (Relative to Comparator)				
95% CI				
P-value				
GFF MDI 14.4/9.6 µg (n=xxx)	Not Applicable	x.xxx (x.xxx, x.xxx) x.xxxx	x.xxx (x.xxx, x.xxx) x.xxxx	x.xxx (x.xxx, x.xxx) x.xxxx
FF MDI 9.6 µg (n=xxx)		Not Applicable	x.xxx (x.xxx, x.xxx) x.xxxx	x.xxx (x.xxx, x.xxx) x.xxxx
GP MDI 14.4 µg (n=xxx)			Not Applicable	x.xxx (x.xxx, x.xxx) x.xxxx
Placebo MDI (n=xxx)				Not Applicable

Notes to Programmer: Use "Time to First COPD Exacerbation of Any Severity (Continued)" if starting a new page.
Repeat above for time to first moderate or severe COPD exacerbation. Replace "Time to First COPD Exacerbation of Any Severity" with "Time to First Moderate or Severe COPD Exacerbation". *Use data up to the last visit date (if on or after the last date of treatment) or up to the date of last treatment if this occurred after the last visit), as long as on or prior to Day 183.*

Time to COPD Exacerbation (weeks) = (date of first COPD exacerbation – first treatment administration date + 1)/7. Treatment comparisons were performed using the Cox regression model, adjusting for baseline percent predicted FEV_1, baseline COPD exacerbation history (yes/no), baseline CAT score, smoking status at baseline (former smoker/current smoker), baseline continuous eosinophil count, and inhaled corticosteroid use at baseline (yes/no).

Report generated by program: pt003014/sasdir/programs/statout/t0214.sas Version YYYY-MM-DD xx:xx (Page n of N)

Figure 2.14.1.x Kaplan-Meier Curves for Time to First COPD Exacerbation of Any Severity Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Notes to Programmer: Use data up to the last visit date (if on or after the last date of treatment) or up to the date of last treatment if this occurred after the last visit), as long as on or prior to Day 183.

Figure 2.14.2.x Kaplan-Meier Curves for Time to First Moderate or Severe COPD Exacerbation Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Notes to Programmer: Use data up to the last visit date (if on or after the last date of treatment) or up to the date of last treatment if this occurred after the last visit), as long as on or prior to Day 183.

Table 2.15 Time to Treatment Failure Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

<CAT Score Subpopulation>

Note to Programmer: Do for "CAT Score Overall" population which will include subjects with missing CAT score and then repeat tabulation below for subpopulations of CAT Score ≥10, Symptomatic Population (CAT Score ≥15),and CAT Score ≥20. The model will be run separately for each category.

	GFF MDI 14.4/9.6 µg (N=xxx)	FF MDI 9.6 µg (N=xxx)	GP MDI 14.4 µg (N=xxx)	Placebo MDI (N=xxx)
Subjects with Treatment Failure, n(%)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Hazard Ratio (Relative to Comparator) 95% CI P-value				
GFF MDI 14.4/9.6 µg (n=xxx)	Not Applicable	x.xxx (x.xxx, x.xxx) x.xxxx	x.xxx (x.xxx, x.xxx) x.xxxx	x.xxx (x.xxx, x.xxx) x.xxxx
FF MDI 9.6 µg (n=xxx)		Not Applicable	x.xxx (x.xxx, x.xxx) x.xxxx	x.xxx (x.xxx, x.xxx) x.xxxx
GP MDI 14.4 µg (n=xxx)			Not Applicable	x.xxx (x.xxx, x.xxx) x.xxxx
Placebo MDI (n=xxx)				Not Applicable

Notes to Programmer: If n is not sufficient, only relevant statistics will be provided.

Treatment failure is defined as occurrence of a moderate/severe COPD exacerbation or early discontinuation for any reason. Time to treatment failure (weeks) = (date of treatment failure – first treatment administration date + 1)/7. Treatment comparisons were performed using the Cox regression model, adjusting for baseline percent predicted FEV_1, baseline COPD exacerbation history (yes/no), baseline CAT score, smoking status at baseline (former smoker/current smoker), baseline continuous eosinophil count, and inhaled corticosteroid use at baseline (yes/no).

Report generated by program: pt003014/sasdir/programs/statout/t0215.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Use data up to the last visit date (if on or after the last date of treatment) or up to the date of last treatment if this occurred after the last visit), as long as on or prior to Day 183.

Figure 2.15.x Kaplan-Meier Curves for Time to Treatment Failure Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Notes to Programmer: Use data up to the last visit date (if on or after the last date of treatment) or up to the date of last treatment if this occurred after the last visit), as long as on or prior to Day 183.

Table 2.16.1 Time to First Clinically Important Deterioration (CID) Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

<CAT Score Subpopulation>

Note to Programmer: Do for the "CAT Score Overall" population which will include subjects with missing CAT score and then repeat tabulation below for subpopulations of CAT Score ≥10, CAT Score ≥15,and CAT Score ≥20. The model will be run separately for each category.

	GFF MDI 14.4/9.6 µg (N=xxx)	FF MDI 9.6 µg (N=xxx)	GP MDI 14.4 µg (N=xxx)	Placebo MDI (N=xxx)
Subjects with first CID, n(%) [a]	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Median time to CID (weeks) [b]	xx.x	xx.x	xx.x	xx.x
Hazard Ratio (Relative to Comparator) 95% CI P-value				
GFF MDI 14.4/9.6 µg (n=xxx)	Not Applicable	x.xxx (x.xxx, x.xxx) x.xxxx	x.xxx (x.xxx, x.xxx) x.xxxx	x.xxx (x.xxx, x.xxx) x.xxxx
FF MDI 9.6 µg (n=xxx)		Not Applicable	x.xxx (x.xxx, x.xxx) x.xxxx	x.xxx (x.xxx, x.xxx) x.xxxx
GP MDI 14.4 µg (n=xxx)			Not Applicable	x.xxx (x.xxx, x.xxx) x.xxxx
Placebo MDI (n=xxx)				Not Applicable

Notes to Programmer: If n is not sufficient, only relevant statistics will be provided.

[a] CID is defined as the first occurrence of one of the following events: 1) >= 100 mL decline in trough FEV1; 2) a treatment emergent moderate/severe COPD exacerbation; or 3) increase of >= 4 units on the SGRQ.
[b] Time to CID (weeks) = (date of CID - first treatment administration date + 1)/7. Treatment comparisons were performed using the Cox regression model, adjusting for baseline percent predicted FEV1, baseline CAT score, baseline COPD exacerbation history (yes/no), smoking status at baseline (former smoker/current smoker), and inhaled corticosteroid use at baseline (yes/no).

Report generated by program: pt003014/sasdir/programs/statout/t021601.sas Version YYYY-MM-DD xx:xx (Page n of N)

Note to Programmers: Time to a CID event will be based on the time of the component event which occurred first. Subjects who did not have a CID event will be censored at the earliest censoring day among the component censoring times. COPD exacerbations occurring past day 183 will not be counted as CID events.

Figure 2.16.1.x Kaplan-Meier Curves for Time to First CID Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Notes to Programmer:

Time to a CID event will be based on the time of the component event which occurred first. Subjects who did not have a CID event will be censored at the earliest censoring day among the component censoring times. COPD exacerbations occurring past day 183 will not be counted as CID event (use data up to the last visit date (if on or after the last date of treatment) or up to the date of last treatment if this occurred after the last visit), as long as on or prior to Day 183).

Table 2.16.2 Time to First Clinically Important Deterioration (CID) With Death and Time to First Occurrence of Each Component of CID with Death Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Notes to Programmer:

Follow the format of Table 2.6.1. Do not display the Median time to CID row in this table.

Time to first CID event will be based on the time of the component event which occurred first. COPD exacerbations occurring past day 183 will not be counted as CID events.

Figure 2.16.2.x Kaplan-Meier Curves for Time to First CID With Death and Time to First Occurrence of Each Component of CID With Death Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Notes to Programmer:

Time to first CID event will be based on the time of the component event which occurred first. Subjects who did not have a CID event will be censored at the earliest censoring day among the component censoring times. COPD exacerbations occurring past Day 183 will not be counted as CID event (use data up to the last visit date (if on or after the last date of treatment) or up to the date of last treatment if this occurred after the last visit), as long as on or prior to Day 183).

Table 2.17 Time to First Sustained Clinically Important Deterioration (CID) and Time to First Occurrence of Each Component of Sustained CID Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Notes to Programmer:

First sustained CID will be defined as the first occurrence of one of the following events: 1) a sustained decline in trough FEV_1; 2) a sustained SGRQ increase; or 3) a treatment emergent moderate/severe COPD exacerbation.

Component Definitions:

A sustained decline in trough FEV_1 will be defined as ≥100 mL decline in trough FEV_1 on 2 consecutive analysis visits or for ≥50% of all subsequent analysis visits with available trough FEV_1.

A sustained SGRQ increase will be defined as ≥4 points increase in SGRQ on 2 consecutive analysis visits or for ≥50% of all subsequent analysis visits with available SGRQ.

For the COX regression, subjects who did not experience a component event will be censored at the Week 24 visit or Day 183, whichever was earlier. The basic assumptions of the model including the proportional hazards assumption will be checked.

Time to first trough FEV_1 event will be the study day of the post-baseline analysis visit when change from baseline in trough FEV_1 was ≤ -100 mL. If this event did not occur, the observation will be censored at the last analysis visit where trough FEV_1 was evaluated. Time to first sustained decline in trough FEV_1 will be the study day of the initial decline, satisfying the sustained definition. If the subject did not experience a sustained trough FEV_1 decline, censoring will occur at the second-last analysis visit where trough FEV_1 was evaluated.

Similar considerations apply to time to first SGRQ event and first sustained SGRQ event.

Time to a sustained CID event will be based on the time of the component event which occurred first. COPD exacerbations occurring past Day 183 will not be counted as sustained CID events.

Figure 2.17.x Kaplan-Meier Curves for Time to First Sustained CID and Time to First Occurrence of Each Component of Sustained CID Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Notes to Programmer:

Time to first sustained CID event will be based on the time of the component event which occurred first. Subjects who did not have a sustained CID event will be censored at the earliest censoring day among the component censoring times. COPD exacerbations occurring past Day 183 will not be counted as CID event (use data up to the last visit date (if on or after the last date of treatment) or up to the date of last treatment if this occurred after the last visit), as long as on or prior to Day 183).

Symptoms

Table 2.18.1 Mean Daily, Daytime, and Nighttime Total Symptom Scores
Analysis Set: ITT Population

Notes to the Programmer:

Add the following footnote for the total daily symptom score tabulation:
Calculation of the mean daily total symptom score was based on scaled Ventolin HFA use over 24 hours with the following categories: 0 = No Ventolin HFA use, 1 = 1-2 puffs, 2 = 3-4 puffs, 3 = 5-6 puffs, 4 = 7-8 puffs, 5 = 9-10 puffs, and 6 = >10 puffs.

Add the following footnote for the daytime symptom score tabulation:
Calculation of the mean daily daytime symptom score was based on scaled Ventolin HFA use with the following categories: 0 = No Ventolin HFA use, 1 = 1-2 puffs, 2 = 3-4 puffs, 3 = 5-6 puffs, and 4 = >6 puffs.

Add the following footnote for the nighttime symptom score tabulation:
Calculation of the mean daily nighttime symptom score was based on scaled Ventolin HFA use with the following categories: 0 = No Ventolin HFA use, 1 = 1-2 puffs, 2 = 3-4 puffs, 3 = 5-6 puffs, and 4 = >6 puffs.

Table 2.18.2 Mean Daily, Daytime, and Nighttime Cough Symptom Scores
Analysis Set: ITT Population

Table 2.18.3 Mean Daily, Daytime, and Nighttime Shortness of Breath Symptom Scores
Analysis Set: ITT Population

Table 2.18.4 Mean Daily, Daytime, and Nighttime Sputum Volume Symptom Scores
Analysis Set: ITT Population

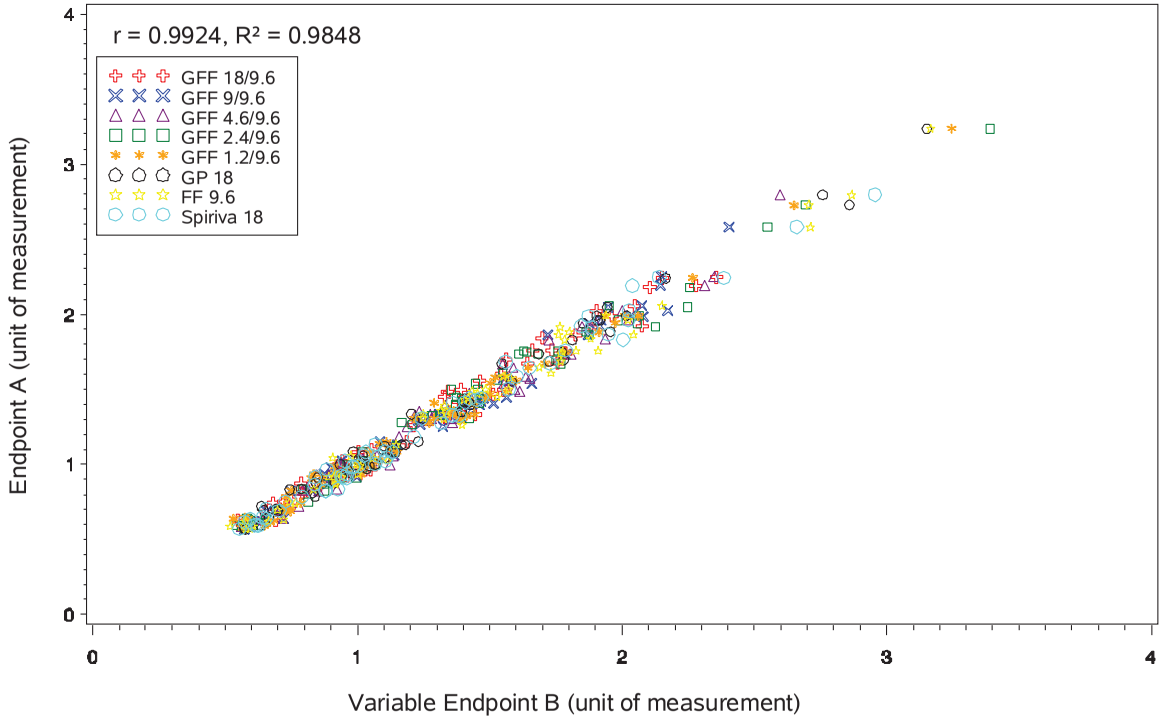
Table 2.18.5 Mean Number of Nighttime Awakenings
Analysis Set: ITT Population

Notes to the Programmer: 'Baseline' column header should be "Baseline Average Awakenings (per night)". Add a footnote to the table: "Nighttime awakenings are coded 0 to 6 ….". (See Table 8 of the SAP)."

Correlations

(Note to Programmer: For all correlation plots below, show the Pearson r correlation coefficient (r) and the Spearman correlation coefficient (r_s). Do not show R^2. The Spearman correlation coefficient may be shown as "Rho" or the symbol for Rho if subscripts are not possible).

Figure 2.19.1 Correlation of Change From Baseline in Morning Pre-dose Trough FEV_1 at Week 24 With Change From Baseline in Morning Pre-dose Trough FEV_1 Over 24 Weeks
Analysis Set: All Available Data



Treatment plotted is treatment received.

Source: Table 2.27

Report generated by program: pt003014/sasdir/programs/statout/f022801.sas Version YYYY-MM-DD hh:mm (Page n of N)

Notes to Programmer: Please redo figures with all treatments, replacing the x and y axis above with the two variables names identified in the title for this figure---the first of the 2 names in the table will be used for the y axis and the 2nd name in the title for the y axis.

Figure 2.19.2 Correlation of Change From Baseline in Morning Pre-dose Trough FEV_1 at Week 24 With Peak Change From Baseline in FEV_1 at Week 24
Analysis Set: All Available Data

Figure 2.19.3 Correlation of Change From Baseline in Morning Pre-dose Trough FEV_1 at Week 24 With Change From Baseline in SGRQ Total Score at Week 24
Analysis Set: All Available Data

Figure 2.19.4 Correlation of Change From Baseline in Morning Pre-dose Trough FEV_1 at Week 24 With Change From Baseline in Rescue Ventolin HFA Usage Over 24 Weeks
Analysis Set: All Available Data

Figure 2.19.5 Correlation of Change From Baseline in Morning Pre-dose Trough FEV_1 at Week 24 With TDI Focal Score Over 24 Weeks
Analysis Set: All Available Data

Figure 2.19.6 Correlation of Change From Baseline in Morning Pre-dose Trough FEV_1 at Week 24 With Peak Change From Baseline in FEV_1 Over 24 Weeks
Analysis Set: All Available Data

Figure 2.19.7 Correlation of Change From Baseline in Morning Pre-dose Trough FEV_1 Over 24 Weeks With Peak Change From Baseline in FEV_1 at Week 24
Analysis Set: All Available Data

Figure 2.19.8 Correlation of Change From Baseline in Morning Pre-dose Trough FEV_1 Over 24 Weeks With Change From Baseline in SGRQ Total Score at Week 24
Analysis Set: All Available Data

Figure 2.19.9 Correlation of Change From Baseline in Morning Pre-dose Trough FEV_1 Over 24 Weeks With Change From Baseline in Rescue Ventolin HFA Usage Over 24 Weeks
Analysis Set: All Available Data

Figure 2.19.10 Correlation of Peak Change From Baseline in FEV_1 at Week 24 With Change From Baseline in SGRQ Total Score at Week 24
Analysis Set: All Available Data

Figure 2.19.11 Correlation of Peak Change From Baseline in FEV_1 at Week 24 With Change From Baseline in Rescue Ventolin HFA Usage Over 24 Weeks
Analysis Set: All Available Data

Figure 2.19.12 Correlation of Peak Change From Baseline in FEV_1 at Week 24 With TDI Focal Score Over 24 Weeks
Analysis Set: All Available Data

Figure 2.19.13 Correlation of Peak Change From Baseline in FEV_1 at Week 24 With Peak Change From Baseline in FEV_1 Over 24 Weeks
Analysis Set: All Available Data

Figure 2.19.14 Correlation of Change From Baseline in SGRQ Total Score at Week 24 With Change From Baseline in Rescue Ventolin HFA Usage Over 24 Weeks
Analysis Set: All Available Data

Figure 2.19.15 Correlation of Change From Baseline in SGRQ Total Score at Week 24 With TDI Focal Score Over 24 Weeks
Analysis Set: All Available Data

Figure 2.19.16 Correlation of Change From Baseline in SGRQ Total Score at Week 24 With Peak Change From Baseline in FEV_1 Over 24 Weeks
Analysis Set: All Available Data

Figure 2.19.17 Correlation of Change From Baseline in Morning Pre-dose Trough FEV_1 Over 24 Weeks With TDI Focal Score Over 24 Weeks
Analysis Set: All Available Data

Figure 2.19.18 Correlation of Change From Baseline in Morning Pre-dose Trough FEV_1 Over 24 Weeks With Peak Change From Baseline in FEV_1 Over 24 Weeks
Analysis Set: All Available Data

Figure 2.19.19 Correlation of TDI Focal Score Over 24 Weeks With Peak Change From Baseline in FEV_1 Over 24 Weeks
Analysis Set: All Available Data

Figure 2.19.20 Correlation of TDI Focal Score Over 24 Weeks With Change From Baseline in Rescue Ventolin HFA Usage Over 24 Weeks
Analysis Set: All Available Data

Figure 2.19.21 Correlation of Peak Change From Baseline in FEV_1 Over 24 Weeks With Change From Baseline in Rescue Ventolin HFA Usage Over 24 Weeks
Analysis Set: All Available Data

Figure 2.19.22 Correlation of Change from Baseline in Morning Pre-dose Trough FEV1 at Week 24 With Morning Pre-dose Trough FEV1 Over Weeks 12-24
Analysis Set: All Available Data

Figure 2.19.23 Correlation of Change from Baseline in Morning Pre-dose Trough FEV_1 at Week 24 With TDI Focal Score Over Weeks 12-24
Analysis Set: All Available Data

Figure 2.19.24 Correlation of Change from Baseline in Morning Pre-dose Trough FEV_1 at Week 24 With Peak Change from Baseline in FEV_1 Over Weeks 12-24
Analysis Set: All Available Data

Figure 2.19.25 Correlation of Change from Baseline in Morning Pre-dose Trough FEV_1 at Week 24 With SGRQ Total Score Over Weeks 12-24
Analysis Set: All Available Data

Figure 2.19.26 Correlation of Change from Baseline in Morning Pre-dose Trough FEV_1 Over Week 24 With Morning Pre-dose Trough FEV_1 Over Weeks 12-24
Analysis Set: All Available Data

Figure 2.19.27 Correlation of Change from Baseline in Morning Pre-dose Trough FEV_1 Over Week 24 With TDI Focal Score Over Weeks 12-24
Analysis Set: All Available Data

Figure 2.19.28 Correlation of Change from Baseline in Morning Pre-dose Trough FEV_1 Over Week 24 With Peak Change from Baseline in FEV_1 Over Weeks 12-24
Analysis Set: All Available Data

Figure 2.19.29 Correlation of Change from Baseline in Morning Pre-dose Trough FEV_1 Over Week 24 With SGRQ Total Score Over Weeks 12-24
Analysis Set: All Available Data

Figure 2.19.30 Correlation of Change from Baseline in Morning Pre-dose Trough FEV_1 Over Weeks 12-24 With TDI Focal Score Over Weeks 12-24
Analysis Set: All Available Data

Figure 2.19.31 Correlation of Change from Baseline in Morning Pre-dose Trough FEV_1 Over Weeks 12-24 With Peak Change from Baseline in FEV_1 Over Weeks 12-24
Analysis Set: All Available Data

Figure 2.19.32 Correlation of Change from Baseline in Morning Pre-dose Trough FEV_1 Over Weeks 12-24 With SGRQ Total Score Over Weeks 12-24
Analysis Set: All Available Data

Figure 2.19.33 Correlation of Change from Baseline in Morning Pre-dose Trough FEV_1 Over Weeks 12-24 With Rescue Ventolin Use Over 24 Weeks
Analysis Set: All Available Data

Figure 2.19.34 Correlation of TDI Focal Score Over 24 Weeks With Morning Pre-dose Trough FEV_1 Over Weeks 12-24
Analysis Set: All Available Data

Figure 2.19.35 Correlation of TDI Focal Score Over 24 Weeks With TDI Focal Score Over Weeks 12-24
Analysis Set: All Available Data

Figure 2.19.36 Correlation of TDI Focal Score Over 24 Weeks With Peak Change from Baseline in FEV_1 Over Weeks 12-24
Analysis Set: All Available Data

Figure 2.19.37 Correlation of TDI Focal Score Over 24 Weeks With SGRQ Total Score Over Weeks 12-24
Analysis Set: All Available Data

Figure 2.19.38 Correlation of TDI Focal Score Over Weeks 12-24 With Peak Change from Baseline in FEV_1 Over Weeks 12-24
Analysis Set: All Available Data

Figure 2.19.39 Correlation of TDI Focal Score Over Weeks 12-24 With SGRQ Total Score Over Weeks 12-24
Analysis Set: All Available Data

Figure 2.19.40 Correlation of TDI Focal Score Over Weeks 12-24 With Rescue Ventolin Use Over 24 Weeks
Analysis Set: All Available Data

Figure 2.19.41 Correlation of Peak Change from Baseline in FEV_1 Within 2 Hours Post-dose at Week 24 With Morning Pre-dose Trough FEV1 Over Weeks 12-24
Analysis Set: All Available Data

Figure 2.19.42 Correlation of Peak Change from Baseline in FEV_1 Within 2 Hours Post-dose at Week 24 With TDI Focal Score Over Weeks 12-24
Analysis Set: All Available Data

Figure 2.19.43 Correlation of Peak Change from Baseline in FEV_1 Within 2 Hours Post-dose at Week 24 With Peak Change from Baseline in FEV_1 Over Weeks 12-24
Analysis Set: All Available Data

Figure 2.19.44 Correlation of Peak Change from Baseline in FEV_1 Within 2 Hours Post-dose at Week 24 With SGRQ Total Score Over Weeks 12-24
Analysis Set: All Available Data

Figure 2.19.45 Correlation of Peak Change from Baseline in FEV_1 Within 2 Hours Post-dose Over 24 Weeks With Morning Pre-dose Trough FEV_1 Over Weeks 12-24
Analysis Set: All Available Data

Figure 2.19.46 Correlation of Peak Change from Baseline in FEV_1 Within 2 Hours Post-dose Over 24 Weeks With TDI Focal Score Over Weeks 12-24
Analysis Set: All Available Data

Figure 2.19.47 Correlation of Peak Change from Baseline in FEV_1 Within 2 Hours Post-dose Over 24 Weeks With Peak Change from Baseline in FEV_1 Over Weeks 12-24
Analysis Set: All Available Data

Figure 2.19.48 Correlation of Peak Change from Baseline in FEV_1 Within 2 Hours Post-dose Over 24 Weeks With SGRQ Total Score Over Weeks 12-24
Analysis Set: All Available Data

Table 2.19.1 Pearson Correlation Matrix of Key Efficacy Endpoints (Excluding Correlations with Efficacy Endpoints Over Weeks 12-24)
Analysis Set: All Available Data

GFF MDI, GP MDI, FF MDI, and Placebo MDI Treatments Combined (N=xxxx)	Morning Pre-dose Trough FEV_1		TDI Focal Score Over 24 Weeks	Peak Change from Baseline in FEV_1		SGRQ Total Score	Rescue Ventolin HFA Use Over 24 Weeks
	At Week 24	Over 24 Weeks		At Week 24	Over 24 Weeks	At Week 24	
Change from Baseline in Morning Pre-dose Trough FEV_1 at Week 24	NA	0.xxx	0.xxx	0.xxx	0.xxx	0.xxx	0.xxx
Change from Baseline in Morning Pre-dose Trough FEV_1 Over Week 24		NA	0.xxx	0.xxx	0.xxx	0.xxx	0.xxx
TDI Focal Score Over 24 Weeks			NA	0.xxx	0.xxx	0.xxx	0.xxx
Peak Change from Baseline in FEV_1 Within 2 Hours Post-dose at Week 24				NA	0.xxx	0.xxx	0.xxx
Peak Change from Baseline in FEV_1 Within 2 Hours Post-dose Over 24 Weeks					NA	0.xxx	0.xxx
Change from Baseline in SGRQ Total Score at Week 24						NA	0.xxx
Change from Baseline in Rescue Ventolin HFA Use Over 24 Weeks							NA

GFF MDI, GP MDI, FF MDI, and Placebo MDI Treatments Combined (N=xxxx)	Morning Pre-dose Trough FEV_1		TDI Focal Score Over 24 Weeks	Peak Change from Baseline in FEV_1		SGRQ Total Score	Rescue Ventolin HFA Use Over 24 Weeks
	At Week 24	Over 24 Weeks		At Week 24	Over 24 Weeks	At Week 24	

Abbreviations: FEV_1=forced expiratory volume in 1 second; FF=formoterol fumarate; GFF=glycopyrronium and formoterol fumarate; GP=glycopyrronium; HFA = hydrofluoroalkane; MDI=metered dose inhaler; NA=not applicable; SGRQ=St. George's Respiratory Questionnaire; TDI=Transition Dyspnea Index.
Note: All column headings represent change from baseline with the exception of TDI focal score.

Report generated by program: pt003014/sasdir/programs/statout/t021901.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Also repeat for each treatment (GFF, GP, FF, and Placebo).

Table 2.19.2 Pearson Correlation Matrix of Key Efficacy Endpoints Over Weeks 12-24 With Other Key Efficacy Endpoints and With Each Other
Analysis Set: All Available Data

	Morning Pre-dose Trough FEV_1 Over Weeks 12-24	TDI Focal Score Over Weeks 12-24	Peak Change from Baseline in FEV_1 Over Weeks 12-24	SGRQ Total Score Over Weeks 12-24	Rescue Ventolin HFA Use Over 24 Weeks
Change from Baseline in Morning Pre-dose Trough FEV_1 at Week 24	0.xxx	0.xxx	0.xxx	0.xxx	See Table 2.19.1
Change from Baseline in Morning Pre-dose Trough FEV_1 Over Week 24	0.xxx	0.xxx	0.xxx	0.xxx	See Table 2.19.1
Change from Baseline in Morning Pre-dose Trough FEV_1 Over Weeks 12-24	NA	0.xxx	0.xxx	0.xxx	0.xxx
TDI Focal Score Over 24 Weeks	0.xxx	0.xxx	0.xxx	0.xxx	See Table 2.19.1
TDI Focal Score Over Weeks 12-24	See above	NA	0.xxx	0.xxx	0.xxx
Peak Change from Baseline in FEV_1 Within 2 Hours Post-dose at Week 24	0.xxx	0.xxx	0.xxx	0.xxx	See Table 2.19.1
Peak Change from Baseline in FEV_1 Within 2 Hours Post-dose Over 24 Weeks	0.xxx	0.xxx	0.xxx	0.xxx	See Table 2.19.1
Peak Change from Baseline Within 2 Hours Post-dose Over Weeks 12-24	See above	See above	NA	0.xxx	0.xxx

	Morning Pre-dose Trough FEV_1 Over Weeks 12-24	TDI Focal Score Over Weeks 12-24	Peak Change from Baseline in FEV_1 Over Weeks 12-24	SGRQ Total Score Over Weeks 12-24	Rescue Ventolin HFA Use Over 24 Weeks
Change from Baseline in SGRQ Total Score at Week 24	0.xxx	0.xxx	0.xxx	0.xxx	See Table 2.19.1
Change from Baseline in SGRQ Total Score Over Weeks 12-24	See above	See above	See above	NA	0.xxx
Change from Baseline in Rescue Ventolin HFA Use Over 24 Weeks	See above	See above	See above	See above	NA

Abbreviations: FEV_1=forced expiratory volume in 1 second; FF=formoterol fumarate; GFF=glycopyrronium and formoterol fumarate; GP=glycopyrronium; HFA = hydrofluoroalkane; MDI=metered dose inhaler; NA=not applicable; SGRQ=St. George's Respiratory Questionnaire; TDI=Transition Dyspnea Index.
Note: All column headings represent change from baseline with the exception of TDI focal score.

Report generated by program: pt003014/sasdir/programs/statout/t021902.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Also repeat for each treatment (GFF, GP, FF, and Placebo).

Subgroup Analyses

Table 2.20.x Subject Disposition by Region and Country: <Region Subgroup or Country>
Analysis Set: All Subjects Randomized

	GFF MDI 14.4/9.6 µg (N=xxx)	FF MDI 9.6 µg (N=xxx)	GP MDI 14.4 µg (N=xxx)	Placebo MDI (N=xxx)	All Subjects (N=xxxx)
	n (%)	n (%)	n (%)	n (%)	n (%)
Not Treated	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Treated	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Completed Week 12	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Completed Week 24	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Completed Follow-up Telephone Call	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Early Discontinuation [a]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
ITT Population [b]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PP Population [c]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Symptomatic Population [d]					
Rescue Ventolin User Population [e]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Safety Population [f]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

[a] Early discontinuation was defined as failure to complete both the final visit and the Follow-up Telephone Call.
[b] The Intent-To-Treat (ITT) Population was defined as all subjects who were randomized to treatment and received at least one dose of study treatment.
[c] The Per Protocol (PP) Population was a subset of the ITT Population defined as all subjects with post-randomization data obtained prior to a major protocol deviation. Data obtained after any major protocol deviation were excluded. Since receiving the wrong treatment is a major protocol deviation, subjects in the PP Population were analyzed according to the treatment they received. Post-randomization visits will be excluded from the per protocol set if there is no evidence in the diary that study medication was used the evening prior to the scheduled visit.
[d] The Symptomatic Population was defined as all subjects in the ITT Population with CAT scores of >=15 at Visit 4.
[e] The Rescue Ventolin User Population was defined as all subjects in the ITT Population with average baseline rescue Ventolin use of ≥1 puff/day.
[f] The Safety Population was defined as all subjects who were randomized to treatment and received at least one dose of the study treatment.

Region Subgroup/Country Category includes the following:
Table 2.20..1 Japan vs. Non-Japan,

Table 2.21.x Reason for Early Discontinuation by Region and Country: <Region Subgroup or Country>
Analysis Set: All Subjects Randomized

	GFF MDI 14.4/9.6 µg (N=xxx)	FF MDI 9.6 µg (N=xxx)	GP MDI 14.4 µg (N=xxx)	Placebo MDI (N=xxx)	All Subjects (N=xxxx)
	n (%)	n (%)	n (%)	n (%)	n (%)
Early Discontinuation	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reason for Early Discontinuation					
Adverse Event(s)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Administrative Reasons	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lack of Efficacy	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject Discretion	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Withdrawal of Consent	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
COPD	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Investigator Considers It to Be in the Best Interest of Subject	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<Specified Reason>	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject Lost to Follow-up	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
On or Before Week 24	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
After Week 24	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Major Protocol Violation	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<Specified Reason>	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Protocol-specified Discontinuation Criteria [a]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Heart Rate Increase	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Systolic Blood Pressure Increase	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Prescription of Any Prohibited Medications	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Decrease in Creatinine Clearance	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Hepatic Impairment	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
QTcF Increase	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
COPD Exacerbations	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
eDiary Non-Compliance	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Other	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Screen Failure (subject randomized in error)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: Reasons of Other are listed by subject in Listing 1.2.
[a] As per Protocol Section 5.7, except for eDiary non-compliance which is per Protocol Section 7.1.3.

Report generated by program: pt003014/sasdir/programs/statout/t0221.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmers; Sort by descending frequency of major category using All Subjects column. Within major category, sort by descending frequency of subcategory using All Subjects column.

Table 2.22.1.x Demographics and Baseline Characteristics by Region and Country: <Region Subgroup or Country>
Analysis Set: ITT Population

Parameter	GFF MDI 14.4/9.6 µg (N=xxx)	FF MDI 9.6 µg (N=xxx)	GP MDI 14.4 µg (N=xxx)	Placebo MDI (N=xxx)	All Subjects (N=xxxx)
n (%) [a]	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Age (Years)[b]					
N	xxx	xxx	xxx	xxx	xxxx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum	xx	xx	xx	xx	xx
Maximum	xx	xx	xx	xx	xx
Age Group, n (%)					
Age < 65 years	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Age >= 65 years	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Missing	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)
Gender, n (%)					
Male	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Female	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Missing	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)
Race, n (%)					
Black or African American	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
White	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Native Hawaiian or Other Pacific Islander	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
American Indian or Alaska Native	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Asian	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Australia or New	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Parameter	GFF MDI 14.4/9.6 µg (N=xxx)	FF MDI 9.6 µg (N=xxx)	GP MDI 14.4 µg (N=xxx)	Placebo MDI (N=xxx)	All Subjects (N=xxxx)
Zealand (Indigenous)					
Other	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ethnicity, n (%)					
Hispanic	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Non-Hispanic	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Missing	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)
Total CAT Score [c]					
N	xxx	xxx	xxx	xxx	xxxx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum	xx.x	xx.x	xx.x	xx.x	xx.x
Maximum	xx.x	xx.x	xx.x	xx.x	xx.x
< 10, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
>=10, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
< 15, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
>=15, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
< 20, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
>=20, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
MMRC Grade [d]					
N	xxx	xxx	xxx	xxx	xxx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum	xx.x	xx.x	xx.x	xx.x	xx.x
Maximum	xx.x	xx.x	xx.x	xx.x	xx.x
< 2, n (%)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
>=2, n (%)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Missing, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Used Inhaled Corticosteroids at Baseline [e], n (%)					
Yes	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

Parameter	GFF MDI 14.4/9.6 µg (N=xxx)	FF MDI 9.6 µg (N=xxx)	GP MDI 14.4 µg (N=xxx)	Placebo MDI (N=xxx)	All Subjects (N=xxxx)
No	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Missing	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Smoking Status [f], n (%)					
Current Smoker	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Former Smoker	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Missing	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of Years Smoked					
n	xxx	xxx	xxx	xxx	xxx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum	xx.x	xx.x	xx.x	xx.x	xx.x
Maximum	xx.x	xx.x	xx.x	xx.x	xx.x
Average Number of Cigarettes Smoked Per Day					
n	xxx	xxx	xxx	xxx	xxx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum	xx.x	xx.x	xx.x	xx.x	xx.x
Maximum	xx.x	xx.x	xx.x	xx.x	xx.x
Number of Pack Years Smoked [g]					
n	xxx	xxx	xxx	xxx	xxx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum	xx.x	xx.x	xx.x	xx.x	xx.x
Maximum	xx.x	xx.x	xx.x	xx.x	xx.x
Weight (kg)					
n	xxx	xxx	xxx	xxx	xxx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.x	xx.x	xx.x	xx.x	xx.x

Parameter	GFF MDI 14.4/9.6 µg (N=xxx)	FF MDI 9.6 µg (N=xxx)	GP MDI 14.4 µg (N=xxx)	Placebo MDI (N=xxx)	All Subjects (N=xxxx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum	xx.x	xx.x	xx.x	xx.x	xx.x
Maximum	xx.x	xx.x	xx.x	xx.x	xx.x
Height (cm)					
n	xxx	xxx	xxx	xxx	xxx
Mean	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
SD	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
Median	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
Minimum	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
Maximum	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
BMI (kg/m2)					
n	xxx	xxx	xxx	xxx	xxx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum	xx.x	xx.x	xx.x	xx.x	xx.x
Maximum	xx.x	xx.x	xx.x	xx.x	xx.x

[a] N refers to overall ITT and n is n within in the category; % refers to percentage of overall population. "
[b] Age is age at Visit 4. The remaining characteristics were based on data from Screening visits prior to the start of the study.
[c] CAT = COPD Assessment Test. The total score is the sum of eight CAT item scores (Range: 0-40)
[d] MMRC = Modified Medical Research Council Scale, grades range between 0 and 4, where 4 represents the highest level of breathlessness.
[e] 'At baseline' means that the medication was taken on the day of the first dose of study medication.
[f] Former Smoker was defined as those who have stopped smoking for at least 6 weeks prior to first Screening Visit.
[g] Number of pack years smoked = (number of cigarettes per day / 20) x number of years smoked.

Notes to Programmer: Calculate BMI using Height at Visit 1. BMI = weight (kg)/height (m)^2.
Keep the summary for a parameter in the same page when breaking the table into multiple pages. Repeat titles, column headers and footnotes on each page. The race/ethnicities of Native Hawaiian or other Pacific Islander OR American Indian or Alaska Native OR Australia or New Zealand (indigenous) can be removed from this table if they do not exist in the database.

Region Subgroup/Country Category includes the following:
Table 2.22.1 *Japan vs. Non-Japan,*
Table 2.22.2 *China*
Table 2.22.3 *Asia*
Table 2.22.4 *EU*
Table 2.22.5 *US*
Table 2.22.6 *Czech Republic*
Table 2.22.7 *Germany*
Table 2.22.8 *Hungary*
Table 2.22.9 Poland
Table 2.22.10 Russia
Table 2.22.11 South Korea
Table 2.22.12 Taiwan
Table 2.22.13 U.K.)

Table 2.22.2 Demographics and Baseline Characteristics by GOLD Category
Analysis Set: ITT Population

Notes to Programmer: repeat table for each category; put row label at top of each iteration of the table above the columns headers: GOLD Category: <A or B or C or D>. Remove last row of table (GOLD Category).

Table 2.22.2 Demographics and Baseline Characteristics by GOLD Severity
Analysis Set: ITT Population

Note to Programmer: GOLD Severity is defined as GOLD 2, 3, and 4.

Table 2.23.x Screening Pre- and Post-Bronchodilator and Baseline Spirometry Parameters by Region and Country: <Region Subgroup or Country>
Analysis Set: ITT Population

	GFF MDI 14.4/9.6 µg (N=xxx)	FF MDI 9.6 µg (N=xxx)	GP MDI 14.4 µg (N=xxx)	Placebo MDI (N=xxx)	All Subjects (N=xxxx)
Screening FEV1 (% predicted)					
Pre-Ventolin HFA:					
n	xx	xx	xx	xx	xx
Mean	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
SD	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
25th Percentile	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Median	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
75th Percentile	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Minimum	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Maximum	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Post-Ventolin HFA:					
n	xx	xx	xx	xx	xx
Mean	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
SD	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
25th Percentile	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Median	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
75th Percentile	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Minimum	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Maximum	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Pre-Atrovent HFA:					
n	xx	xx	xx	xx	xx
Mean	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
SD	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
25th Percentile	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Median	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
75th Percentile	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Minimum	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Maximum	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Post-Atrovent HFA:					
n	xx	xx	xx	xx	xx

Mean	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
SD	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
25th Percentile	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Median	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
75th Percentile	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Minimum	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Maximum	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx

Notes to Programmer:

Repeat above for these Screening parameters:
Screening FEV1 (L) Pre-Bronchodilator
Screening FEV1 (L) Post-Bronchodilator
Screening FVC (% predicted) Pre-Bronchodilator
Screening FVC (% predicted) Post-Bronchodilator
Screening FVC (L) Pre-Bronchodilator
Screening FVC (L) Post-Bronchodilator

Also, provide for the following Baseline parameters:
Baseline FEV1 (% predicted)
Baseline FEV1 (L)
Baseline FVC (% predicted)
Baseline FVC (L)

Show only 2 significant digits for the % predicted statistics.

Baseline is defined as the mean of all evaluable 60 and 30 minute pre-dose values on Day 1 (Visit 4).

Table 2.24.1.x Severity and Duration of COPD by Region and Country: <Region Subgroup or Country>
Analysis Set: ITT Population

	GFF MDI 14.4/9.6 µg (N=xxx)	FF MDI 9.6 µg (N=xxx)	GP MDI 14.4 µg (N=xxx)	Placebo MDI (N=xxx)
COPD Severity [a], n (%)				
Moderate (GOLD 2)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Severe (GOLD 3)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Very Severe (GOLD 4)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Duration of COPD (yrs) [b]				
n	xxx	xxx	xxx	xxx
Mean	xx.x	xx.x	xx.x	xx.x
SD	xx.x	xx.x	xx.x	xx.x
25th Percentile	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x
75th Percentile	xx.x	xx.x	xx.x	xx.x
Minimum	xx.x	xx.x	xx.x	xx.x
Maximum	xx.x	xx.x	xx.x	xx.x
GOLD Category, n (%)				
A	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
B	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
C	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
D	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

[a] Severity of COPD defined in Appendix 3 of the protocol was based on the non-missing post-Ventolin HFA assessment at Screening Visit 2 (or if the assessment was missing, the non-missing post-Atrovent assessment at Screening Visit 3).
[b] The duration of COPD is calculated relative to the start of study treatment Day 1 (Visit 4).

Report generated by program: pt003014/sasdir/programs/statout/t022401.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Duration of COPD = (First Dose date of Study Treatment - Date COPD First Diagnosed)/365.25, where day of COPD diagnosed is assumed to be the 1st of the month. Add a footnote noting how many missing values there are for severity if this is true for the final data.

Table 2.24.2 Severity and Duration of COPD by GOLD Category
Analysis Set: ITT Population

<GOLD Category>

	GFF MDI 14.4/9.6 µg (N=xxx)	FF MDI 9.6 µg (N=xxx)	GP MDI 14.4 µg (N=xxx)	Placebo MDI (N=xxx)	All Subjects (N=xxxx)
n (%) [a]	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
COPD Severity [a], n (%)					
Moderate (GOLD 2)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Severe (GOLD 3)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Very Severe (GOLD 4)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx(xx.x)
Duration of COPD (yrs) [b]					
n	xxx	xxx	xxx	xxx	xxxx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.x	xx.x	xx.x	xx.x	xx.x
25th Percentile	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x	xx.x
75th Percentile	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum	xx.x	xx.x	xx.x	xx.x	xx.x
Maximum	xx.x	xx.x	xx.x	xx.x	xx.x

[a] Severity of COPD defined in Appendix 3 of the protocol was based on the non-missing post-Ventolin HFA assessment at Screening Visit 2 (or if the assessment was missing, the non-missing post-Atrovent assessment at Screening Visit 3).
[b] The duration of COPD is calculated relative to the start of study treatment Day 1 (Visit 4).

Report generated by program: PT003014/sasdir/programs/statout/t022402.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Duration of COPD = (First Dose date of Study Treatment - Date COPD First Diagnosed)/365.25, where day of COPD diagnosed is assumed to be the 1st of the month. Add a footnote noting how many missing values there are for severity if this is true for the final data.

Table 2.24.3 Severity and Duration of COPD by GOLD Severity
Analysis Set: ITT Population

Table 2.25.1.x Reversibility to Ventolin HFA by Region and Country: <Region Subgroup or Country>
Analysis Set: ITT Population

Table 2.25.2 Reversibility to Ventolin HFA by GOLD Category
Analysis Set: ITT Population

Table 2.25.3 Reversibility to Ventolin HFA by GOLD Severity
Analysis Set: ITT Population

Table 2.26.1.x Reversibility to Atrovent HFA by Region and Country: <Region Subgroup or Country>
Analysis Set: ITT Population

Table 2.26.2 Reversibility to Atrovent HFA by GOLD Category
Analysis Set: ITT Population

Table 2.26.3 Reversibility to Atrovent HFA by GOLD Severity
Analysis Set: ITT Population

Table 2.27.1.x Study Treatment Exposure and Compliance by Region and Country: <Region Subgroup or Country>
Analysis Set: Safety Population

<Region Subgroup: <subcategory>>

Note that this does not apply when tabulation is for an individual country.

		GFF MDI 14.4/9.6 µg (N=xxx)	FF MDI 9.6 µg (N=xxx)	GP MDI 14.4 µg (N=xxx)	Placebo MDI (N=xxx)	All Subjects (N=xxxx)
Exposure [a]	n	xxx	xxx	xxx	xxx	xxx
	Mean	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
	SD	xx.x	xx.x	xx.x	xx.x	xx.x
	Median	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
	Minimum	xxx	xxx	xxx	xxx	xxx
	Maximum	xxx	xxx	xxx	xxx	xxx
Total Person-Years of Exposure [b]		xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Number of Puffs of Study Medication	n	xxx	xxx	xxx	xxx	xxx
	Mean	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
	SD	xx.x	xx.x	xx.x	xx.x	xx.x
	Median	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
	Minimum	xxx	xxx	xxx	xxx	xxx
	Maximum	xxx	xxx	xxx	xxx	xxx
Percent Compliance [c], n (%)	0 - < 20%	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)
	20 - < 40%	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)
	40 - < 60%	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)
	60 - < 80%	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)
	80 - 100%	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)
	>100 - 120%	x(xx.x)	x(xx.x)	x(xx.x)	x(xx.x)	x(xx.x)
	>120%	x(xx.x)	x(xx.x)	x(xx.x)	x(xx.x)	x(xx.x)
	Missing	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)

n	xxx	xxx	xxx	xxx	xxx
Mean	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
SD	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
Minimum	xxx	xxx	xxx	xxx	xxx
Maximum	xxx	xxx	xxx	xxx	xxx

[a] Exposure (days) = (End date of treatment – Date of first dose of treatment) + 1.
[b] Total person-years of exposure for a treatment group is the total exposure in the study across all subjects in the treatment.
[c] Percent compliance is defined as (total number of puffs of study treatment taken on a study day/total expected puffs taken on a study day) averaged across all days of a subject's dosing between start of study treatment and last day on study treatment x 100.
The expected number of puffs on dates prior to the last date of treatment was 4.
The expected number of puffs for a test day which was the last date of treatment was 2.
The expected number of puffs for the last date of treatment which was not a test day was 4 when a PM dose was taken and then 2 otherwise.

Report generated by program: pt003014/sasdir/programs/statout/t022701.sas Version YYYY-MM-DD xx:xx (Page n of N)

Table 2.27.2 Study Treatment Exposure and Compliance by GOLD Category
Analysis Set: Safety Population

Table 2.27.3 Study Treatment Exposure and Compliance by GOLD Severity
Analysis Set: Safety Population

Table 2.28.1.x Morning Pre-dose Trough FEV_1 (L) by Region and Country: <Region Subgroup or Country>
Analysis Set: ITT Population

<Region Subgroup: <subcategory>>

Note that this does not apply when tabulation is for an individual country.

			LS Mean Differences Between Treatments		
				FF MDI	GP MDI
Treatment	Baseline FEV1	Change From Baseline	Placebo MDI	9.6 µg	14.4 µg
Over 24 Weeks					
GFF MDI 14.4/9.6 µg					
n	Xx				
Mean	x.xxx				
SD	x.xxx				
Median	x.xxx				
Min-Max	x.xxx-x.xxx				
LS Mean (SE)		x.xxx (x.xxxx)	x.xxx (x.xxxx)	x.xxx (x.xxxx)	x.xxx (x.xxxx)
95% CI		(x.xxx, x.xxx)	(x.xxx, x.xxx)	(x.xxx, x.xxx)	(x.xxx, x.xxx)
P-value			x.xxxx	x.xxxx	x.xxxx
FF MDI 9.6 µg					
n	xx				
Mean	x.xxx				
SD	x.xxx				
Median	x.xxx				
Min-Max	x.xxx-x.xxx				
LS Mean (SE)		x.xxx (x.xxxx)	x.xxx (x.xxxx)	Not Applicable	x.xxx (x.xxxx)
95% CI		(x.xxx, x.xxx)	(x.xxx, x.xxx)		(x.xxx, x.xxx)
P-value			x.xxxx		x.xxxx
GP MDI 14.4 µg					
n	xx				
Mean	x.xxx				
SD	x.xxx				

<Region Subgroup: <subcategory>>

Note that this does not apply when tabulation is for an individual country.

			LS Mean Differences Between Treatments		
Treatment	Baseline FEV1	Change From Baseline	Placebo MDI	FF MDI 9.6 µg	GP MDI 14.4 µg
Median	x.xxx				
Min-Max	x.xxx-x.xxx				
LS Mean (SE)		x.xxx (x.xxxx)	x.xxx (x.xxxx)	Shown Above	Not Applicable
95% CI		(x.xxx, x.xxx)	(x.xxx, x.xxx)		
P-value			x.xxxx		
Placebo					
n	xx				
Mean	x.xxx				
SD	x.xxx				
Median	x.xxx				
Min-Max	x.xxx-x.xxx				
LS Mean (SE)		x.xxx (x.xxxx)	Not Applicable	Shown Above	Shown Above
95% CI		(x.xxx, x.xxx)			

Note to Programmer: Repeat for 12-24 Weeks and for each post-baseline visit from Week 2 to Week 24. The raw change from baseline will be added for each individual visit, but not for 4-24 weeks or 12-24 weeks. Do not split a treatment across a page. The baseline summary statistics are based on subjects who were included in the model used for analysis. (.e.g., subjects who had at least one data point post-baseline from Week 2 to Week 24 and had non-missing data for all covariates used for the analysis). Repeat for each subgroup category.

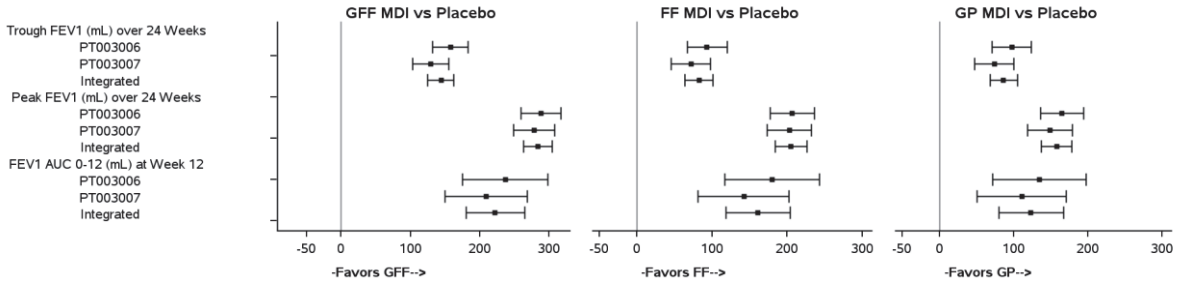
LS Mean = least squares mean from the linear repeated measures model which included the following covariates: baseline FEV1, percent reversibility to Ventolin HFA, treatment, visit, and treatment by visit interaction.

Report generated by program: pt003014/sasdir/programs/statout/t022801.sas Version YYYY-MM-DD hh:mm (Page n of N)

Figure 2.28.1.1 Forest Plot for Morning Pre-dose Trough FEV_1 (L) ± SE (Regions/Countries)
Analysis Set: ITT Population

Notes to Programmer: Use the example 2-page portrait-orientation forest plot below. Replace PT003006, PT003007, and Integrated with the regional subgroups and countries. USE THIS EXAMPLE FOR ALL REGIONS/COUNTRIES FOREST PLOTS.
Replace Trough FEV1 row label with 'Morning Trough FEV1 at Week 24'.
Replace Peak FEV1 row label with 'Morning Trough FEV1 Over 24 Weeks'.
Replace FEV1 AUC 0-12 row label with 'Morning Pre-dose Trough FEV1 over Weeks 12-24.

(Programmers: This is Page 1 with Comparisons of GFF MDI to Placebo, FF MDI, and GP MDI).



(Programmers: This is Page 2 with Comparisons of FF MDI and GP MDI to Placebo.)

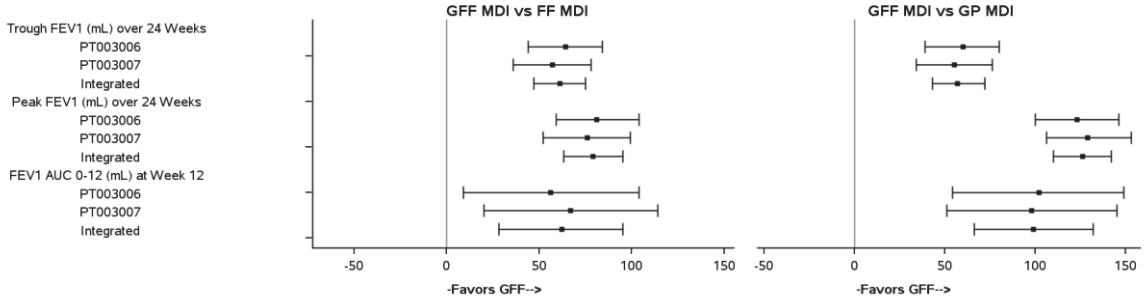
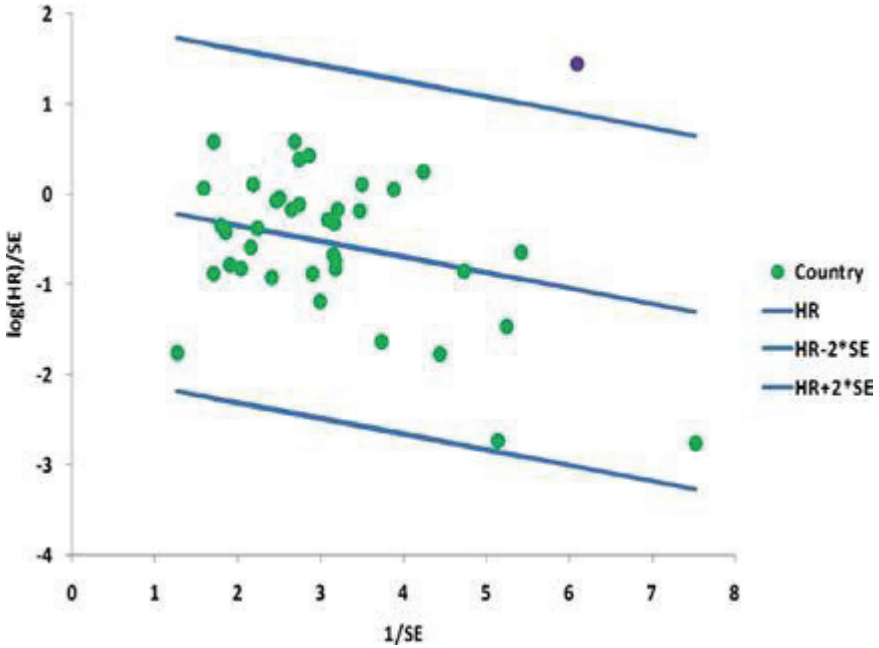


Figure 2.28.1.2.1 Galbraith Plot for Adjusted Mean Change From Baseline in Morning Pre-dose Trough FEV_1 (L) ± SE at Week 24 (All Countries)
Analysis Set: ITT Population



Notes to Programmer: y axis with "Effect Estimate/SE". Replace 'HR' with "Estimate".

Figure 2.28.1.2.2 Galbraith Plot for Adjusted Mean Change From Baseline in Morning Pre-dose Trough FEV_1 (L) ± SE Over 24 Weeks (All Countries)
Analysis Set: ITT Population

Figure 2.28.1.2.3 Galbraith Plot for Adjusted Mean Change From Baseline in Morning Pre-dose Trough FEV_1 (L) ± SE Over Weeks 12-24 (All Countries)
Analysis Set: ITT Population

Figure 2.28.1.3.1 Q-Q Plot for Adjusted Mean Change From Baseline in Morning Pre-dose Trough FEV_1 (L) ± SE at Week 24 (All Countries)
Analysis Set: ITT Population

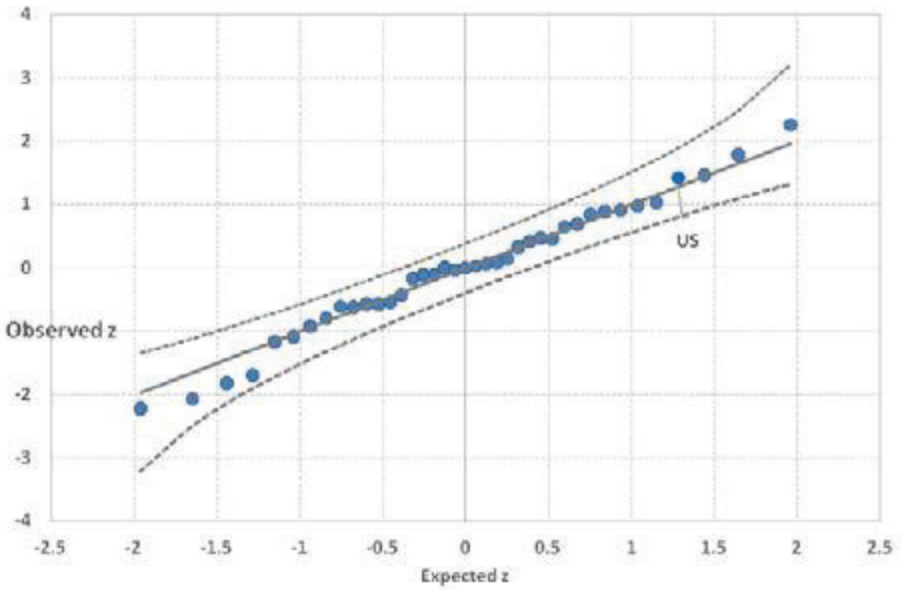


Figure 2.28.1.3.2 Q-Q Plot for Adjusted Mean Change From Baseline in Morning Pre-dose Trough FEV_1 (L) ± SE Over 24 Weeks (All Countries)
Analysis Set: ITT Population

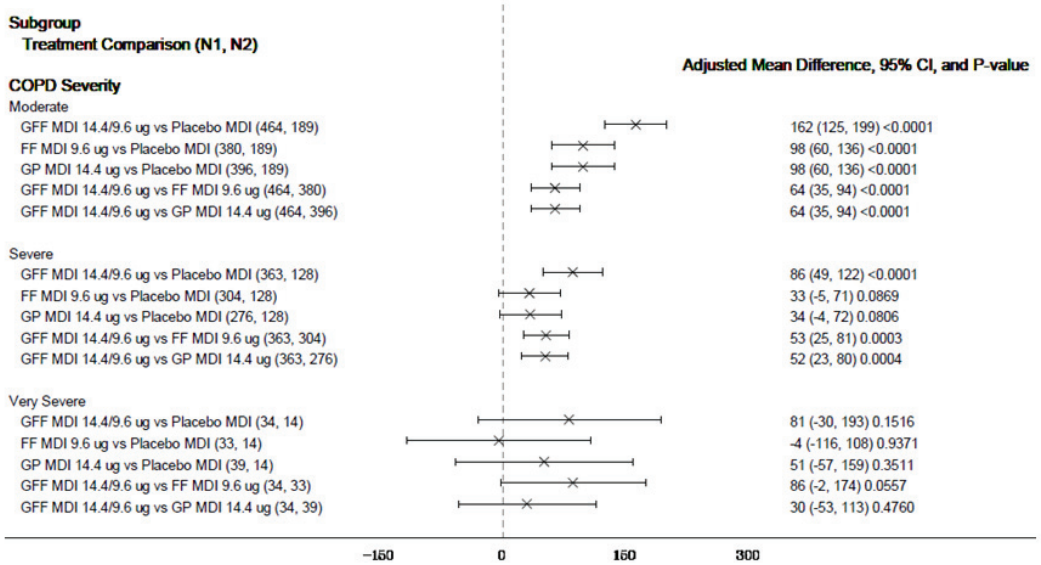
Figure 2.28.1.3.3 Q-Q Plot for Adjusted Mean Change From Baseline in Morning Pre-dose Trough FEV_1 (L) ± SE Over Weeks 12-24 (All Countries)
Analysis Set: ITT Population

Table 2.28.2 Morning Pre-dose Trough FEV_1 (L) by GOLD Category
Analysis Set: ITT Population

Figure 2.28.2.1 Forest Plot for Morning Pre-dose Trough FEV_1 (L) ± SE at Week 24 by GOLD Category
Analysis Set: ITT Population

Notes to Programmer: Please replace GOLD Severity in the example below with GOLD Category. USE THIS EXAMPLE FOR ALL GOLD FOREST PLOTS.

Figure 3-46. Forest Plot of Change from Baseline in Morning Pre-Dose Trough FEV_1 (L) at Week 24 By COPD Severity (PT003006/PT003007 ITT Population)



Abbreviations: CI=confidence interval; COPD=chronic obstructive pulmonary disease; FEV_1=forced expiratory volume in 1 second; FF=formoterol fumarate; GFF=glycopyrronium and formoterol fumarate; GP=glycopyrronium; ITT=intent-to-treat; MDI=metered dose inhaler; N1=number of subjects for first treatment in comparison; N2=number of subjects for second treatment in comparison.

Source: ISE Table 2.21.4.

Figure 2.28.2.2 Forest Plot for Morning Pre-dose Trough FEV_1 (L) ± SE Over 24 Weeks by GOLD Category
Analysis Set: ITT Population

Figure 2.28.2.3 Forest Plot for Morning Pre-dose Trough FEV_1 (L) ± SE Over Weeks 12-24 by GOLD Category
Analysis Set: ITT Population

Table 2.28.3 Morning Pre-dose Trough FEV_1 (L) by GOLD Severity
Analysis Set: ITT Population

Figure 2.28.3.1 Forest Plot for Morning Pre-dose Trough FEV_1 (L) ± SE at Week 24 by GOLD Severity
Analysis Set: ITT Population

Figure 2.28.3.2 Forest Plot for Morning Pre-dose Trough FEV_1 (L) ± SE Over 24 Weeks by GOLD Severity
Analysis Set: ITT Population

Figure 2.28.3.3 Forest Plot for Morning Pre-dose Trough FEV_1 (L) ± SE Over Weeks 12-24 by GOLD Severity
Analysis Set: ITT Population

Table 2.29.x TDI Focal Score by Region and Country: <Region Subgroup or Country>
Analysis Set: ITT Population

			LS Mean Differences Between Treatments		
				FF MDI	GP MDI
Treatment	BDI Focal Score	TDI Focal Score	Placebo MDI	9.6 µg	14.4 µg
Over 24 Weeks					
GFF MDI 14.4/9.6 µg					
n	xx				
Mean	x.x				
SD	x.x				
Median	x.x				
Min-Max	x.x-x.x				
LS Mean (SE)		x.x (x.xx)	x.xx (x.xxx)	x.xx (x.xxx)	x.xx (x.xxx)
95% CI		(x.x, x.x)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xxx)
P-value			x.xxxx	x.xxxx	x.xxxx
FF MDI 9.6 µg					
n	xx				
Mean	x.x				
SD	x.x				
Median	x.x				
Min-Max	x.x-x.x				
LS Mean (SE)		x.x (x.xx)	x.xx (x.xxx)	Not Applicable	x.xx (x.xxx)
95% CI		(x.x, x.x)	(x.xx, x.xx)		(x.xx, x.xx)
P-value			x.xxxx		x.xxxx
GP MDI 14.4 µg					
n	xx				
Mean	x.x				
SD	x.x				
Median	x.x				
Min-Max	x.x-x.x				
LS Mean (SE)		x.x (x.xx)	x.xx (x.xxx)	Shown Above	Not Applicable

			LS Mean Differences Between Treatments		
Treatment	BDI Focal Score	TDI Focal Score	Placebo MDI	FF MDI 9.6 µg	GP MDI 14.4 µg
95% CI		(x.x, x.x)	(x.xx, x.xx)		
P-value			x.xxxx		
Placebo					
n	xx				
Mean	x.x				
SD	x.x				
Median	x.x				
Min-Max	x.x-x.x				
LS Mean (SE)		x.x (x.xx)	Not Applicable	Shown Above	Shown Above
95% CI		(x.x, x.x)			

Note to Programmer: Repeat for over Weeks 12-24 and for each post-baseline visit from Week 4 to Week 24. Descriptive statistics for the raw TDI will be added for each individual visit, but not for 0-24 weeks or Over Weeks 12-24. Do not split a treatment across a page. Repeat for each subgroup category.

LS Mean = least squares mean from the linear repeated measures model which included the following covariates: BDI focal score, percent reversibility to Ventolin HFA, visit, and treatment by visit interaction.

Report generated by program: pt003014/sasdir/programs/statout/t0229.sas Version YYYY-MM-DD hh:mm (Page n of N)

Figure 2.29.1 Forest Plot for TDI Focal Score ± SE (Regions/Countries)
Analysis Set: ITT Population

Notes to Programmer: show for Over 24 Weeks and for Over Weeks 12-24 (use the format of Figure 2.28.1.1).

Figure 2.29.2.1 Galbraith Plot for Adjusted Mean TDI Focal Score ± SE Over 24 Weeks (All Countries)
Analysis Set: ITT Population

Figure 2.29.2.2 Galbraith Plot for Adjusted Mean TDI Focal Score ± SE Over Weeks 12- 24 (All Countries)
Analysis Set: ITT Population

Figure 2.29.3.1 Q-Q Plot for Adjusted Mean TDI Focal Score ± SE Over 24 Weeks (All Countries)
Analysis Set: ITT Population

Figure 2.29.3.2 Q-Q Plot for Adjusted Mean TDI Focal Score ± SE Over Weeks 12-24 (All Countries)
Analysis Set: ITT Population

Table 2.30.1.1.x Peak Change From Baseline in FEV1 (L) Within 2 Hours Post-dose by Region and Country: <Region Subgroup or Country>
Analysis Set: ITT Population

Figure 2.30.1.1 Forest Plot for Peak Change from Baseline in FEV_1 (L) ± SE Within 2 Hours Post-dose (Regions/Countries)
Analysis Set: ITT Population

Figure 2.30.1.2.1 Galbraith Plot for Adjusted Mean Peak Change from Baseline in FEV_1 (L) ± SE at Week 24 (All Countries)
Analysis Set: ITT Population

Figure 2.30.1.2.2 Galbraith Plot for Adjusted Mean Peak Change from Baseline in FEV_1 (L) ± SE Over 24 Weeks (All Countries)
Analysis Set: ITT Population

Figure 2.30.1.2.3 Galbraith Plot for Adjusted Mean Peak Change from Baseline in FEV_1 (L) ± SE Over Weeks 12-24 (All Countries)
Analysis Set: ITT Population

Figure 2.30.1.3.1 Q-Q Plot for Adjusted Mean Peak Change from Baseline in FEV_1 (L) ± SE at Week 24 (All Countries)
Analysis Set: ITT Population

Figure 2.30.1.3.2 Q-Q Plot for Adjusted Mean Peak Change from Baseline in FEV_1 (L) ± SE Over 24 Weeks (All Countries)
Analysis Set: ITT Population

Figure 2.30.1.3.3 Q-Q Plot for Adjusted Mean Peak Change from Baseline in FEV_1 (L) ± SE Over Weeks 12-24 (All Countries)
Analysis Set: ITT Population

Table 2.30.2 Peak Change From Baseline in FEV1 (L) Within 2 Hours Post-dose by GOLD Category
Analysis Set: ITT Population

Figure 2.30.2.1 Forest Plot for Mean Peak Change from Baseline in FEV_1 (L) ± SE Within 2 Hours Post-dose by GOLD Category
Analysis Set: ITT Population

Table 2.30.3 Peak Change From Baseline in FEV1 (L) Within 2 Hours Post-dose by GOLD Severity
Analysis Set: ITT Population

Figure 2.30.3.1 Forest Plot for Mean Peak Change from Baseline in FEV_1 (L) ± SE Within 2 Hours Post-dose at Week 24 by GOLD Severity
Analysis Set: ITT Population

Figure 2.30.3.2 Forest Plot for Mean Peak Change from Baseline in FEV_1 (L) ± SE Within 2 Hours Post-dose Over 24 Weeks by GOLD Severity
Analysis Set: ITT Population

Figure 2.30.3.3 Forest Plot for Mean Peak Change from Baseline in FEV_1 (L) ± SE Within 2 Hours Post-dose Over Weeks 12-24 by GOLD Severity
Analysis Set: ITT Population

Table 2.31.1.x SGRQ Total Score (units) by Region and Country: < Region Subgroup or Country>
Analysis Set: ITT Population

Notes to Programmer: display descriptive statistics only, without model-based estimates. Remove the model footnote.

Figure 2.31.1.1 Forest Plot for SGRQ Total Score (units) ± SE at Week 24 by Region and Country
Analysis Set: ITT Population

Notes to Programmer: show for At Week 24 and for Over Weeks 12-24 (use the format of Figure 2.28.1.1).

Figure 2.31.2.1 Galbraith Plot for Adjusted Mean Change from Baseline in SGRQ Total Score (units) ± SE at Week 24 (All Countries)
Analysis Set: ITT Population

Figure 2.31.2.2 Galbraith Plot for Adjusted Mean Change from Baseline in SGRQ Total Score (units) ± SE Over Weeks 12-24 (All Countries)
Analysis Set: ITT Population

Figure 2.31.3.1 Q-Q Plot for Adjusted Mean Change from Baseline in SGRQ Total Score (units) ± SE at Week 24 (All Countries)
Analysis Set: ITT Population

Figure 2.31.3.2 Q-Q Plot for Adjusted Mean Change from Baseline in SGRQ Total Score (units) ± SE Over Weeks 12-24 (All Countries)
Analysis Set: ITT Population

Table 2.32.x Response in SGRQ Total Score (Achievment of a Minimum Clinically Important Difference Threshold of ≥4 Units on Average) by Region and Country: <Region Subgroup or Country>
Analysis Set: ITT Population

Notes to Programmer: Display descriptive statistics only, without model-based estimates. Remove the model footnote. Forest plots will show percentage with a response for Week 24 and also Over Weeks 12-24 for all regional subgroups and countries. Similar to Figure 2.28.1.1.

Figure 2.32 Forest Plot for Response in SGRQ Total Score ± 95% CI (Regions/Countries)
Analysis Set: ITT Population

Notes to Programmer: Forest plots will show percentage with a response for Week 24 and also Over Weeks 12-24 for all regional subgroups and countries (use the format of Figure 2.28.1.1).

Table 2.33.1.x Mean Daily Number of Puffs of Rescue Ventolin by Region and Country: <Region Subgroup or Country>
Analysis Set: ITT Population

Figure 2.33.1.1 Forest Plot for Change from Baseline in Daily Number of Puffs of Rescue Ventolin ± SE Over 24 Weeks (Regions/Countries)
Analysis Set: ITT Population

Notes to Programmer: show for Over 24 Weeks and for Over Weeks 12-24 (use the format of Figure 2.28.1.1).

Figure 2.33.1.2 Galbraith Plot for Adjusted Mean Change from Baseline in Daily Number of Puffs of Rescue Ventolin ± SE Over 24 Weeks (All Countries)
Analysis Set: ITT Population

Figure 2.33.1.3 Q-Q Plot for Adjusted Mean Change from Baseline in Daily Number of Puffs of Rescue Ventolin ± SE Over 24 Weeks (All Countries)
Analysis Set: ITT Population

Table 2.33.2.x Mean Daily Number of Puffs of Rescue Ventolin by Region and Country: <Region Subgroup or Country>
Analysis Set: Rescue Ventolin User Population

Figure 2.33.2.1 Forest Plot for Change from Baseline in Daily Number of Puffs of Rescue Ventolin ± SE (Regions/Countries)
Analysis Set: Rescue Ventolin User Population

Figure 2.33.2.2 Galbraith Plot for Adjusted Mean Change from Baseline in Daily Number of Puffs of Rescue Ventolin ± SE Over 24 Weeks (All Countries)
Analysis Set: Rescue Ventolin User Population

Figure 2.33.2.3 Q-Q Plot for Adjusted Mean Change from Baseline in Daily Number of Puffs of Rescue Ventolin ± SE Over 24 Weeks (All Countries)
Analysis Set: Rescue Ventolin User Population

Table 2.34 Change from Baseline in FEV_1 at 5 Min Post-dose on Day 1 by Region and Country: <Region Subgroup or Country>
Analysis Set: ITT Population

Figure 2.34.1 Forest Plot for FEV_1 at 5 Min Post-dose on Day 1 (Regions/Countries)
Analysis Set: ITT Population

Figure 2.34.2 Galbraith Plot for Adjusted Mean Change from Baseline in FEV_1 at 5 Min Post-dose ± SE on Day 1 (All Countries)
Analysis Set: ITT Population

Figure 2.34.3 Q-Q Plot for Adjusted Mean Change from Baseline in FEV_1 at 5 Min Post-dose ± SE on Day 1 (All Countries)
Analysis Set: ITT Population

Table 2.35 Change from Baseline in FEV_1 at 15 Min Post-dose on Day 1 by Region and Country: <Region Subgroup or Country>
Analysis Set: ITT Population

Figure 2.35.1 Forest Plot for FEV_1 at 15 Min Post-dose on Day 1 (Regions/Countries)
Analysis Set: ITT Population

Figure 2.35.2 Galbraith Plot for Adjusted Mean Change from Baseline in FEV_1 at 15 Min Post-dose ± SE on Day 1 (All Countries)
Analysis Set: ITT Population

Figure 2.35.3 Q-Q Plot for Adjusted Mean Change from Baseline in FEV_1 at 15 Min Post-dose ± SE (All Countries)
Analysis Set: ITT Population

Table 2.36 Interaction of Treatment and Subgroup for Each Subgroup Analysis
Analysis Set: ITT Population

	Treatment-by-Subgroup Interaction P-value (Subgroup Main Effect P-value)						
Subgroup Analysis	Change from baseline in pre-dose trough FEV_1	TDI Focal Score	Peak change from baseline in FEV_1 within 2 hours post-dose	Change from baseline in SGRQ total score	Change from baseline in mean daily number of puffs of rescue Ventolin HFA	Time to Onset at 5 min post-dose on Day 1 (change from baseline in FEV1 at 5 min post-dose)	Time to Onset at 15 min post-dose on Day 1 (change from baseline in FEV1 at 15 min post-dose)
Region Subgroup (Japan vs Non-Japan)	0.xxxx (x.xxxx)	0.xxxx (x.xxxx)	0.xxxx (x.xxxx)	Not Applicable	0.xxxx (x.xxxx)	0.xxxx (x.xxxx)	0.xxxx (x.xxxx)
Country	0.xxxx (x.xxxx)	0.xxxx (x.xxxx)	0.xxxx (x.xxxx)	Not Applicable	0.xxxx (x.xxxx)	0.xxxx (x.xxxx)	0.xxxx (x.xxxx)
GOLD Category A, B, C, and D	0.xxxx (x.xxxx)	Not Applicable	0.xxxx (x.xxxx)	Not Applicable	Not Applicable	Not Applicable	Not Applicable
GOLD Category 2, 3, and 4	0.xxxx (x.xxxx)	Not Applicable	0.xxxx (x.xxxx)	Not Applicable	Not Applicable	Not Applicable	Not Applicable

For each subgroup analysis, treatment-by-subgroup interaction was tested using the following model: baseline, percent reversibility to Ventolin HFA, treatment, visit, treatment, treatment-by-visit interaction, subgroup, and the treatment-by-subgroup interaction.

Report generated by program: pt003014/sasdir/programs/statout/t0237.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Baseline in the model is baseline FEV1 for the change in trough FEV_1 analyses and BDI for the TDI analyses.

Healthcare Resource Utilization

Table 2.37.1 Healthcare Resource Utilization: Number of Days Missed From Work
Analysis Set: Safety Population

Number of Days Missed From Work Per Subject	GFF MDI 14.4/9.6 µg (N=xxx)	FF MDI 9.6 µg (N=xxx)	GP MDI 14.4 µg (N=xxx)	Placebo MDI (N=xxx)	All Subjects (N=xxxx)
By Subject					
Unadjusted					
n	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum	xx	xx	xx	xx	xx
Maximum	xx	xx	xx	xx	xx
Adjusted (per year)					
n	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum	xx	xx	xx	xx	xx
Maximum	xx	xx	xx	xx	xx
By Family Members of Subject	xx	xx	xx	xx	xx
Unadjusted					
n	xx.x	xx.x	xx.x	xx.x	xx.x
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx	xx	xx	xx	xx
Minimum					
Maximum					

Number of Days Missed From Work Per Subject	GFF MDI 14.4/9.6 µg (N=xxx)	FF MDI 9.6 µg (N=xxx)	GP MDI 14.4 µg (N=xxx)	Placebo MDI (N=xxx)	All Subjects (N=xxxx)
REPEAT FOR 'Adjusted (per year)'					

Subjects with 'Not applicable' for number of days missed from work are excluded.
Adjusted (per year) summary statistics are those obtained when the number of days are extrapolated out to a 52 week period, based on the number of days observed during the subject's participation in Study PT003014.

Report generated by program: pt003014/sasdir/programs/statout/t023801.sas Version YYYY-MM-DD xx:xx Page n of N)

Notes to Programmer: For 'Adjusted (per year)', convert data to 52 weeks using the following formula:
52 x (weeks missed/xx weeks actually completed in study)

Table 2.37.2 Healthcare Resource Utilization by Relationship to COPD and Treatment
Analysis Set: Safety Population

COPD Related

Utilization Parameter	GFF MDI 14.4/9.6 µg (N=xxx)	FF MDI 9.6 µg (N=xxx)	GP MDI 14.4 µg (N=xxx)	Placebo MDI (N=xxx)	All Subjects (N=xxxx)
Telephone Calls to Health Care Provider					
Unadjusted					
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum	xx.x	xx.x	xx.x	xx.x	xx.x
Maximum	xx.x	xx.x	xx.x	xx.x	xx.x
Adjusted (per year)					
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum	xx.x	xx.x	xx.x	xx.x	xx.x
Maximum	xx.x	xx.x	xx.x	xx.x	xx.x
n of Subjects (%)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)

For the Telephone calls to HCP and Visits to HCP row header, show "Telephone Calls to Healthcare Provider, n of Subjects (%)" and "Visits to Healthcare Provider", n of Subjects (%). Same for ER Visits. For Hospitalizations row header, use "Hospitalizations, n of Subjects (%)". For Intubations row header, use "Intubations During

*Hospitalization, n of Subjects (%
of Subjects Hospitalized"*

Notes to Programmer:

Put "COPD Related' at the top of each page of this output.

Repeat for the following:
- *COPD Related Visits to Health Care Providers*
- *COPD Related ER Visits*

Repeat for Non-COPD Related. Put "Non-COPD Related' at the top of each page of this output.
Repeat for Combined which is defined as COPD Related and Non-COPD Related combined. Put 'COPD Related and Non-COPD Related' at the top of each page.
Then repeat format for the following items for hospitalizations:
- *COPD Related Hospitalizations*
- *COPD Related Number of Days in the Hospital*
- *COPD Related Number of Days in Intensive Care Unit (ICU)*
- *COPD Related Number of Days in Coronary Care Unit (CCU)*
- *COPD Related Intubations During Hospitalization.*

For Intubations During Hospitalization, do not show Mean, SD, Median, Minimum, or Maximum. N1 for this category is the number of subjects hospitalized in the treatment.

Repeat the hospitalization items for Drug-Related.
Repeat these for Non-COPD Related.
Repeat these for Combined which is defined as COPD Related and Non-COPD Related combined.

For Adjusted (per year) summary statistics, convert the Median, Minimum, and Maximum for each parameter to 52 weeks using the following formula: 52 x (weeks missed/xx weeks actually completed in study)

Adjusted (per year) summary statistics were those obtained when the number of utilization events were extrapolated out to a 52 week period, based on the number of utilization events observed during the subject's participation in Study PT003014.
If it was unknown whether a subject stayed in the ICU (CCU), the number of days in the ICU (CCU) was imputed as 0 days. If the subject reported a stay in the ICU (CCU), but the number of days was missing, then the number of days was imputed as the average of the number of days that subjects with non-missing data in the treatment group reported.
Report generated by program: pt003014/sasdir/programs/statout/t023802.sas Version YYYY-MM-DD xx:xx (Page n of N)

3. Safety

Adverse Events

Table 3.1.1 Overall Summary of Adverse Events
Analysis Set: Safety Population

	GFF MDI 14.4/9.6 µg (N=xxx)	FF MDI 9.6 µg (N=xxx)	GP MDI 14.4 µg (N=xxx)	Placebo MDI (N=xxx)	All Subjects (N=xxxx)
	n (%) [Events]	n (%) [Events]	n (%) [Events]]	n (%) [Events]	n (%) [Events]
Subjects With at Least One TEAE [a]	xx (xx.x) [xxx]	xx (xx.x) [xxx]	xx (xx.x) [xxx]	xx (xx.x) [xxx]	xx (xx.x) [xx.x]
Subjects With TEAEs Related to Study Treatment [b]	xx (xx.x) [xxx]	xx (xx.x) [xxx]	xx (xx.x) [xxx]	xx (xx.x) [xxx]	xx (xx.x) [xx.x]
Subjects With Serious TEAEs	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]
Subjects With Serious TEAEs Related to Study Treatment [b]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]
Subjects With TEAEs Leading to Early Discontinuation	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]
Deaths - All Causes					
During Treatment Period [c]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
During Treatment Period + 14 Days [c]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Deaths - Probable Cardiovascular Cause					
During Treatment Period [c]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
During Treatment Period + 14 Days [c]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Deaths - Probable Respiratory Cause					
During Treatment Period [c]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
During Treatment Period + 14 Days [c]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Deaths - Probable Cause Other than Cardiovascular or Respiratory					
During Treatment Period [c]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
During Treatment Period + 14 Days [c]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

[a] TEAE = Treatment-Emergent Adverse Event
[b] Related = Possibly, Probably, or Definitely.
[c] For the purpose of determining that a death occurred during the Treatment Period, the end of the Treatment Period was defined as the date of Visit 11 or the last date of treatment, the date of the Discontinuation Visit or the last date of treatment whichever was later, or if these dates were missing, the date of the last data collection (i.e., date of death).

Report generated by program: pt003014/sasdir/programs/statout/t030101.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: For deaths tabulations, Cardiovascular and Respiratory Deaths are those indicated on the Adjudications CRF.

Table 3.1.2.x Overall Summary of Adverse Events by Region and Country: <Region Subgroup or Country>
Analysis Set: Safety Population

Notes to Programmer: follow numbering used for Subgroup efficacy tables, starting with 3.1.2.

Table 3.2.1.1.1 Adverse Events by MedDRA Primary System Organ Class and Preferred Term
Analysis Set: Safety Population

System Organ Class Preferred Term	GFF MDI 14.4/9.6 µg (N=xxx) n (%) [Events]	FF MDI 9.6 µg (N=xxx) n (%) [Events]	GP MDI 14.4 µg (N=xxx) n (%) [Events]	Placebo MDI (N=xxx) n (%) [Events]	All Subjects (N=xxxx) n (%) [Events]
At Least One TEAE [a]	xx (xx.x) [xx]	xx (xx.x) [xx]	xx (xx.x) [xx]	xx (xx.x) [xx]	xx (xx.x) [xx]
System Organ Class 1	xx (xx.x) [xx]	xx (xx.x) [xx]	xx (xx.x) [xx]	xx (xx.x) [xx]	xx (xx.x) [xx]
Preferred Term 1	xx (xx.x) [xx]	xx (xx.x) [xx]	xx (xx.x) [xx]	xx (xx.x) [xx]	xx (xx.x) [xx]
Preferred Term 2	xx (xx.x) [xx]	xx (xx.x) [xx]	xx (xx.x) [xx]	xx (xx.x) [xx]	xx (xx.x) [xx]
System Organ Class 2	xx (xx.x) [xx]	xx (xx.x) [xx]	xx (xx.x) [xx]	xx (xx.x) [xx]	xx (xx.x) [xx]
Preferred Term 1	xx (xx.x) [xx]	xx (xx.x) [xx]	xx (xx.x) [xx]	xx (xx.x) [xx]	xx (xx.x) [xx]
Preferred Term 2	xx (xx.x) [xx]	xx (xx.x) [xx]	xx (xx.x) [xx]	xx (xx.x) [xx]	xx (xx.x) [xx]
Etc…					

[a] TEAE = Treatment-Emergent Adverse Event

Table 3.2.1.1.x Adverse Events by Region and Country, MedDRA Primary System Organ Class and Preferred Term: <Region Subgroup or Country>
Analysis Set: Safety Population

Notes to Programmer: follow numbering used for Subgroup efficacy tables, starting with 3.2.1.1.2.

Table 3.2.1.2.1 Adverse Events With Onset After the Last Date of Treatment by MedDRA Primary System Organ Class and Preferred Term
Analysis Set: Safety Population

Notes to Programmer: Instead of 'At Least One TEAE", use "At Least One Post-Treatment AE".

Table 3.2.1.2.x Adverse Events With Onset After the Last Date of Treatment by Region and Country, MedDRA Primary System Organ Class, and Preferred Term: <Region Subgroup or Country>
Analysis Set: Safety Population

Table 3.2.2.1 Adverse Events Occurring in >=2% of Subjects in a Treatment by Descending Frequency
Analysis Set: Safety Population

Notes to Programmer: Sort preferred terms by descending frequency of subjects, then by number of events for Total column, and then in alphabetical order. Use the format of Table 3.2.1, but delete the "At Least One" row from this table. SOCs will not be used in this table. Only include AEs with incidence of 2.0% or greater (prior to rounding).

Table 3.2.2.x Adverse Events Occurring in >=2% of Subjects in a Treatment by Descending Frequency by Region and Country: <Region Subgroup or Country>
Analysis Set: Safety Population

Table 3.2.3.1 Adverse Events in MedDRA SMQs/Groupings of Interest by Term
Analysis Set: Safety Population

Notes to Programmer:

Replace the columns for SOC and Preferred Term with the following 2 columns as found in Appendix 5 of the SAP:

1. *SMQ / Grouping*
2. *Preferred Term (or Lower Level Term).*

Start a new page for each new SMQ and insert the SMQ label and MedDRA number for the SMQ underneath the column headers at the start of each new page.

There will be a footnote to flag when an LLT is summarized instead of a Preferred Term.

Table 3.2.3.x Adverse Events in MedDRA SMQs/Groupings of Interest by Term by Region and Country: <Region Subgroup or Country>
Analysis Set: Safety Population

Table 3.2.4.1 Non-serious Adverse Events Occurring in ≥5% of Subjects in a Treatment by MedDRA Primary System Organ Class and Preferred Term
Analysis Set: Safety Population

Notes to Programmer: Do not provide n(%) summary statistics for the SOC rows, but show the label for each SOC. The n and % for the "At Least One Non-Serious TEAE [a]" row should be calculated using all subjects in the treatment group as the denominator and all subjects with non-serious AEs as the numerator. Add a footnote "`[a] TEAE = Treatment-Emergent Adverse Event`*".*

Table 3.2.4.x Non-serious Adverse Events Occurring in ≥5% of Subjects in a Treatment by Region and Country. MedDRA Primary System Organ Class, and Preferred Term: <Region Subgroup or Country>
Analysis Set: Safety Population

Table 3.3.1 Rate of Adverse Events Adjusted for Exposure by MedDRA Primary System Organ Class and Preferred Term
Analysis Set: Safety Population

System Organ Class Preferred Term	GFF MDI 14.4/9.6 µg (N=xxx) Events (Rate)	FF MDI 9.6 µg (N=xxx) Events (Rate)	GP MDI 14.4 µg (N=xxx) Events (Rate)	Placebo MDI (N=xxx) Events (Rate)	All Subjects (N=xxxx) Events (Rate)
Total Person-Years of Exposure	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Total AEs	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
System Organ Class 1	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Preferred Term 1	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Preferred Term 2	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
System Organ Class 2	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Preferred Term 1	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Preferred Term 2	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
…	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

Rate = the rate of AEs per 1000 Person-Years = 1000 x (Total number of AEs / Total years of exposure across all subjects for the treatment). Total person-years of exposure for a treatment group is the total exposure (years) in the study across all subjects in the treatment group.

Report generated by program: pt003014/sasdir/programs/statout/t0303.sas Version YYYY-MM-DD xx:xx (Page n of N)

Table 3.3.x Rate of Adverse Events Adjusted for Exposure by Region and Country, MedDRA Primary System Organ Class, and Preferred Term: : <Region Subgroup or Country>
Analysis Set: Safety Population

Table 3.4.1 Adverse Events Suspected to be Drug-Related by MedDRA Primary System Organ Class and Preferred Term
Analysis Set: Safety Population

```
[a]   TEAE = Treatment-Emergent Adverse Event
[b]   Suspected to be drug-related = possibly, probably, or definitely.
```

Report generated by program: pt003014/sasdir/programs/statout/t0304.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Instead of 'At Least One TEAE', use "At Least One Drug-Related TEAE [a] [b]".

Table 3.4.x Adverse Events Suspected to be Drug-Related by Region and Country:, MedDRA Primary System Organ Class, and Preferred Term: <Region Subgroup or Country>
Analysis Set: Safety Population

Table 3.5.1 Adverse Events Causing Study Drug Discontinuation by MedDRA Primary System Organ Class and Preferred Term
Analysis Set: Safety Population

```
[a]  TEAE = Treatment-Emergent Adverse Event
[b]  An AE leading to treatment discontinuation is an AE with 'Action Taken' = 'Permanently Discontinued', or 'Outcome' = 'Fatal',
     or 'Death' as reason for Seriousness on Adverse Event' CRF.

Report generated by program: pt003014/sasdir/programs/statout/t0305.sas  Version  YYYY-MM-DD xx:xx   (Page n of N)
```

Notes to Programmer: Instead of 'At Least One TEAE", use "At Least One TEAE Leading to Discontinuation [a] [b]".

Table 3.5.x Adverse Events Causing Study Drug Discontinuation by Region and Country, MedDRA Primary System Organ Class and Preferred Term: <Region Subgroup or Country>
Analysis Set: Safety Population

Table 3.6 Listing of Adverse Events Leading to Permanent Discontinuation of Study Treatment
Analysis Set: All Subjects Randomized

Subject ID (Age (yrs)/ Gender/ Race)	Primary System Organ Class	AE Verbatim (Preferred Term)	Treat. Emerg.	Event Serious	Onset Date (Study Day) [a]	Duration of Event	Severity	Relation -ship	Action	AE Treated	Outcome (Death)	Study Day Resolved/ Death [a]
Treatment: GFF MDI 14.4/9.6 µg, FF MDI 9.6 µg, GP MDI 14.4 µg, or Placebo MDI												
Country Center # (Investigator): xxxxxxxxxxxxxxxxxx Center ### (xxxxxxxxxx)												
xxxxxx (54/F/W)	xxx xxx xxxxx	AE 1 (xxxxxxxxxx)	Yes	No	YYYY-MM-DD (2)		Moderate	Not Related	None	No	Ongoing (No)	
	xxx xxx xxxx	AE 2 (xxxxxxxxxx)	Yes	Yes	YYYY-MM-DD (P1)	xx	Moderate	Possibly	Interrupted	Yes	Resolved (Yes)	P3
	…	…										

Race: B=Black, W=White, NHPI=Native Hawaiian or other Pacific Islander, AIAN=American Indian or Alaska Native, ANZ=Australia or New Zealand (indigenous), A=Asian, O=Other.
[a] A negative number for study day denotes the number of days prior to the start of study treatment. Pxx = Days after last dose.

Report generated by program: pt003014/sasdir/programs/statout/t0306.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort by Actual Treatment, Country, Center, Subject ID, Primary System Organ Class, and Onset Day of AE. Page by treatment and not by Treatment and Center.

Table 3.7.1.1 Serious Adverse Events by MedDRA Primary System Organ Class and Preferred Term
Analysis Set: Safety Population

Notes to Programmer: Instead of "At Least One TEAE", use "At Least One Serious TEAE [a]". Add the footnote:
[a] TEAE = Treatment-Emergent Adverse Event

Table 3.7.1.x Serious Adverse Events by Region Subgroup or Country, MedDRA Primary System Organ Class, and Preferred Term
Analysis Set: Safety Population

Notes to Programmer: follow numbering used for Subgroup efficacy tables, starting with 3.7.1.2.

Table 3.7.2.1 Serious Adverse Events With Onset After the Last Date of Treatment by MedDRA Primary System Organ Class and Preferred Term
Analysis Set: Safety Population

Table 3.7.2.x Serious Adverse Events With Onset After the Last Date of Treatment by Region and Country, MedDRA Primary System Organ Class and Preferred Term: <Region Subgroup or Country>
Analysis Set: Safety Population

Table 3.8.1 Listing of Serious Adverse Events (SAEs)
Analysis Set: All Subjects Screened

Subject ID	Age (yrs) / Gender /Race	Primary System Organ Class	SAE Verbatim (Preferred Term)	Reason for Being Serious (Day) [a]	Treat. Emerg.	Onset Day [a] Day of Most Recent Dose	Duration of Event	Severity/ Relation-ship	Action/ (Outcome) (AE Treated)	Study Day Resolved [a]
Treatment: Subjects Not Randomized, GFF MDI 14.4/9.6 µg, FF MDI 9.6 µg, GP MDI 14.4 µg, or Placebo MDI										
Country Center # (Investigator): xxxxxxxxxxxxxxxxx Center ### (xxxxxxxxxx)										
xxxxxx	70/F/W	xxxx xxx xx xxx xxx xxxxx xxxxxxx xxxx	(xxxxxxxxxxxxxxxxxx)	Hospitalization / prolongation of existing Hospitalization (Day 5-Day 8)	Yes	5 (4)	4	Moderate / Not Related	None/ (Resolved) (Yes) Interrupted, Date Stopped: YYYY-12-07; AE abated: Yes; Date restarted: YYYY_12_08: AE reoccur? Yes	8

Race: B=Black, W=White, NHPI=Native Hawaiian or other Pacific Islander, AIAN=American Indian or Alaska Native, ANZ=Australia or New Zealand (indigenous), A=Asian, O=Other.
[a] A negative number for study day denotes the number of days prior to the start of study treatment. Pxx = Days after last dose.

Report generated by program: pt003014/sasdir/programs/statout/t030801.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort by Actual Treatment, Country, Center, Subject ID, Primary System Organ Class Preferred Term, and Onset Day. If Reason for Seriousness is Hospitalization or Prolongation of Existing Hospitalization, also present in parentheses the days subject admitted into and discharged from Hospital "(Day xx – Day xx)". If the Reason for Seriousness is death, also present the day of death.

Table 3.8.2 Listing of SAE-Specific Report Information
Analysis Set: All Subjects Screened

Subject ID	Diagnosis, Details and Relevant Diagnostic Tests	Last Treatment and Date (YYYY-MM-DD)	Date of SAE Onset (YYYY-MM-DD)	Serious Reason (YYYY-MM-DD)	Action Taken with Study Drug	Severity/ Relationship/ (Outcome YYYY-MM-DD)	SAE Treated
Treatment: Subjects Not Randomized, GFF MDI 14.4/9.6 µg, FF MDI 9.6 µg, GP MDI 14.4 µg, or Placebo MDI							
Country Center # (Investigator): xxxxxxxxxxxxxxxxx Center ### (xxxxxxxxxx)							
xxxxxx	Diagnosis: xxxxxxxxxxxxxxxxxxxxxx Details: signs, symptoms, time course, and relevant medical history. Relevant Diagnostic Tests: Confirmatory procedures and Results, if any.	xxxx MDI YYYY-MM-DD	YYYY-MM-DD	Death (YYYY-MM-DD) Autopsy: yes or no Life-threatening Hospitalization or prolongation of existing hospitalization (YYYY-MM-DD-YYYY-MM-DD) A persistent or significant disability/incapacity Congenital anomaly/birth defect A significant medical event that requires medical or surgical intervention to prevent one of the serious outcomes listed above.	None Interrupted (Stopped: YYYY-MM-DD SAE Abated: Yes/No Treatment Restarted: YYYY-MM-DD SAE Reoccur: Yes/no) Permanently Discontinued	Moderate / Possibly / (Resolved YYYY-07-27)	Yes/No

Notes TO Programmer: Sort by Actual Treatment, Country, Center, Subject ID, and Onset Day of SAE.

Table 3.9.1 Rate of Serious Adverse Events Adjusted for Exposure, by MedDRA Primary System Organ Class and Preferred Term
Analysis Set: Safety Population

System Organ Class Preferred Term	GFF MDI 14.4/9.6 µg (N=xxx) Events (Rate)	FF MDI 9.6 µg (N=xxx) Events (Rate)	GP MDI 14.4 µg (N=xxx) Events (Rate)	Placebo MDI (N=xxx) Events (Rate)	All Subjects (N=xxxx) Events (Rate)
Total Person-Years of Exposure	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Total SAEs[a]	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
System Organ Class 1	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Preferred Term 1	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Preferred Term 2	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
System Organ Class 2	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Preferred Term 1	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Preferred Term 2	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
…	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

[a] SAE = Serious Adverse Event.
Rate = the rate of SAEs per 1000 Person-Years = 1000 x (Total number SAEs / Total years of exposure across all subjects for the treatment). Total person-years of exposure for a treatment group is the total exposure (years) in the study across all subjects in the treatment group.
0
Report generated by program: pt003014/sasdir/programs/statout/t0309.sas Draft YYYY-MM-DD xx:xx (Page n of N)

Table 3.9.x Rate of Serious Adverse Events Adjusted for Exposure, by Region and Country, MedDRA Primary System Organ Class and Preferred Term: <Region Subgroup or Country>
Analysis Set: Safety Population

Table 3.10.1 Serious Adverse Events Suspected to be Drug-Related by MedDRA Primary System Organ Class and Preferred Term
Analysis Set: Safety Population

[a] TEAE = Treatment-Emergent Adverse Event[b] Suspected to be drug-related = possibly, probably, or definitely.

Notes to Programmer: Instead of 'At Least One TEAE', use "At Least one Serious Related TEAE [a][b]".

Table 3.10.x Serious Adverse Events Suspected to be Drug-Related by Region and Country, MedDRA Primary System Organ Class and Preferred Term: <Region Subgroup or Country>
Analysis Set: Safety Population

Table 3.11.1.1 TEAEs by Primary System Organ Class, Preferred Term, and Highest Severity – GFF MDI 14.4/9.6 µg
Analysis Set: Safety Population

Primary System Organ Class Preferred Term	GFF MDI 14.4/9.6 µg (N=xxx) Mild n (%)	 Moderate n (%)	 Severe n (%)	 Any Severity n (%)
At Least One TEAE [a]	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
System Organ Class 1	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Preferred Term 1	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Preferred Term 2	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
System Organ Class 2	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Preferred Term 1	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Preferred Term 2	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
….				

[a] TEAE = Treatment-Emergent Adverse Event
Only the highest severity is counted for multiple occurrences of the same adverse event in one individual.

Report generated by program: pt003014/sasdir/programs/statout/t031101.sas Version YYYY-MM-DD xx:xx (Page n of N)

Table 3.11.1.x TEAEs by Region and Country, Primary System Organ Class, Preferred Term, and Highest Severity – GFF MDI 14.4/9.6 µg: <Region Subgroup or Country>
Analysis Set: Safety Population

Table 3.11.2.1 TEAEs by Primary System Organ Class, Preferred Term, and Highest Severity – FF MDI 9.6 µg
Analysis Set: Safety Population

Table 3.11.2.x TEAEs by TEAEs by Region and Country, Primary System Organ Class, Preferred Term, and Highest Severity – FF MDI 9.6 µg: <Region Subgroup or Country>
Analysis Set: Safety Population

Table 3.11.3.1 TEAEs by Primary System Organ Class, Preferred Term, and Highest Severity – GP MDI 14.4 µg
Analysis Set: Safety Population

Table 3.11.3.x TEAEs by TEAEs by Region and Country, Primary System Organ Class, Preferred Term, and Highest Severity – GP MDI 14.4 µg: <Region Subgroup or Country>
Analysis Set: Safety Population

Table 3.11.4.1 TEAEs by Primary System Organ Class, Preferred Term, and Highest Severity – Placebo MDI
Analysis Set: Safety Population

Table 3.11.4.x TEAEs by TEAEs by Region and Country, Primary System Organ Class, Preferred Term, and Highest Severity Placebo MDI: <Region Subgroup or Country>
Analysis Set: Safety Population

Table 3.12.1 Death Events, by MedDRA Primary System Organ Class and Preferred Term
Analysis Set: Safety Population

[a] TEAE = Treatment-Emergent Adverse Event

Notes to Programmer: Use 'At Least One TEAE [a]".

Table 3.12.x Death Events, by Region and Country, MedDRA Primary System Organ Class and Preferred Term: <Region Subgroup or Country>
Analysis Set: Safety Population

Table 3.13 Listing of Deaths
Analysis Set: All Subjects Screened

Subject ID	Number of Days on Treatment (Treatment Start and End Dates) [a]	Date (YYYY-MM-DD) of Death	Days Since Last Dose at Time of Death	Adverse Event	Cause of Death Category	Relationship to Study Drug
Subjects Not Randomized, During Treatment or Within 14 Days Post-Treatment, or After 14 Days Post-Treatment						
Treatment: Subjects Not Randomized, GFF MDI 14.4/9.6 µg, FF MDI 9.6 µg, GP MDI 14.4 µg, or Placebo MDI						
Country Center # (Investigator): xxxxxxxxxxxxxxxxx Center ### (xxxxxxxxxx)						
xxxxxx	xxx (YYYY-MM-DD - YYYY-MM-DD)	YYYY-MM-DD	x	AE verbatim	Cardiovascular	Possibly
xxxxxx	xxx (YYYY-MM-DD - YYYY-MM-DD)	YYYY-MM-DD	x	AE verbatim	Respiratory	Definitely
xxxxxx	xxx (YYYY-MM-DD - YYYY-MM-DD)	YYYY-MM-DD	x	AE verbatim	Cancer	Probably
xxxxxx	xxx (YYYY-MM-DD - YYYY-MM-DD)	YYYY-MM-DD	x	AE verbatim	Unknown	Definitely

NA = Not applicable.[a] Study Day of Last Dose of study treatment = Study date of last dose for study treatment - Date of first dose of study treatment + 1.

Report generated by program: pt003014/sasdir/programs/statout/t0313.sas Version YYYY-MM-DD xx:xx (Page n of N)

NOTE TO PROGRAMMER: Sort by Time Period (Subjects Not Randomized, During Treatment or Within 14 Days Post-Treatment, OR After 14 Days Post-Treatment), Actual Treatment, Country, Center, and Subject ID within Center. Put NA in second and 4th columns if subject was not randomized.

Laboratory Parameters

Table 3.14.1 Laboratory Parameters by Visit and Time of Assessment – Hematology Panel
Analysis Set: Safety Population

Parameter (unit)	Visit/Timepoint	Statistic	GFF MDI 14.4/9.6 µg (N=xxx)	FF MDI 9.6 µg (N=xxx)	GP MDI 14.4 µg (N=xxx)	Placebo MDI (N=xxx)	All Subjects (N=xxxx)
Parameter 1 (unit)	Baseline (Day 1 Pre-dose)	Actual Value:					
		n	xxx	xxx	xxx	xxx	xxx
		Mean	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
		SD	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
		Median	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
		Minimum	x.xx	x.xx	x.xx	x.xx	x.xx
		Maximum	x.xx	x.xx	x.xx	x.xx	x.xx
	Week xx Pre-dose	Actual Value:					
		n	xxx	xxx	xxx	xxx	xxx
		Mean	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
		SD	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
		Median	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
		Minimum	x.xx	x.xx	x.xx	x.xx	x.xx
		Maximum	x.xx	x.xx	x.xx	x.xx	x.xx
		Change From Baseline:					
		n	xxx	xxx	xxx	xxx	xxx
		Mean	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
		SD	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
		Median	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
		Minimum	x.xx	x.xx	x.xx	x.xx	x.xx
		Maximum	x.xx	x.xx	x.xx	x.xx	x.xx

Notes to Programmer:
Repeat for all remaining post-baseline visits and also for "End of Treatment" is defined as the last non-missing assessment during the treatment period.

Baseline is defined as the last available measurement prior to the start of treatment on Day 1 (Visit 4).
End of Treatment is defined as the last non-missing assessment during the treatment period.

Report generated by program: pt003014/sasdir/programs/statout/t031401.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Repeat the parameter at the beginning of each page under column header.

Table 3.14.2 Laboratory Parameters by Visit and Time of Assessment – Blood Chemistry Panel
Analysis Set: Safety Population

Parameter (unit)	Visit/Timepoint	Statistic	GFF MDI 14.4/9.6 µg (N=xxx)	FF MDI 9.6 µg (N=xxx)	GP MDI 14.4 µg (N=xxx)	Placebo MDI (N=xxx)	All Subjects (N=xxxx)
Parameter 1 (unit)	Baseline	Actual Value:					
	(Day 1 Pre-dose)	n	xxx	xxx	xxx	xxx	xxx
		Mean	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
		SD	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
		Median	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
		Minimum	x.xx	x.xx	x.xx	x.xx	x.xx
		Maximum	x.xx	x.xx	x.xx	x.xx	x.xx
	Week xx Pre-dose	Actual Value:					
		n	xxx	xxx	xxx	xxx	xxx
		Mean	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
		SD	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
		Median	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
		Minimum	x.xx	x.xx	x.xx	x.xx	x.xx
		Maximum	x.xx	x.xx	x.xx	x.xx	x.xx
		Change From Baseline:					
		n					
		Mean	xxx	xxx	xxx	xxx	xxx
		SD	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
		Median	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
		Minimum	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
		Maximum	x.xx	x.xx	x.xx	x.xx	x.xx
			x.xx	x.xx	x.xx	x.xx	x.xx

Notes to Programmer: Repeat the parameter at the beginning of each page under column header.

Baseline is defined as the last available measurement prior to the start of treatment on Day 1 (Visit 4).
End of Treatment is defined as the last non-missing assessment during the treatment period.

Report generated by program: pt003014/sasdir/programs/statout/t031402.sas Version YYYY-MM-DD xx:xx (Page n of N)

Table 3.14.3 Laboratory Parameters by Visit and Time of Assessment – Kidney Function
Analysis Set: Safety Population

Table 3.14.4 Laboratory Parameters by Visit and Time of Assessment – Urinalysis pH and Specific Gravity
Analysis Set: Safety Population

Notes to Programmer: Repeat format of Table 3.14.2 for pH and Specific Gravity.

Table 3.14.5 Shift Table for Laboratory Hematology Data: NCI-CTC Grading
Analysis Set: Safety Population

Hemoglobin Increased

		Post-Baseline Highest Grade					
		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Missing
Treatment	Baseline Grade	n (%)	n (%)	n (%)	n (%)	n (%)	n
GFF MDI 14.4/9.6 µg	Grade 0 (N=xxx)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x
	Grade 1 (N=xxx)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x
	Grade 2 (N=xxx)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x
	Grade 3 (N=xxx)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x
	Grade 4 (N=xxx)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x
	Any Grade (N=xxx)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x
	Missing	x	x	x	x	x	x
FF MDI 9.6 µg	Grade 0 (N=xxx)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x
	Grade 1 (N=xxx)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x
	Grade 2 (N=xxx)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x
	Grade 3 (N=xxx)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x
	Grade 4 (N=xxx)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x
	Any Grade (N=xxx)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x
	Missing	x	x	x	x	x	x
GP MDI 14.4 µg	Grade 0 (N=xxx)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x
	Grade 1 (N=xxx)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x
	Grade 2 (N=xxx)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x
	Grade 3 (N=xxx)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x
	Grade 4 (N=xxx)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x
	Any Grade (N=xxx)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x
	Missing	x	x	x	x	x	x
Placebo MDI	Grade 0 (N=xxx)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x
	Grade 1 (N=xxx)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x
	Grade 2 (N=xxx)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x
	Grade 3 (N=xxx)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x
	Grade 4 (N=xxx)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x
	Any Grade (N=xxx)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x
	Missing	x	x	x	x	x	x

Baseline is defined as the last available measurement prior to the start of treatment on Day 1 (Visit 4).
Grading criteria according to National Cancer Institute Common Toxicity Criteria (NCI-CTC, CTCAE) Version 4.03.

Grade 0 = No Grade.
N = number of subjects who received the treatment and had data in the baseline category with non-missing data Post-Baseline.
n = number of subjects in baseline and post-baseline category. % = 100 x n/N.

Report generated by program: pt003014/sasdir/programs/statout/t031405.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: repeat for each laboratory test required within Hematology. Add Grade 5 to post-baseline categories shown if there are any deaths for the parameter.

Table 3.14.6 Shift Table for Laboratory Chemistry Data: NCI-CTC Grading
Analysis Set: Safety Population

Table 3.14.7 Shift Table for Kidney Function: NCI-CTC Grading
Analysis Set: Safety Population

Table 3.14.8 Post-Baseline Newly Occurring or Worsening Potentially Clinically Significant Laboratory Values Based on CTCAE 4.03 and Other Criteria
Analysis Set: Safety Population

CTCAE_4.03 and Other Criteria	Threshold [a]	GFF MDI 14.4/9.6 µg (N=xxx) n (%)	FF MDI 9.6 µg (N=xxx) n (%)	GP MDI 14.4 µg (N=xxx) n (%)	Placebo MDI (N=xxx) n (%)	All Subjects (N=xxxx) n (%)
Hematology						
Hemoglobin	<80 g/L	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Increase >40 g/L to a value > ULN	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
White Blood Cell Count	<2 x 10^9/L	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	>100 x 10^9/L	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Platelet Count	<50 x 10^9/L	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	>700 x 10^9/L	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Chemistry						
GGT	>2.5 x ULN [b]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
AST	>3 x ULN [b]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
ALT	>3 x ULN [b]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Alkaline Phosphatase	>5 x ULN	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Total Bilirubin	>1.5 x ULN [b]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Triglycerides	>5.65 mmol/L	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Cholesterol	>10.34 mmol/L	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Albumin	<20 g/L	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Potassium	<3.0 mmol/L	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	>6.0 mmol/L	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Glucose	<2.2 mmol/L	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	>13.9 mmol/L	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Kidney Function						
eGFR - EPI [c]	<30 mL/min/1.73 m^2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

n = number of subjects in the category. N1= number of subjects with data for the parameter. % = 100 x n/N1.
Criteria for Platelet Count increase is not based on CTCAE 4.03 criteria.
[a] CTCAE Threshold is Grade >=3 for all laboratory parameters except for GGT, AST, ALT, Total Bilirubin.
[b] CTCAE Threshold is Grade >=2.
[c] eGFR - EPI is estimated glomerular filtration rate using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula.

Report generated by program: pt003014/sasdir/programs/statout/t031408.sas Version YYYY-MM-DD xx:xx (Page n of N)

Table 3.14.9 All Potassium Records for Subjects With Newly Occurring or Worsening Potentially Clinically Significant Potassium Values Post-Baseline
Analysis Set: Safety Population

Notes to Programmer: Please use Listing 8.1 and add a column after Subject ID identifying which criterion in Table 3.14.8.1 is used for the PCS value. Put age, gender, and race underneath Subject ID in the first column.

Table 3.14.10 All Glucose Records for Subjects With Newly Occurring or Worsening Potentially Clinically Significant Glucose Values Post-Baseline
Analysis Set: Safety Population

Table 3.14.11 All Records for Subjects With Newly Occurring or Worsening Potentially Clinically Significant Values Post-Baseline Other Than Those for Glucose and Potassium
Analysis Set: Safety Population

Vital Signs

Table 3.15.1 Vital Sign Measurements by Visit and Time of Assessment
Analysis Set: Safety Population

Parameter (Unit) / Visit	Timepoint	Statistic	GFF MDI 14.4/9.6 µg (N=xxx)	FF MDI 9.6 µg (N=xxx)	GP MDI 14.4 µg (N=xxx)	Placebo MDI (N=xxx)	All Subjects (N=xxxx)
Heart Rate (beats/min)							
Day 1	Baseline	Actual Value:					
		n	xx	xx	xx	xx	xx
		Mean	x.x	x.x	x.x	x.x	x.x
		SD	x.x	x.x	x.x	x.x	x.x
		Median	x.x	x.x	x.x	x.x	x.x
		Minimum	x.x	x.x	x.x	x.x	x.x
		Maximum	x.x	x.x	x.x	x.x	x.x
	Post-dose 30 Min	Actual Value:					
		n	xx	xx	xx	xx	xx
		Mean	x.x	x.x	x.x	x.x	x.x
		SD	x.x	x.x	x.x	x.x	x.x
		Median	x.x	x.x	x.x	x.x	x.x
		Minimum	x.x	x.x	x.x	x.x	x.x
		Maximum	x.x	x.x	x.x	x.x	x.x
		Change From Baseline:					
		n	xx	xx	xx	xx	xx
		Mean	x.x	x.x	x.x	x.x	x.x
		SD	x.x	x.x	x.x	x.x	x.x
		Median	x.x	x.x	x.x	x.x	x.x
		Minimum	x.x	x.x	x.x	x.x	x.x
		Maximum					
	Post-dose 2 Hours	Actual Value:					
		n	xx	xx	xx	xx	xx
		Mean	x.x	x.x	x.x	x.x	x.x
		SD	x.x	x.x	x.x	x.x	x.x
		Median	x.x	x.x	x.x	x.x	x.x
		Minimum	x.x	x.x	x.x	x.x	x.x

Parameter (Unit) / Visit	Timepoint	Statistic	GFF MDI 14.4/9.6 µg (N=xxx)	FF MDI 9.6 µg (N=xxx)	GP MDI 14.4 µg (N=xxx)	Placebo MDI (N=xxx)	All Subjects (N=xxxx)
		Maximum	x.x	x.x	x.x	x.x	x.x
		Change From Baseline:					
		n	xx	xx	xx	xx	xx
		Mean	x.x	x.x	x.x	x.x	x.x
		SD	x.x	x.x	x.x	x.x	x.x
		Median	x.x	x.x	x.x	x.x	x.x
		Minimum	x.x	x.x	x.x	x.x	x.x
		Maximum	x.x	x.x	x.x	x.x	x.x
Week xx							
End of Treatment							
<timepoint>							

Baseline is defined as the average of the pre-dose measurements taken prior to the start of treatment at Day 1 (Visit 4).
End of Treatment for a timepoint is defined as the last non-missing on-treatment assessment available for the timepoint.

Report generated by program: pt003014/sasdir/programs/statout/t031501.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer:

Repeat the parameter at the beginning of each page under column header.
Repeat for all parameters
End of Treatment" will be provided for each scheduled post-baseline timepoint (pre-dose, post-dose 30 minutes, and post-dose 2 hours). End of Treatment for each of these assessment points is defined as the last non-missing on-treatment assessment available for the timepoint.

Table 3.15.2 Post-Baseline Potentially Clinically Significant Vital Sign Values
Analysis Set: Safety Population

Parameter	Post-baseline Criteria	GFF MDI 14.4/9.6 µg (N=xxx) n (%) [%][a]	FF MDI 9.6 µg (N=xxx) n (%) [%][a]	GP MDI 14.4 µg (N=xxx) n (%) [%][a]	Placebo MDI (N=xxx) n (%) [%][a]	All Subjects (N=xxxx) n (%) [%][a]
Systolic Blood Pressure, increase	≥180 mmHg and increase from Baseline ≥20 mmHg	xx (xx.x) (xx.x)	xx (xx.x) (xx.x)	xx (xx.x) (xx.x)	xx (xx.x) (xx.x)	xx (xx.x) (xx.x)
Systolic Blood Pressure, decrease	≤90 mmHg and decrease from Baseline ≥20 mmHg	xx (xx.x) (xx.x)	xx (xx.x) (xx.x)	xx (xx.x) (xx.x)	xx (xx.x) (xx.x)	xx (xx.x) (xx.x)
Diastolic Blood Pressure, increase	≥105 mmHg and increase from Baseline ≥15 mmHg	xx (xx.x) (xx.x)	xx (xx.x) (xx.x)	xx (xx.x) (xx.x)	xx (xx.x) (xx.x)	xx (xx.x) (xx.x)
Diastolic Blood Pressure, decrease	≤50 mmHg and decrease from Baseline ≥15 mmHg	xx (xx.x) (xx.x)	xx (xx.x) (xx.x)	xx (xx.x) (xx.x)	xx (xx.x) (xx.x)	xx (xx.x) (xx.x)
Tachycardia Event	≥110 bpm and increase ≥15% from Baseline	xx (xx.x) (xx.x)	xx (xx.x) (xx.x)	xx (xx.x) (xx.x)	xx (xx.x) (xx.x)	xx (xx.x) (xx.x)
Bradycardia Event	≤50 bpm and decrease ≥15% from Baseline	xx (xx.x) (xx.x)	xx (xx.x) (xx.x)	xx (xx.x) (xx.x)	xx (xx.x) (xx.x)	xx (xx.x) (xx.x)

Baseline is defined as the average of the pre-dose measurements taken prior to the start of treatment at Day 1 (Visit 4).
n is the number of subjects meeting the Post-baseline Criteria at any time after the start of treatment. N1= number of subjects with data for the parameter. % = 100 x n/N1.
[a] The second percentage provided for each treatment group is the percentage of all visits where a post-baseline value at the visit was PCS.

Report generated by program: pt003014/sasdir/programs/statout/t031502.sas Version YYYY-MM-DD xx:xx (Page n of N)

Table 3.15.3 Listing of Potentially Clinically Significant Systolic and Diastolic Blood Pressure Increases and Decreases
Analysis Set: Safety Population

Notes to Programmer: please use these definitions for this data listing and the next 3 data listings.

Systolic Blood Pressure, increase ≥180 mmHg and increase from Baseline ≥20 mmHg

Systolic Blood Pressure, decrease ≤90 mmHg and decrease from Baseline ≥20 mmHg

Diastolic Blood Pressure, increase ≥105 mmHg and increase from Baseline ≥15 mmHg

Diastolic Blood Pressure, decrease ≤50 mmHg and decrease from Baseline ≥15 mmHg

Notes to Programmer: Please use Listing 9.1 and add 2 columns after Subject ID identifying which criteria of the in the table above is being displayed for a subject (criteria also shown in Table 3.15.2). Put age, gender, and race underneath Subject ID in the first column. In the last column display Visit 1 Height, weight, and BMI.

Table 3.15.4 Listing of Potentially Clinically Significant Tachycardia and Bradycardia Events
Analysis Set: All Subjects Randomized

12-Lead Electrocardiogram (ECG)

Table 3.16.1 ECG Parameters by Visit and Time of Assessment
Analysis Set: Safety Population

Parameter (Unit) / Visit	Timepoint	Statistic	GFF MDI 14.4/9.6 µg (N=xxx)	FF MDI 9.6 µg (N=xxx)	GP MDI 14.4 µg (N=xxx)	Placebo MDI (N=xxx)	All Subjects (N=xxxx)
Heart Rate (beats/min)							
Day 1	Baseline	Actual Value:					
		n	xx	xx	xx	xx	xx
		Mean	x.x	x.x	x.x	x.x	x.x
		SD	x.x	x.x	x.x	x.x	x.x
		Median	x.x	x.x	x.x	x.x	x.x
		Minimum	x.x	x.x	x.x	x.x	x.x
		Maximum	x.x	x.x	x.x	x.x	x.x
	Post-dose 30 Min	Actual Value:					
		n	xx	xx	xx	xx	xx
		Mean	x.x	x.x	x.x	x.x	x.x
		SD	x.x	x.x	x.x	x.x	x.x
		Median	x.x	x.x	x.x	x.x	x.x
		Minimum	x.x	x.x	x.x	x.x	x.x
		Maximum	x.x	x.x	x.x	x.x	x.x
		Change From Baseline:	xx	xx	xx	xx	xx
		n	x.x	x.x	x.x	x.x	x.x
		Mean	x.x	x.x	x.x	x.x	x.x
		SD	x.x	x.x	x.x	x.x	x.x
		Median	x.x	x.x	x.x	x.x	x.x
		Minimum	x.x	x.x	x.x	x.x	x.x
		Maximum					
	Post-dose 2 Hours	Actual Value:					
		n	xx	xx	xx	xx	xx
		Mean	x.x	x.x	x.x	x.x	x.x
		SD	x.x	x.x	x.x	x.x	x.x
		Median	x.x	x.x	x.x	x.x	x.x
		Minimum	x.x	x.x	x.x	x.x	x.x

Parameter (Unit) Visit	Timepoint	Statistic	GFF MDI 14.4/9.6 µg (N=xxx)	FF MDI 9.6 µg (N=xxx)	GP MDI 14.4 µg (N=xxx)	Placebo MDI (N=xxx)	All Subjects (N=xxxx)
		Maximum	x.x	x.x	x.x	x.x	x.x
		Change From Baseline:					
		n	xx	xx	xx	xx	xx
		Mean	x.x	x.x	x.x	x.x	x.x
		SD	x.x	x.x	x.x	x.x	x.x
		Median	x.x	x.x	x.x	x.x	x.x
		Minimum	x.x	x.x	x.x	x.x	x.x
		Maximum	x.x	x.x	x.x	x.x	x.x
Week xx							
End of Treatment <timepoint>							

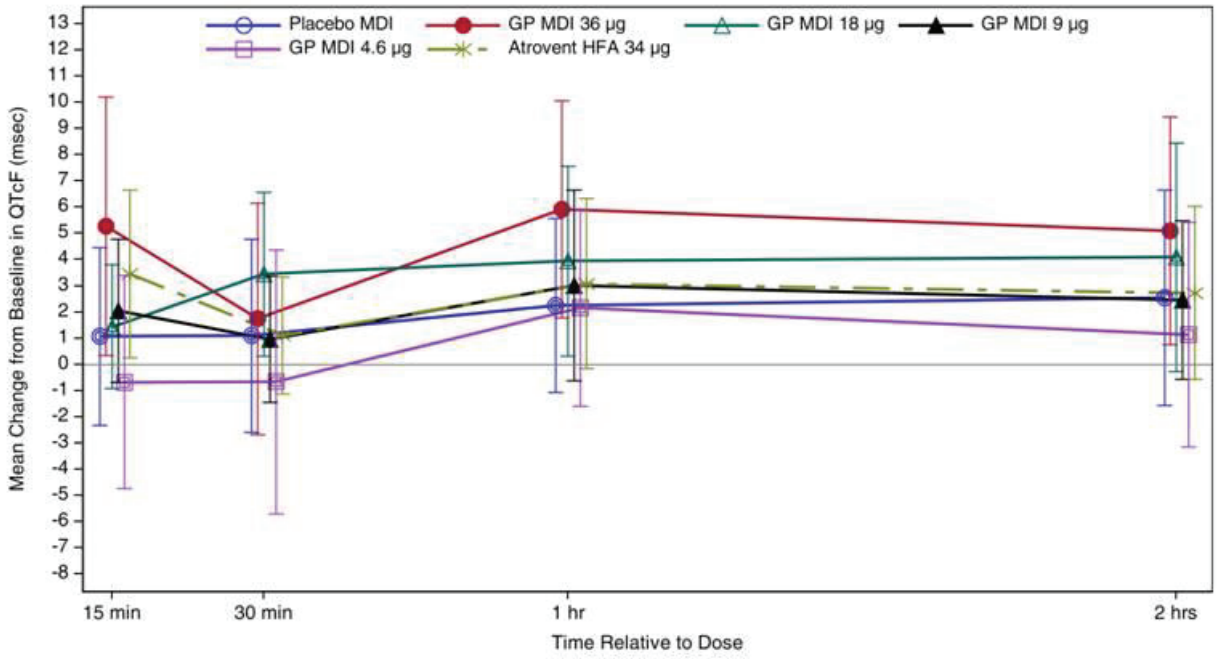
Notes to Programmer:

Repeat above assessments for each parameter (except for RR Interval).
Include "Pre-dose Mean" for all visits after Visit 1.
Repeat the parameter at the beginning of each page under column header.
Repeat for all parameters.
End of Treatment" will be provided for each scheduled post-baseline timepoint (pre-dose, post-dose 30 minutes, and post-dose 2 hours). End of Treatment for each of these assessment points is defined as the last non-missing on-treatment assessment available for the timepoint.

Baseline is defined as the average of the pre-dose measurements taken prior to the start of treatment at Day 1 (Visit 4).
End of Treatment for a timepoint is defined as the last non-missing on-treatment assessment available for the timepoint.

Report generated by program: pt003014/sasdir/programs/graph/f3_16_1.sas Version YYYY-MM-DD HH:MM YYYY (Page n of N)

Figure 3.16.1a Mean Change From Baseline for QTcF (ms) ± SE Over Time During Treatment
Analysis Set: Safety Population



The pre-dose mean value at each visit is plotted.
Source: Table 3.16.1

Report generated by program: pt003014/sasdir/programs/graph/f3_16_1.YYYYsas Version YYYY-MM-DD HH:MM (Page 1 of 1)

Note to Programmer: The above legend will be replaced by GP MDI 14.4/9.6 µg, GP MDI 14.4 µg, FF MDI 9.6 µg, and Placebo MDI. The x axis label will be replaced by "Weeks Post-Baseline" and "Week 0 (Day 1)" and all subsequent weeks post-baseline will be plotted ("Week 2", "Week 4", "Week 8", "Week 12", "Week 16", "Week 20", and "Week 24").

Figure 3.16.1b Mean Change From Baseline for QTcF (ms) ± SE Over 2 Hours Post-dose on Day 1
Analysis Set: Safety Population

Notes to Programmer: Plot 30 minutes and 2 hours post-dose.

Figure 3.16.1c Mean Change From Baseline for Heart Rate (bpm) ± SE Over Time During Treatment
Analysis Set: Safety Population

Notes to Programmer: "Week 0 (Day 1)" and all subsequent weeks post-baseline will be plotted ("Week 2", "Week 4", "Week 8", "Week 12", "Week 16", "Week 20", and "Week 24".

Figure 3.16.1d Mean Change From Baseline for Heart Rate (bpm) ± SE Over 2 Hours Post-dose on Day 1
Analysis Set: Safety Population

Notes to Programmer: Plot 30 minutes and 2 hours post-dose.

Table 3.16.2 Post-Baseline Potentially Clinically Significant (PCS) ECG Values
Analysis Set: Safety Population

Parameter	Post-baseline Criteria	GFF MDI 14.4/9.6 µg (N=xxx) n (%)	FF MDI 9.6 µg (N=xxx) n (%)	GP MDI 14.4 µg (N=xxx) n (%)	Placebo MDI (N=xxx) n (%)	All Subjects (N=xxxx) n (%)
QTcF Prolongation	Value is >450 ms for a male subject or >470 ms for a female subject	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Value is >500 ms	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Increase from baseline is >30 ms	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Increase from baseline is >60 ms	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Value is >500 ms and increase from baseline >30 ms	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Value is >500 ms and increase from baseline >60 ms	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PR Interval Increase	Increase from baseline of >50 ms	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
QRS Prolongation	Prolongation of >40 ms from baseline	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Baseline is defined as the average of the pre-dose measurements taken prior to the start of treatment at Day 1 (Visit 4).
n is the number of subjects in the category. N1= number of subjects with data for the parameter. % = 100 x n/N1.

Report generated by program: pt003014/sasdir/programs/statout/t031602.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Subject will be counted as meeting the criteria as long as there is one Post-Baseline assessment meeting the criteria.

Table 3.16.3 Listing of ECG's Meeting QTcF Interval Prolongation Criteria
Analysis Set: All Subjects Randomized

Notes to Programmer: Please use Listing 9.2 and add a column after Subject ID identifying which QTcF criteria of the first 6 in the table above is being displayed (criteria shown in Table 3.16.2 above). Put age, gender, and race underneath Subject ID in the first column.

Table 3.16.4 Listing of PR Interval Increases: Post-Baseline Increases of >50 ms From Baseline
Analysis Set: All Subjects Randomized

Table 3.16.5 Listing of QRS Prolongations: Post-Baseline Prolongations of >40 ms From Baseline
Analysis Set: All Subjects Randomized

4. Subject Data Listings

4.1 Subject Discontinuations/Completions

Listing 1.1 Study Centers
Analysis Set: All Subjects Screened

Center	Investigator	Location
xxxxxx	xxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxx City Country
xxxxxx	xxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxx City Country
xxxxxx	xxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxx City Country

Source: xxxxxxx.sas7bdat

Report generated by program: pt003014/sasdir/programs/statout/l0101.sas Version YYYY-MM-DD xx:xx (Page n of N)

Listing 1.2 Subject Disposition and Demographic Data
Analysis Set: All Subjects Screened

			Smoking History							
Subject ID (Randomization Strata)	Age (yrs)/ Gender (Race/ Ethni-city)	Height(cm)/ Weight (kg) / BMI (kg/ m^2)	Smoking Status [a]	Number of Weeks Since Day Quit	Number of Years Smoked	Average Number of Ciga-rettes Smoked Per Day	Number of Pack Years Smoked [b]	Random-ized? (Study Day) [c]	Subject Study Status (Date of Discontinuation [Study Day)} (Follow-up Call? Date) Date of Death [d]
Treatment: Subjects Not Randomized, GFF MDI 14.4/9.6 µg, FF MDI 9.6 µg, GP MDI 14.4 µg, or Placebo MDI									
Country Center # (Investigator): xxxxxxxxxxxxxxxxx Center ### (xxxxxxxxxx)									
Xxxxxx Randomization Strata Description>	Xx/M (x/xx)	xxx.x/ xx.x/ xx.x	Current Smoker	xx.x	xx	xx	xx.x	Yes/No (xx)	Completed Study (YYYY-MM-DD [xxx]) (Yes YYYY-DD-MM) NA
Xxxxxx <Randomization Strata Description>	Xx/M (x/xx)	xxx.x/ xx.x/ xx.x	Former Smoker	xx.x	xx	xx	xx.x	Yes/No (xx)	Discontinued Investigator's Decision (YYYY-MM-DD [xxx]) (No)
Xxxxxx <Randomization Strata Description>	Xx/M (x/xx)	xxx.x/ xx.x/ xx.x	Current Smoker	xx.x	xx	xx	xx.x	Yes/No (xx)	Discontinued Subject Lost to Follow up (YYYY-MM-DD [xxx]) (No)
Xxxxxx <Randomization Strata Description>	Xx/M (x/xx)	xxx.x/ xx.x/ xx.x	Non-Smoker	xx.x	xx	xx	xx.x	No (NA)	Discontinued Investigator's Decision (YYYY-MM-DD [xxx]) (No)
Xxxxxx <Randomization	Xx/M (x/xx)	xxx.x/ xx.x/	Current Smoker	xx.x	xx	xx	xx.x	No (NA)	Discontinued Adverse Event

Strata Description>	xx.x	(YYYY-MM-DD [xxx]) (No) Death: YYYY-MM-DD

Race: B=Black, W=White, NHPI=Native Hawaiian or other Pacific Islander, AIAN=American Indian or Alaska Native, ANZ=Australia or New Zealand (indigenous), A=Asian, O=Other. Ethnicity: H=Hispanic, NH=Non-Hispanic.
NA = Not Applicable.
[a] Former Smoker is defined as those who have stopped smoking for at least 6 weeks prior to first Screening Visit.
[b] Number of pack years smoked = (number of cigarettes per day / 20) x number of years smoked.
[c] Study Day of randomization = date of randomization – first dose of study treatment + 1.
[d] The Date of Discontinuation is the later of the last visit date, the date of the last dose of study medication, or the date of last contact for subjects lost-to-followup. For subjects not randomized, date of discontinuation Study Day is the last visit date - date of Screening Visit 1; for treated subjects, Study Day is the date of discontinuation - date of first dose of study treatment+1.

Source: xxxxxxx.sas7bdat

Report generated by program: PT003014/sasdir/programs/statout/l0102.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort by Actual Treatment, Country, Center, and Subject ID within Center. Last Contact Date on the Study Completion/Early Discontinuation CRF is date of last contact. If Race = Other, concatenate the specified race after 'O' within parenthesis, e.g., "O (specified)".

Listing 1.3 Randomized Treatment, Actual Treatment, and Duration of Treatment
Analysis Set: All Subjects Randomized

Subject ID	Randomization Date	Randomized Treatment	Actual Treatment	Start Date of Treatment (Study Day) and time (24 hr clock)	End Date of Treatment (Study Day) and time (24 hr clock)
Country Center # (Investigator): xxxxxxxxxxxxxxxxx Center ### (xxxxxxxxxx)					
xxxxxx	YYYY-MM-DD	xxxxxxxxxx	xxxxxxxxxx [a]	YYYY-MM-DD (xxx) hh:mm	YYYY-MM-DD (xxx) hh:mm
xxxxxx	YYYY-MM-DD	xxxxxxxxxx	xxxxxxxxxx	YYYY-MM-DD (xxx) hh:mm	YYYY-MM-DD (xxx) hh:mm
xxxxxx	YYYY-MM-DD	xxxxxxxxxx	xxxxxxxxxx	YYYY-MM-DD (xxx) hh:mm	YYYY-MM-DD (xxx) hh:mm

[a] Subject received a treatment other than their randomized treatment.

Source: xxxxxxx.sas7bdat

Report generated by program: pt003014/sasdir/programs/statout/l0103.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort by Country, Center, and Subject ID within Center. Start day and time will come from the Dosing CRF. End Study Day is the last dosing date, either from the diary data or from the Dosing CRF, whichever is the latest dosing date.

Listing 1.4 Reasons Subjects Were Not Randomized
Analysis Set: Non-Randomized Analysis Set

Subject ID	Date of Screening	Age (yrs)	Gender	Race	Reason Not Randomized
Country Center # (Investigator): xxxxxxxxxxxxxxxxx Center ### (xxxxxxxxxx)					
xxxxxx	YYYY-MM-DD	xx	Male	W	xxxxxxxxxxxxxx (Inclusion Criterion #n)
xxxxxx	YYYY-MM-DD	xx	Female	W	xxxxxxxxxxxxxx (Inclusion Criterion #n)
xxxxxx	YYYY-MM-DD	xx	Male	W	xxxxxxxxxxxxxx (Inclusion Criterion #n)
xxxxxx	YYYY-MM-DD	xx	Male	W	xxxxxxxxxxxxxx (Inclusion Criterion #n)
Xxxxxx	YYYY-MM-DD	Xx	Female	W	<reason for discontinuation from the Discontinuation/Completion CRF>

Race: B=Black, W=White, NHPI=Native Hawaiian or other Pacific Islander, AIAN=American Indian or Alaska Native, ANZ=Australia or New Zealand (indigenous), A=Asian, O=Other.

Source: xxxxxxx.sas7bdat

Report generated by program: pt003014/sasdir/programs/statout/l0104.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort by Country, Center, and Subject ID within Center. If Race = Other ("O"), concatenate the specified race after 'O' within parenthesis, e.g., **"e.g., "O: xxxxxx".**

Listing 1.5 Changes in Smoking Status During Study
Analysis Set: All Subjects Randomized

		Did smoking status change since the last visit?									
Subject ID Age (yrs)/ Gender/ Race	Visit 1 Screening Smoking Status	Screening Visit 2	Screening Visit 3	Day 1 (Visit 4)	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
Treatment: GFF MDI 14.4/9.6 µg, FF MDI 9.6 µg, GP MDI 14.4 µg, or Placebo MDI											
Country Center # (Investigator): xxxxxxxxxxxxxxxxx Center ### (xxxxxxxxxx)											
xxxxxx xx/F/W	Former Smoker	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
xxxxxx xx/F/W	Current Smoker	No	No	No	No	No	No	No	No	No	No

Race: B=Black, W=White, NHPI=Native Hawaiian or other Pacific Islander, AIAN=American Indian or Alaska Native, ANZ=Australia or New Zealand (indigenous), A=Asian, O=Other.

Source: xxxxxxx.sas7bdat

Report generated by program: pt003014/sasdir/programs/statout/l0105.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: If an unscheduled visit occurred between Visit X and Visit Y, please add a second row, showing change in status for a visit occurring after Visit X on the second line underneath the Visit x column. Repeat if necessary If more than one line needed per subject, please add the following footnote to the table: Changes in status at an Unscheduled visit are shown on the additional line shown for a subject beneath the visit after which the unscheduled visit occurred.
Sort by Randomized Treatment, Country, Center, and Subject ID within Center.

4.2 Protocol Deviations

Listing 2.1 Violation of Inclusion/Exclusion Criteria and Waivers
Analysis Set: All Subjects Randomized

							Eligibility					
Subject ID	Age (yrs)	Gender	Race	Informed Consent Signed	Informed Consent Study Day [a]	Visit	Study Day [a]	Inclusion/ Exclusion Criteria Satisfied	Type of Failed Criteria	Failed Criteria Number	Was Waiver Granted	Reason for Waiver Granted
Treatment: GFF MDI 14.4/9.6 µg, FF MDI 9.6 µg, GP MDI 14.4 µg, or Placebo MDI												
Country Center # (Investigator): xxxxxxxxxxxxxxxxxx Center ### (xxxxxxxxxx)												
xxxxxx	xx	Male	x	Yes	-xx	Visit 1	-xx	No	Inclusion	6	Yes	xxxx xxxxxx xxxx

Race: B=Black, W=White, NHPI=Native Hawaiian or other Pacific Islander, AIAN=American Indian or Alaska Native, ANZ=Australia or New Zealand (indigenous), A=Asian, O=Other.
[a] A negative number for study day denotes the number of days prior to the start of study treatment.

Source:xxxxxxx.sas7bdat

Report generated by program: pt003014/sasdir/programs/statout/l0201.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: If Race = Other ("O"), concatenate the specified race after 'O' within parenthesis, e.g., "O (specified)". Sort by Actual Treatment, Country, Center, and Subject ID within Center.

Listing 2.2 Screening Lung Function and Ventolin HFA and Atrovent HFA Reversibility
Analysis Set: All Subjects Randomized

Subject ID	Age (yrs)	Gender	Race	Visit Effort Date (Nominal Time)	Time of BD Dose (24 hr clock)	Pre-dose FEV1 (L)	Pre-dose FEV1 Rank	Pre-dose FVC (L)	Pre-dose FVC Rank	Pre-dose PEFR (L/min)	Post-dose FEV1 (L)	Post-dose FEV1 Rank	Post-dose FVC (L)	Post-dose FVC Rank	Post-dose PEFR (L/min)	Reversibility %
Treatment: GFF MDI 14.4/9.6 µg, FF MDI 9.6 µg, GP MDI 14.4 µg, or Placebo MDI																
Country Center # (Investigator): xxxxxxxxxxxxxxxxx Center ### (xxxxxxxxxx)																
xxxxxx	xx	Female	W	Visit 1 YYYY-MM-DD (NA)	xx:xx	x.xxx	x	x.xxx	x	xxx.xxx	x.xxx	x	x.xxx	x	xxx.xx x	
				Visit 2 YYYY-MM-DD (-60 min.)	xx:xx	x.xxx	x	x.xxx	x	xxx.xxx	x.xxx	x	x.xxx	x	xxx.xx x (V)	xx.x
				Visit 2 YYYY-MM-DD (-30 min.)		x.xxx	x	x.xxx	x	xxx.xxx	x.xxx	x	x.xxx	x	xxx.xx x (V)	xx.x
				Visit 3 YYYY-MM-DD (-60 min.)	xx:xx	x.xxx	x	x.xxx	x	xxx.xxx	x.xxx	x	x.xxx	x	xxx.xx x (A)	xx.x
				Visit 3 YYYY-MM-DD (-30 min.)		x.xxx	x	x.xxx	x	xxx.xxx	x.xxx	x	x.xxx	x	xxx.xx x (V)	xx.x

Race: B=Black, W=White, NHPI=Native Hawaiian or other Pacific Islander, AIAN=American Indian or Alaska Native, ANZ=Australia or New Zealand (indigenous), A=Asian, O=Other.
NA = Not Applicable.
BD = Bronchodilator.
(V) = Ventolin HFA.
(A) = Atrovent HFA.

Source: xxxxxxx.sas7bdat

Report generated by program: pt003014/sasdir/programs/statout/l0202.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort by Actual Treatment, Country, Center, and Subject ID within Center.

4.3 Subjects Excluded From the ITT, PP, Symptomatic, and Safety Populations

See Table 1.1.4 in Section 1.

4.4 Baseline Characteristics

Listing 4.1 COPD Diagnosis
Analysis Set: All Subjects Randomized

			COPD First Diagnosed	
Subject ID	Age (yrs)/ Gender / Race	Severity of COPD (Screening Visit 2)	Date [a]	Years Prior to First Dose [b]
Treatment: GFF MDI 14.4/9.6 µg, FF MDI 9.6 µg, GP MDI 14.4 µg, or Placebo MDI				
Country Center # (Investigator): xxxxxxxxxxxxxxxxx Center ### (xxxxxxxxxx)				
xxxxxx	xx / Male/ xxxx	Mild	YYYY-MM	x.x
	xx / Female / xxxx		YYYY-06*	xx.x

Race: B=Black, W=White, NHPI=Native Hawaiian or other Pacific Islander, AIAN=American Indian or Alaska Native, ANZ=Australia or New Zealand (indigenous), A=Asian, O=Other.
[a] Missing month of Date COPD First Diagnosed will be imputed as June, or the month in which 1st will be the latest before informed consent date; '*' indicates the month displayed was imputed.
[b] Years Prior to First Dose When COPD was First Diagnosed = (Date of First Dose of Study Treatment – Date COPD First Diagnosed)/365.25. Day of Diagnosis will be imputed for all subjects as the 1st of the month.

Source: xxxxxxx.sas7bdat

Report generated by program: pt003014/sasdir/programs/statout/l0401.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort by Actual Treatment, Country, Center, and Subject ID within Center.

Listing 4.2 Screening CAT Assessment
Analysis Set: All Subjects Randomized

	CAT Analysis Score [a]								
Subject ID	1 [b]	2	3	4	5	6	7	8	Total
Treatment: GFF MDI 14.4/9.6 µg, FF MDI 9.6 µg, GP MDI 14.4 µg, or Placebo MDI									
Country Center # (Investigator): xxxxxxxxxxxxxxxxxx Center ### (xxxxxxxxxx)									
xxxxx	3	4	0	1	5	0	2	1	16
xxxxx									ND

ND = Not Done
[a] The eight test items (1-8) correspond to cough, phlegm (mucus) in my chest, chest feels tight, walk up a hill or one flight of stairs breathless, limited doing any activities at home, confident leaving my home despite my lung condition, sleep soundly, and lots of energy, respectively.
[b] Scores are rated on 0-5 scale, anchored from no problem (0) to worst possible rating (5).

Source: xxxxxxx.sas7bdat

Report generated by program: pt003014/sasdir/programs/statout/l0402.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort by Actual Treatment, Country, Center, and Subject ID.

Listing 4.3 Screening MMRC Scale
Analysis Set: All Subjects Randomized

Subject ID	MMRC Scale Grade [a]
Treatment: GFF MDI 14.4/9.6 µg, FF MDI 9.6 µg, GP MDI 14.4 µg, or Placebo MDI	
Country Center # (Investigator): xxxxxxxxxxxxxxxxxx Center ### (xxxxxxxxxx)	
xxxxxx	3
xxxxxx	ND

ND = Not Done
[a] Grades range between 0 and 4, where 4 represents the highest level of breathlessness.

Source: xxxxxxx.sas7bdat

Report generated by program: pt003014/sasdir/programs/statout/l0403.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort by Actual Treatment, Country, Center, and Subject ID.

Listing 4.4 History of Moderate or Severe COPD Exacerbations
Analysis Set: All Subjects Randomized

Subject ID	COPD exacerbation within the past 12 months prior to Screening [a]	Number of Exacerbations	Admitted to hospital or received ER Treatment in the past 12 months prior to Screening [b]	Number of Hospitalizations
Treatment: GFF MDI 14.4/9.6 µg, FF MDI 9.6 µg, GP MDI 14.4 µg, or Placebo MDI				
Country Center # (Investigator): xxxxxxxxxxxxxxxxx Center ### (xxxxxxxxxx)				
xxxxxx	Yes	2	Yes	1

[a] Within the past 12 months, subject experienced a worsening in his/her respiratory symptoms (dyspnea, cough, sputum volume, sputum, purulence) beyond normal day to day variation that led the treating physician to prescribe treatment with systemic (oral or IV) corticosteroids and/or antibiotics for at least 3 days?
[b] Subject been admitted to hospital (including intensive care unit) or received emergency room (including urgent care centers) treatment in the past 12 months due to a worsening in his/her respiratory symptoms (dyspnea, cough, sputum volume, sputum purulence) beyond normal day to day variation?

Source: xxxxxxx.sas7bdat

Report generated by program: pt003014/sasdir/programs/statout/l0404.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort by Actual Treatment, Country, Center, and Subject ID.

Listing 4.5.1 Relevant Medical and Surgical History
Analysis Set: All Subjects Randomized

Subject ID	Age/ Gender/ Race	Category	System Organ Class	Diagnosis or Surgery/ (Preferred Term)	Onset Date	Onset Day [a]	Still Present?	End Date (Year/ Month)	End Day [b]
Treatment: GFF MDI 14.4/9.6 µg, FF MDI 9.6 µg, GP MDI 14.4 µg, or Placebo MDI									
Country Center # (Investigator): xxxxxxxxxxxxxxxxx Center ### (xxxxxxxxxx)									
xxxxxx	xx/x/x	Drug Allergy	xxxxxxxx	xxxxx/(xxxx)	YYYY-MM	-xxx	No	YYYY-MM	xxx
		Malignancy	xxxxxx	xxxxx/(xxxx)	YYYY-MM	-xxx	No	YYYY-MM	xxx
xxxxxx	xx/x/x	CNS/Neurological	xxxxxxxxxxxxxxx	xxxxx/(xxxx)	YYYY-MM	-xxx	No	YYYY-MM	xxx
		Endocrine/Metabolic	xxxxxxxxxx	xxxxx/(xxxx)	YYYY-MM	-xxx	Yes		Ongoing
xxxxxx	xx/x/x	Eyes/Ear/Nose/Throat	xxxxxxxxxxx	xxxxx/(xxxx)	YYYY-MM	-xx	No	YYYY-MM	xxx
		Hepatic	xxxxxxxxxxxxx	xxxxx/(xxxx)	YYYY-MM	-xxx	No	YYYY-MM	xxx
xxxxxx	xx/x/x	Other	xxxxxxxxxx	xxxxx/(xxxx)	YYYY-MM	-xxx	No	YYYY-MM	xxx

Race: B=Black, W=White, NHPI=Native Hawaiian or other Pacific Islander, AIAN=American Indian or Alaska Native, ANZ=Australia or New Zealand (indigenous), A=Asian, O=Other.
[a] Onset Day=Onset date of condition - date of the first dose of study treatment. Day is imputed as 1st of the month.
[b] End Day=End date of condition - date of the first dose of study treatment. Day is imputed as 1st of the month.

Source: xxxxxxx.sas7bdat

Report generated by program: pt003014/sasdir/programs/statout/l040501.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort by Actual Treatment, Country, Center, Subject ID, and Onset Day.

Listing 4.5.2 Cardiovascular Risk Factors of Interest
Analysis Set: All Subjects Randomized

Subject ID	Age/ Gender/ Race	Cardiovascular History	Type of Diabetes	Surgery	Onset Date	Onset Day [a]	Treated?	End Date (Year/ Month)	End Day [b]
Treatment: GFF MDI 14.4/9.6 µg, FF MDI 9.6 µg, GP MDI 14.4 µg, or Placebo MDI									
Country Center # (Investigator): xxxxxxxxxxxxxxxxx Center ### (xxxxxxxxxx)									
xxxxxx	xx/x/x	Diabetes	Type II		YYYY-MM	-xxx	No	YYYY-MM	xxx
		High Total Cholesterol			YYYY-MM	-xxx	No	YYYY-MM	xxx
xxxxxx	xx/x/x	Myocardial Infarction		**Angioplasty Stents**	**YYYY-MM**	**-xxx**	**No**	**YYYY-MM**	**xxx**
xxxxxx	xx/x/x	Angina	Type I	No Surgery	YYYY-MM	-xx	No	YYYY-MM	xxx
xxxxxx	xx/x/x	Stroke			YYYY-MM	-xxx	No	YYYY-MM	xxx

Race: B=Black, W=White, NHPI=Native Hawaiian or other Pacific Islander, AIAN=American Indian or Alaska Native, ANZ=Australia or New Zealand (indigenous), A=Asian, O=Other.
[a] Onset Day=Onset date of condition – date of the first dose of study treatment. Day is imputed as 1st of the month.
[b] End Day=End date of condition – date of the first dose of study treatment. Day is imputed as 1st of the month.

Source: xxxxxxx.sas7bdat

Report generated by program: pt003014/sasdir/programs/statout/l040502.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort by Actual Treatment, Country, Center, Subject ID, and Onset Day.

Listing 4.6 Screening Reproductive Status and Pregnancy Test Results
Analysis Set: All Subjects Randomized

			Pregnancy Test			
Subject ID	Age(yrs)/Gender /Race	Screening Female Reproductive Status	Visit	Type of Pregnancy Test	Study Day of Test [a]	Result
Treatment: GFF MDI 14.4/9.6 µg, FF MDI 9.6 µg, GP MDI 14.4 µg, or Placebo MDI						
Country Center # (Investigator): xxxxxxxxxxxxxxxxxx Center ### (xxxxxxxxxx)						
xxxxxx	xx/F/xxxx	NA – Woman of non-childbearing potential	Visit 1	Not Done	NA	NA
xxxxxx	xx/F/O(xxxx)	Woman of childbearing potential	Visit 1	Serum Pregnancy Test	xxx	Positive
Etc…						

Race: B=Black, W=White, NHPI=Native Hawaiian or other Pacific Islander, AIAN=American Indian or Alaska Native, ANZ=Australia or New Zealand (indigenous), A=Asian, O=Other.
a] Study Day is defined as date of test – date of the first dose of study treatment.

Source: xxxxxxx.sas7bdat

Report generated by program: pt003014/sasdir/programs/statout/l0406.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort by Actual Treatment, Country, Center, Investigator, Subject ID within Center, Visit, and Study Day of Pregnancy Test.

Listing 4.7 Prior, Concomitant, and Post-Treatment COPD Medications
Analysis Set: All Subjects Randomized

Subject ID	Medication Verbatim Term (Preferred Term) (ATC Term)	Dose/ Unit/ Route/ Frequency	Reason for Use	Begin Date (YYYY-MM-DD)	Stop Date (YYYY-MM-DD)	Con-tin-uing	Duration (Days)	Study Day Begin Day [a]	Study Day Stop Day [a]	Prior/ Concomitant/Post-Treatment
Treatment: GFF MDI 14.4/9.6 µg, FF MDI 9.6 µg, GP MDI 14.4 µg, or Placebo MDI										
Country Center # (Investigator): xxxxxxxxxxxxxxxxxx Center ### (xxxxxxxxxx)										
1001	xxxxxxxxxxxx (xxxxxx) (xxxxxx)	90/ MCG/ IH/ PRN	COPD	2008-XX-XX		Yes		-22		Yes/Yes/No

All COPD-related medications taken within 30 days of Screening and while on study are listed.
Medications were considered to be prior medications if taken prior to the start of study treatment. Medications were considered concomitant if they were reported as being taken at any point from the start of randomized study medication to the date of Visit 11a, the date of the Discontinuation Visit, or the last contact date (the date of the last in-clinic or last diary data collection or after). Medications with an onset date of the date of Visit 11a, the date of a Discontinuation Visit, or the last contact date or after were considered post-treatment medications.
All subjects were allowed sponsor provided Ventolin HFA which was reported on the Concomitant Medications CRF.
XX = Unknown month or day.
[a] A negative number for study day denotes the number of days prior to the start of study treatment. Pxx = Days after last dose.

Sources: xxxxxxx.sas7bdat

Report generated by program: pt003014/sasdir/programs/statout/l0407.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort by Actual Treatment, Country, Center, Subject ID, Preferred Term, and Begin Date of COPD medication. Show Anatomic and chemical portion of ATC code. Only medications with Reason for Use of COPD on eCRF will be listed here.

Listing 4.8 Prior, Concomitant, and Post-Treatment Non-COPD-Related Medications
Analysis Set: All Subjects Randomized

Note to Programmer: Add the following footnote: All non-COPD-related medications taken within 30 days of Screening and while on study are listed. Show Anatomic and chemical portion of ATC code. Only medications with Reason for Use of 'Other' on eCRF will be listed here. Note that "Other: <Specify> will be provided in Reason for Use column.

Listing 4.9 Suspect Drug Assessment for SAEs
Analysis Set: All Subjects Randomized

Subject ID	SAE Verbatim Term/ Preferred Term/ Onset Date	Medication	Dose/ Unit/ Route/ Frequency	Started Treatment/ Start Date of Study Treatment	Begin Date/ Stop Date (YYYY-MM-DD)	Con-tin-uing	Duration (Days)	Begin Day/ Stop Day [a]	SAE Causally Related to This Product/Does Principal Investigator feel that SAE may be related to other factor? (Specify)
Treatment: GFF MDI 14.4/9.6 µg, FF MDI 9.6 µg, GP MDI 14.4 µg, or Placebo MDI									
Country Center # (Investigator): xxxxxxxxxxxxxxxxx Center ### (xxxxxxxxxx)									
xxxx (x/x)	Xxxxxxxxxx/ Xxxxxxxxx/ YYYY-MM-DD	Ventolin HFA	90/µg/ IH/PRN	Yes/ YYYY-MM-DD/Blinded or Open-Label	2008-XX-XX	Yes		-22	Yes / Yes (Pre-existing /Underlying disease or Prior or Concomitant Medication
xxxx (x/x)	Xxxxxxxxxx/ Xxxxxxxxx/ YYYY-MM-DD	Atrovent HFA	34/µg/ IH/QID	No	2008-XX-XX/ 2008-XX-XX	No	5	T1_P1/ T1_P5	No

XX = Unknown month or day.
[a] A negative number for study day denotes the number of days prior to the start of study treatment. Otherwise, Study Day is Date – Date of first dose in the Period + 1. Tx_y = Treatment Period and Day within Treatment Pxx = Days after last dose in period.

Sources: xxxxx.sas7bdat
Report generated by program: PT003013/final/programs/statout/l0409.sas Version YYYY-MM-DD xx:xx (Page x of y)

Notes to Programmer: for last column, 2nd question, "Does Principal Investigator feel that SAE may be related to other factor? (Specify)") is only listed on first line for each subject.

4.5 Dosing and Compliance

Listing 5.1.1 Study Drug Dosing, Dispensing, and Return
Analysis Set: All Subjects Randomized

Subject ID	Visit	Dispensed/ Dosing/ Returned	Date Dispensed/ Returned	Study Day [a] (Time of On-Site Dose) (24 hr clock)	Primary/ Replacement Kit Study Medication Component ID	Was Replacement Kit used?	Dose Indicator Reading for Visit Dispensed/ Returned (Major discrepancy between eDiary and Dose Indicator reading as read by the site?)	Week 2 Dose Indicator Reading (Pre-dose / Post-dose)
Treatment: GFF MDI 14.4/9.6 µg, FF MDI 9.6 µg, GP MDI 14.4 µg, or Placebo MDI								
Country Center # (Investigator): xxxxxxxxxxxxxxxxx Center ### (xxxxxxxxxx)								
xxxxxx	Day 1	Dispensed PD		1 (hh:mm)	xxxxx			
		Dispensed PD	YYYY-MM-DD		xxxxx			
		Dispensed RD	YYYY-MM-DD		xxxxx			
	Week 2	Dosing P		15 (hh:mm)	xxxxx		(yes, subject error, site error, other: xxxxxxxx)	xxx/xxx
		Dosing R		xx (hh:mm)	xxxxx		(yes, subject error, site error, other: xxxxxxxx)	xxx/xxx
		Dispensed R	YYYY-MM-DD		xxxxx		xxx	
		Returned	YYYY-MM-DD		xxxxx			
	Week 4	Returned P	YYYY-MM-DD	xx (hh:mm)	xxxxx	Yes	xxx (yes, subject error, site error, other: xxxxxxxx)	
		Returned R	YYYY-MM-DD	xx (hh:mm)	xxxxx		xxx (yes, subject error, site error, other:	

xxxxxxxx)

Etc…

PD = primary kit dispensed.
RD = replacement kit dispensed.
P = primary study drug dosing at visit.
R = replacement kit used at the visit.
Major discrepancy is defined as a >20 puff difference as per Protocol Section 7.1.5.
[a] Study Day = Date of on-site study medication dose – First dose of study treatment in the study + 1.

Source: xxxxxxx.sas7bdat

Report generated by program: pt003014/sasdir/programs/statout/l050101.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort by Actual Treatment, Country, Center, Subject ID within Center, Visit, Dispensed/Dosing/Returned. An asterisk will be placed next to a kit number where it is known that the kit did not contain the randomized assigned treatment. In the event that this happens, a footnote will be added to indicate '* = test kit did not contain the randomized assigned treatment'.

Listing 5.1.2 Atrovent HFA and Ventolin HFA Dispensing
Analysis Set: All Subjects Randomized

Subject ID	Atrovent HFA/Ventolin HFA	Date Dispensed	Component ID
Treatment: GFF MDI 14.4/9.6 µg, FF MDI 9.6 µg, GP MDI 14.4 µg, or Placebo MDI			
Country Center # (Investigator): xxxxxxxxxxxxxxxxx Center ### (xxxxxxxxxx)			
xxxxxx	Atrovent HFA	YYYY-MM-DD	Xxxxxx
	Ventolin HFA	YYYY-MM-DD	Xxxxxx

Source: xxxxxxx.sas7bdat

Report generated by program: pt003014/sasdir/programs/statout/l050102.sas Version YYYY-MM-DD
xx:xx (Page n of N)

Notes to Programmer: Sort by Actual Treatment, Country, Center, Subject ID within Center, and Atrovent HFA/Ventolin HFA.

Listing 5.2 Compliance and Exposure to Study Treatment
Analysis Set: All Subjects Randomized

Subject ID	Age (yrs)	Gender	Race	Treatment Day	Number of Puffs Taken	Number of Puffs Expected [a]	Daily Compliance [b] (%)	Taken Overall	Overall Compliance [c] (%)	Exposure (days) [d]
Treatment: GFF MDI 14.4/9.6 µg, FF MDI 9.6 µg, GP MDI 14.4 µg, or Placebo MDI										
Country Center # (Investigator): xxxxxxxxxxxxxxxxx Center ### (xxxxxxxxxx)										
xxxxxx	58	Male	W	1	4	4	xxx.x	xx	xx.xx	xxx.x
				2	4	x	xxx.x	xx		
				3	x	x	xxx.x	xx		
				4	x	x	xxx.x	xx		
				5	x	x	xxx.x	xx		
				6	x	x	xxx.x	xx		
				7	x	x	xxx.x	xx		
				Etc...						

Race: B=Black, W=White, NHPI=Native Hawaiian or other Pacific Islander, AIAN=American Indian or Alaska Native, ANZ=Australia or New Zealand (indigenous), A=Asian, O=Other.

[a] The expected number of puffs for a test day which was the last date of treatment was 2, the expected number of puffs for the last date of treatment which was not a test day was 4 when a PM dose was taken and then 2 otherwise; the expected number of puffs on dates prior to the last date of treatment was 4.

[b] Daily compliance = (# of puffs of study treatment taken / # of puffs of study treatment expected) x 100.

[c] Overall % Compliance = (total number of puffs of study treatment taken on a study day/total expected puffs taken on a study day) averaged across all days of a subject's dosing between start of study treatment and last day on study treatment x 100.

[d] Exposure = last date of study treatment – first date of study treatment + 1).

Sources: xxxxxxx.sas7bdat

Report generated by program: pt003014/sasdir/programs/statout/l0502.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort by Actual Treatment, Country, Center, Subject ID within Center, and Treatment Day.

4.6 Individual Efficacy Data and HCRU Data

4.6.1 Efficacy

Listing 6.1.1 Subjects Who Failed Restrictions Prior to Spirometry Assessment
Analysis Set: All Subjects Randomized

					Prior to Study Visit, Subject has		
Subject ID	Visit	Study Time Window of Assessment	Effort Date	Effort Time (24 hr clock)	Not Smoked for at Least 4 Hours	Not Had Xanthine Containing Products for at Least 6 Hours	Withheld COPD Medications Including Corticosteroids for at Least 6 Hours
Treatment: GFF MDI 14.4/9.6 µg, FF MDI 9.6 µg, GP MDI 14.4 µg, or Placebo MDI							
Country Center # (Investigator): xxxxxxxxxxxxxxxxx Center ### (xxxxxxxxxx)							
xxxxxx	Day 1	Pre-dose 60 Min	YYYY-MM-DD	8:14:57	No	No	

Note that subjects with missing data for any of the 3 restrictions are also listed.

Source: xxxxxxx.sas7bdat

Report generated by program: pt003014/sasdir/programs/statout/l060101.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort by Randomized Treatment, Country, Center, Subject ID, and Effort Date. If Race is 'O' (other), concatenate it with the specified race. Only subjects with 'No' or missing responses should be listed.

Listing 6.1.2 Reason for Missingness Overall and by Visit
Analysis Set: All Subjects Randomized

Subject ID	Visit (Study Day)	Assessment Missed	Reason Assessment Missed
Treatment: GFF MDI 14.4/9.6 µg, FF MDI 9.6 µg, GP MDI 14.4 µg, or Placebo MDI			
Country Center # (Investigator): xxxxxxxxxxxxxxxxx Center ### (xxxxxxxxxx)			
xxxxxx	Missing from Week xx Onward (xx)	Change in Morning Pre-dose Trough FEV1/TDI	Reason for Early Discontinuation from CRF
xxxxxx	Day 1 (xx)	TDI	TDI not assessed at the visit.
	Week 12 (xx)	Change in Morning Pre-dose Trough FEV1	Spirometry Grade 3 assessment is missing.
	Week 20 (xx)	Change in Morning Pre-dose Trough FEV1/TDI	Visit missed for reasons of COPD-Related, Not COPD-Related, or Unknown.

Source: xxxxxxx.sas7bdat

Report generated by program: pt003014/sasdir/programs/statout/l060102.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort by Randomized Treatment, Country, Center, Subject ID within Center, and Overall/Visit.

Listing 6.1.3 Spirometry Measurements
Analysis Set: All Subjects Randomized

Subject ID	Age (yrs)/ Gender/ Race/ Height (cm)	Visit	Treatment Date/Time (24 hr clock)	Assessment Date	Ventolin HFA used? (Time)	Study Time Window (Actual Time of Assessment 24 hr clock)	Spirometry Assessments Raw Value [Predicted Value at Screening] (Percent of Predicted Value) (grade) [a] FEV1 (L)	FEV6 (L)	FVC (L)	FEV1/ FVC(%)	FEF 25-75 (L/sec)	PEFT (ms)
Treatment: GFF MDI 14.4/9.6 µg, FF MDI 9.6 µg, GP MDI 14.4 µg, or Placebo MDI												
Country Center # (Investigator): xxxxxxxxxxxxxxxxx Center ### (xxxxxxxxxx)												
xxxxxx	53/F/W/xx x	Visit 1		YYYY-MM-DD	Yes (xx:xx AM/PM)	NA (xx:xx)	x.xxx [x.xxx] (xx.x) (x)	x.xxx	x.xxx [x.xxx] (xx.x) (x)	xx.x	x.xxx [x.xxx] (xx.x)	xxx
		Repeat for Visit 2, Visit 3, Day 1 and all other visits.	YYYY-MM-DD hh:mm	YYYY-MM-DD	Yes (xxxxxx)	Pre-dose xx Min (xx:xx)	x.xxx (xx.x) (x)	x.xxx	x.xxx (xx.x) (x)	xx.x	x.xxx (xx.x)	xxx

NA = Not applicable.
Race: B=Black, W=White, NHPI=Native Hawaiian or other Pacific Islander, AIAN=American Indian or Alaska Native, ANZ=Australia or New Zealand (indigenous), A=Asian, O=Other
[a] Grade is coded: 1=Acceptable 2=Borderline Acceptable 3=Unacceptable.

Source: xxxxxxx.sas7bdat
Report generated by program: pt003014/sasdir/programs/statout/l060103.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort by Randomized Treatment, Country, Center, Subject ID, Assessment Date, and Nominal Time of Assessment. Show Predicted Value only for Screening Visits. Study Time Window is the SAP-specified derived time window.

Listing 6.1.4 FEV_1 (L) at Each Post-dose Timepoint Through 2 Hours on a Test Day
Analysis Set: ITT Population

Subject ID	Age (yrs)/ Gender/ Race	Visit	FEV1 Pre-dose 60 Min/ 30 Min	FEV1 Post-dose 5 Min	15 Min	30 Min	1 Hour	2 Hours
Treatment: GFF MDI 14.4/9.6 µg, FF MDI 9.6 µg, GP MDI 14.4 µg, or Placebo MDI								
Country Center # (Investigator): xxxxxxxxxxxxxxxxx Center ### (xxxxxxxxxx)								
xxxxxx	xx/F/x	Day 1	x.xxx/ x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
		Week xx	x.xxx/ x.xxx		x.xxx	x.xxx	x.xxx	x.xxx

Race: B=Black, W=White, NHPI=Native Hawaiian or other Pacific Islander, AIAN=American Indian or Alaska Native, ANZ=Australia or New Zealand (indigenous), A=Asian, O=Other.

Source: xxxxxxx.sas7bdat

Report generated by program: pt003014/sasdir/programs/statout/l060104.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort by Randomized Treatment, Country, Center, Subject, and Visit.

Listing 6.1.5 FVC (L) at Each Post-dose Timepoint Through 2 Hours on a Test Day
Analysis Set: ITT Population

Listing 6.1.6 Subject Dosing and Symptoms Diary, Including Rescue Ventolin Use
Analysis Set: All Subjects Randomized

Subject ID	Study Day [a] Morning or Evening	Took study med? / Study med time Number of puffs of study med Did your dose indicator display a reading of 10 or 0? (Dose indicator reading) Do you have a clinic visit tomorrow? Did you open your drug replacement package? / How many times did you trigger the device after opening package or cleaning the device?	Symptoms Questions: How often coughed last night (today)	Symptoms Questions: How much mucus (phlegm) did you cough up last night (today)?	Symptoms Questions: AM: How short of breath were you last night? PM: Did you feel short of breath today?	Symptoms Questions: When did you feel short of breath today?	Symptoms Questions: How many times did you wake up last night?	Rescue Ventolin Use: Number of Puffs since last/ AM/PM study med
Treatment: GFF MDI 14.4/9.6 µg, FF MDI 9.6 µg, GP MDI 14.4 µg, or Placebo MDI								
Country Center # (Investigator): xxxxxxxxxxxxxxxxx Center ### (xxxxxxxxxx)								
xxxxxx	Screening	N/A / N/A	Not at all, Rarely, Frequently, Almost constantly	<1 tsp 1-2 tsp >2 tsp	Not at all, Mild, Moderate, Severe, and Very Severe	During exercise	xx	xx
	AM	NA						
	PM	NA						
		NA						
		NA/NA			Yes No, active Or No, rested. Or			
	Day 3	(No, I have a clinic visit today, NA / Yes hh:mm)	Not at all, Rarely, Frequently, Almost constantly	<1 tsp 1-2 tsp >2 tsp	Not at all, Mild, Moderate, Severe, and Very Severe	During exercise	xx	xx
	AM	Xx						
	PM	Yes/no						
		(xx)						
		No			Yes No, active Or No, rested. Or			
		Yes/No) / x						

NA = Not Applicable.
[a] Study Day = Diary card date - Date of first dose of study treatment + 1.
How Often Coughed: not at all (0), rarely (1), frequently (2), almost constantly (3).
How much mucus: none (0), <1 tsp (1), 1-2 tsp (2), >2 tsp (3).
How short of breath were you last night? Not at all (0), mild (1), moderate (2), severe (3), or very severe (4).
Did you feel short of breath Not at all, and I was active (0); not at all, and I rested today (1);
When Short of Breath: During exercise (2); walking up stairs, uphill, or quickly (3); walking slowly or during light activity (4);
washing or dressing (5); Sitting or resting (6).
Times woke up last night: 0, 1, 2, 3, 4, 5 or more times, I was awake most or all of the night.

Source: xxxxxxx.sas7bdat

Report generated by program: pt003014/sasdir/programs/statout/l060106.sas Version YYYY-MM-DD xx:xx (Page n of N)

Note to Programmer: Sort by Randomized Treatment, Country, Center, Subject ID within Center, Diary Day, and AM/PM. *Number of puffs of study medication: 2 or Other.*

Listing 6.1.7 COPD Exacerbations
Analysis Set: All Subjects Randomized

Subject ID Age (yrs)/ Gender/ Race	Study Day [a]	Start Date	End Date	Ongoing	Were antibiotics administered? (Number of Days Dosed)	Severity	Were injected or oral cortico-steroids administered? (Number of Days Dosed)	Was subject hospitalized?	Did the Exacerbation Result in Death
Treatment: GFF MDI 14.4/9.6 µg, FF MDI 9.6 µg, GP MDI 14.4 µg, or Placebo MDI									
Country Center # (Investigator): xxxxxxxxxxxxxxxxx Center ### (xxxxxxxxxx)									
Xxxxxx xx/F/W	-xx	YYYY-MM-DD	YYYY-MM-DD		Yes (xx)		No	No	No
	1	YYYY-MM-DD	YYYY-MM-DD	Yes	No	Moderate	Yes (xx)	Yes	No
	xx	YYYY-MM-DD	YYYY-MM-DD	No	No	Severe	Yes (xx)	Yes	Yes

Race: B=Black, W=White, NHPI=Native Hawaiian or other Pacific Islander, AIAN=American Indian or Alaska Native, ANZ=Australia or New Zealand (indigenous), A=Asian, O=Other.
[a] A negative number for study day denotes that the number of days prior to the start of study treatment Pxx = Days after the last dose.

Source: xxxxxxx.sas7bdat

Report generated by program: pt003014/sasdir/programs/statout/l060107.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Severity is taken from the SAE CRF. Sort by Randomized Treatment, Country, Center, Subject ID within Center, Start Date and End Date/Ongoing.

Listing 6.1.8 Baseline Dyspnea Index (BDI) /Transition Dyspnea Index (TDI)
Analysis Set: All Subjects Randomized

Subject ID	Visit	BDI/TDI Tiredness Score (practice)	BDI/TDI Focal Score	BDI/TDI Functional Impairment Component Score	BDI / TDI Magnitude of Task Component Score	BDI/TDI Magnitude of Effort Component Score
Treatment: GFF MDI 14.4/9.6 µg, FF MDI 9.6 µg, GP MDI 14.4 µg, or Placebo MDI						
Country Center # (Investigator): xxxxxxxxxxxxxxxxxx Center ### (xxxxxxxxxx)						
xxxxxx	Week 6	x/x	x/x	x/x	x/x	x/x
	Week xx	x/x	x/x	x/x	x/x	x/x

NA = Not Applicable.
Baseline is Day 1 (Visit 4). BDI scores range from 0 (very severe impairment) to 4 (no impairment); the BDI focal score, from 0 to 12, where the lower the score, the worse the severity of dyspnea. The TDI Component scores range from -3 (major deterioration) to +3 (major improvement); the TDI focal score ranges from -9 to +9, where the lower the score, the more deterioration in the severity of dyspnea.

Source: xxxxxxx.sas7bdat

Report generated by program: PT003014/sasdir/programs/statout/l060108.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort by Actual Treatment, Country, Center, Subject ID within Center, and Over 24 Weeks/Week xx.

Listing 6.1.9 St. George Respiratory Questionnaire (SGRQ)
Analysis Set: All Subjects Randomized

		Baseline/Weekly Visit Values			
Subject ID	Visit	SGRQ Total Score	Symptoms Domain Score	Activity Domain Score	Impacts Domain Score
Treatment: GFF MDI 14.4/9.6 µg, FF MDI 9.6 µg, GP MDI 14.4 µg, or Placebo MDI					
Country Center # (Investigator): xxxxxxxxxxxxxxxxx Center ### (xxxxxxxxxx)					
xxxxxx	Week 12	x.xx/x.xx	x.xx/x.xx	x.xx/x.xx	x.xx/x.xx
	Week xx	x.xx/x.xx	x.xx/x.xx	x.xx/x.xx	x.xx/x.xx

NA = Not Applicable.
Baseline is Day 1 (Visit 4).
SGRQ total and domain scores are percentages ranging from 0 to 100, where higher values represent greater impairment of quality of life.

Source: xxxxxxx.sas7bdat

Report generated by program: pt003014/sasdir/programs/statout/l060109.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort by Actual Treatment, Country, Center, Subject ID within Center, and Day 1/Week xx.

Listing 6.1.10 Individual Items of the St. George Respiratory Questionnaire (SGRQ)
Analysis Set: All Subjects Randomized

		Individual Item on the Questionnaire																
		1	4	7	10	13	16	19	22	25	28	31	34	37	40	43	46	
		2	5	8	11	14	17	20	23	26	29	32	35	38	41	44	47	49
Subject ID	Visit	3	6	9	12	155	18	21	24	27	30	33	36	39	42	45	48	51
Treatment: GFF MDI 14.4/9.6 µg, FF MDI 9.6 µg, GP MDI 14.4 µg, or Placebo MDI																		
Country Center # (Investigator): xxxxxxxxxxxxxxxxxx Center ### (xxxxxxxxxx)																		
xxxxxx	Day 1	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
	Week	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	6	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
	Week	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	xx	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	

NA = Not Applicable.
Please refer to Appendix 7 of the protocol for Individual item questions and response.

Source: xxxxxxx.sas7bdat

Report generated by program: pt003014/sasdir/programs/statout/l060110.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort by Actual Treatment, Country, Center, Subject ID within Center, and Over 24 Weeks/Week xx.

4.6.2 Healthcare Resource Utilization

Listing 6.2 Healthcare Resource Utilization
Analysis Set: Safety Population

		Days Missed From Work			Since the last visit?			Hospitalizations			
Subject ID	Visit	By Subject	By Family Members of Subject	COPD Related?	Calls to Health Care Provider (Number)	Visits to Health Care Provider (Number)	ER Visits (Number)	Hospitalized? (Number of Days)	ICU (Number of Days)	CCU (Number Of Days)	Intubated?
Treatment: GFF MDI 14.4/9.6 µg, FF MDI 9.6 µg, GP MDI 14.4 µg, or Placebo MDI											
Country Center # (Investigator): xxxxxxxxxxxxxxxxxx Center ### (xxxxxxxxxx)											
xxxxxx	Day 1	x	NA	Yes	Yes (x)	Yes (x)	Yes (x)	Yes (x)	Yes (x)	No (NA)	Yes
	Week xx	x	NA	No	Yes (x)	Yes (x)	Yes (x)	Yes (x)	Yes (x)	Yes (x)	No
xxxxxx	Day 1	NA,	x	Yes	Yes (x)	Yes (x)	Yes (x)	No (NA)	NA (NA)	NA (NA)	NA
	Week xx	NA,	x	Yes	Yes (x)	Yes (x)	Yes (x)	No (NA)	NA (NA)	NA (NA)	NA

NA = Not Applicable.

Source: xxxxxxx.sas7bdat

Report generated by program: pt003014/sasdir/programs/statout/l0602.sas Version YYYY-MM-DD xx:xx (Page n of N)

4.7 Adverse Event Listings

Listing 7.1 Adverse Events by Primary System Organ Class, Preferred Term, Treatment, Country, Center, Subject ID, and Onset Day
Analysis Set: All Subjects Randomized

Primary System Organ Class: xxxxxxxxxxxxxxxx

Preferred Term	Treatment	Country Center # (Investigator)	Subject ID (Age / Gender/ Race)	Treatment Emergent / Serious AE?	Onset Date (Day) [a]/ Occur before or after start of a treatment On Day 1	Dura-tion of Event	Severity / Relationship	Action / Outcome (AE Treated)	Study Day Resolved /Death[a]
xxxxxxxxxxxxxxx	xxxxxxxxx xxxxxxx	xxxxxxxxx ### (xxxxxxxxxx)	xxxxxx (61/F/W)	Yes / No	YYYY-MM-DD (P1)/NA	xx	Moderate / Probably	None/Resolved (Yes)	P5
			xxxxxx (xx/x/x)	Yes / No	YYYY-MM-DD (10)/NA	xx	Moderate/ Possibly	Interrupted / Ongoing (Yes)	
	xxxxxxxxx xxxxxxx	xxxxxxxxx ### (xxxxxxxxxx)	xxxxxx (xx/x/x)	Yes / Yes	YYYY-MM-DD (4)/NA	xx	xxxxxxxx/ xxxxxxxxx	None/ Ongoing (No)	
		xxxxxxxx ### (xxxxxxxxxx)	xxxxxx (xx/x/x)	Yes / No	YYYY-MM-DD (2)/NA	xx	xxxxxxxx/ xxxxxxxxx	None/ Ongoing (No)	
…									
xxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxx	xxxxxxxxxx	xxxxxx	No /No	YYYY-MM-DD	xx	xxxxxxxx/	None/ Resolved	
xx	xxxxxxx	### (xxxxxxxxxx)	(xx/x/x)		(1)/Before		xxxxxxxxx	(Yes)	
			xxxxxx (xx/x/x)	Yes / Yes	YYYY-MM-DD (3)/NA	xx	xxxxxxxx/ xxxxxxxxx	Permanently Discontinued / Ongoing (Yes)	
xxxxxxxxxxxxxxxxxx	xxxxxxxxx x	### (xxxxxxxxxx)	xxxxxx (xx/x/x)	Yes / Yes	YYYY-MM-DD (65)	xx	xxxxxxxx/ xxxxxxxxx	None/ Resolved (No)	

Race: B=Black, W=White, NHPI=Native Hawaiian or other Pacific Islander, AIAN=American Indian or Alaska Native, ANZ=Australia or New Zealand (indigenous), A=Asian, O=Other.

[a] A negative number for study day denotes the number of days prior to the start of study treatment.
Pxx = Days after last dose.

Source: xxxx.sas7bdat

generated by program: pt003014/sasdir/programs/statout/l0701.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort by Primary System Organ Class, Preferred Term, Actual Treatment, Country, Center, Subject ID within Center, and Onset Day. Put a blank line after each Center. Present the preferred term, treatment, country, center (investigator name), Subject ID (Actual Treatment and Age/gender/Race only if start a new value or at the first line of each page.
When a date of onset or date resolved is only partial, put full date in parenthesis under Study Day.

Listing 7.2 Glossary of Adverse Event Preferred Terms vs. Investigator's Verbatim

MedDRA Adverse Event Coding Dictionary		
Primary System Organ Class	Preferred Term	Investigator's AE Verbatim
xxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
	xxxxxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
		xxxxxxxxxxxx
xxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxx
		xxxxxxxxxx
	xxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
xxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxx
		xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

MedDra Version xx.x was used for coding.

Source: xxxxxxx.sas7bdat

Report generated by program: pt003014/sasdir/programs/statout/l0702.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort by Primary System Organ Class, Preferred Term, and Verbatim Term. List all unique investigators' AE verbatim.

Listing 7.3 Adverse Events by Treatment, Country, Center, Subject ID, and Onset Day
Analysis Set: All Subjects Randomized

Subject ID (Age/ Gender/ Race)	Onset Date (Day) [a]	Primary System Organ Class	AE Verbatim (Preferred Term)	Onset Date (Day) [a]/ Occur before or after start of a treatment On Day 1	Duration of Event	Sever- ity	Relation -ship	Action	AE Treated?	Outcome (Death?)	Day Resolved / Death [b]
Treatment: GFF MDI 14.4/9.6 µg, FF MDI 9.6 µg, GP MDI 14.4 µg, or Placebo MDI											
Country Center # (Investigator): xxxxxxxxxxxxxxxxxx Center ### (xxxxxxxxxx)											
Xxxxxx (61/F/W)	YYYY-MM-DD (P1)	xxx xxx xxxxx	AE 1 (xxxxxxxxxxxx)	YYYY-MM-DD (P1)/NA	xx	Moderate	Not related	None	No	Ongoing	
		xxx xxx xxxx	AE 2 (xxxxxxxxxx)	YYYY-MM-DD (10)/NA	xx	Moderate	Possibly	Interrupted	Yes	Resolved (Yes)	P3
		…	…								

Race: B=Black, W=White, NHPI=Native Hawaiian or other Pacific Islander, AIAN=American Indian or Alaska Native, ANZ=Australia or New Zealand (indigenous), A=Asian, O=Other.
[a] @ indicates that it could not be determined whether the AE had onset during study treatment.
[b] A negative number for study day denotes the number of days prior to the start of study treatment. Pxx = Days after last dose.

Sources: adae.sas7bdat

Report generated by program: pt003014/sasdir/programs/statout/l0703.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort by Actual Treatment, Country, Center, Subject ID, Primary System Organ Class, Preferred Term, and Onset Day. Put a blank line after each subject. Present the preferred term, latest treatment, country, center (investigator name), Subject ID, and Age/gender/Race when value changes start a new value or at the first line of each page.

See Section 3 Tables 3.8.1 and 3.8.2 for Serious Adverse Events data listings.

See Section 3 Table 3.6 for data listing of adverse events leading to permanent study discontinuation.

See Section 3 Table 3.13 for data listing of deaths.

4.8 Laboratory Values

Listing 8.1 Laboratory Test Results (Hematology Panel)
Analysis Set: All Subjects Randomized

Subject ID	Age (yrs) /Gender /Race	Visit	Treatment Time (24 hr clock)	Collection Date (Study Day) [a]	Nominal Time of Collection	Study Time Window of Assessment/ (Actual Time of Collection [24 hour clock])	Lab Name	Lab Parameter (Unit)	Assay Value	Reference Range Low-High	Flag [b]	Change From Baseline [c]
Treatment: GFF MDI 14.4/9.6 µg, FF MDI 9.6 µg, GP MDI 14.4 µg, or Placebo MDI												
Country Center # (Investigator): xxxxxxxxxxxxxxxxx Center ### (xxxxxxxxxx)												
xxxxxx	58/M/W	Day 1	10:13	YYYY-MM-DDPREDOSE (1)		Pre-dose 60 Min (09:30)	xxxxxx	xxxxxxxxxx	xxx	xxx-xxx	L/H	x.xxx

Race: B=Black, W=White, NHPI=Native Hawaiian or other Pacific Islander, AIAN=American Indian or Alaska Native, ANZ=Australia or New Zealand (indigenous), A=Asian, O=Other.
[a] A negative number for study day denotes the number of days prior to the start of study treatment. Pxx = Days after last dose.
[b] L = Low; H = High.
[c] For change from baseline, baseline is defined as the last available measurement prior to the start of treatment on Day 1 (Visit 4).

Source: adlb.sas7bdat

Report generated by program: pt003014/sasdir/programs/statout/l0801.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort by Actual Treatment, Country, Center, Subject ID, Date of Visit, Nominal Time of Collection, and Lab Parameter. *Add 'I = Indeterminate' if the dataset contains an Indeterminate value. Check the dataset for other flags that need to be added here.*

Listing 8.2 Laboratory Test Results (Morphology)
Analysis Set: All Subjects Randomized

Listing 8.3 Laboratory Test Results (Chemistry Panel and Kidney Function)
Analysis Set: All Subjects Randomized

Listing 8.4 Laboratory Test Results (Urinalysis Panel)
Analysis Set: All Subjects Randomized

Notes to Programmer: The change from baseline column is not needed for this data listing.

Listing 8.5 Laboratory Test Comments
Analysis Set: All Subjects Randomized

Subject ID	Date (Study Day) [a]	Study Time Window of Assessment	Lab Name	Lab Group	Lab Parameter (Unit)	Assay Value	Reference Range Low-High	Flag [b]	Result Comments
Treatment: GFF MDI 14.4/9.6 µg, FF MDI 9.6 µg, GP MDI 14.4 µg, or Placebo MDI									
Country Center # (Investigator): xxxxxxxxxxxxxxxxxx Center ### (xxxxxxxxxx)									
xxxxxx	YYYY-MM-DD (P7)	Pre-dose 60 Min	LabCorp	Chemistry	Bicarbonate (mmol/L)	18.000	19-34	L	xxxxxx

[a] A negative number for study day denotes the number of days prior to the start of study treatment. Pxx = Days after last dose.
[b] N = Normal: L = Low; H = High; Abn. = Abnormal.

Source: adlb.sas7bdat

Report generated by program: pt003014/sasdir/programs/statout/l0805.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort by Actual Treatment, Country, Center, Subject ID, Date of Visit, Nominal Time of Collection, and Lab Parameter.

See Section 3 Tables 3.14.9 to 3.14.11 for potentially clinically significant value listings.

4.9 Other Clinical Observations and Measurements

Listing 9.1 Vital Signs, Weight, and Height
Analysis Set: All Subjects Randomized

Subject ID Age (yrs)/ Gender/ Race	Visit Visit Date (Study Day) [a]	Time of treatment (24 hr clock)	Nominal Time of Assessment	Study Time Window (Actual Time) of Assessment (24 hr clock)	Temperature (Change from baseline) [b] (°C)	Systolic BP (Change from baseline) [b] (mmHg)	Diastolic BP (Change from baseline) [b] (mmHg)	Heart Rate (Change from baseline) [b] (beats/min)	Height (cm)	Weight (kg)	BMI (kg/m2)
Treatment: GFF MDI 14.4/9.6 µg, FF MDI 9.6 µg, GP MDI 14.4 µg, or Placebo MDI											
Country Center # (Investigator): xxxxxxxxxxxxxxxxxx Center ### (xxxxxxxxxx)											
Xxxxxx 58/M/W	Visit 1 YYYY-MM-DD (-xx)		NA	NA (NA)	xx.x	xxx	xxx	xx	xxx	xxx.x	xxx.x
	Visit 2 YYYY-MM-DD (-xx)		NA	NA (NA)	xx.x	xxx	xxx	xx	xxx	xxx.x	xxx.x
	Visit 3 YYYY-MM-DD (-xx)		NA	NA (NA)	xx.x	xxx	xxx	xx	xxx	xxx.x	xxx.x
	Day 1 YYYY-MM-DD (1)	hh:mm	Pre-dose xx Min.	Pre-dose xx Min (xx:xx) (xx)	xx.x (xx.x) or NA	xxx	xxx	xx			
			Post-dose x Hours	Post-dose x Hours (xx:xx) (xx) Etc…	xx.x (xx.x) or NA	xxx (xx)	xxx (xx)	xx (xx)			
	Week xx YYYY-MM-DD (xx)	hh:mm	Pre-dose xx Min.	Pre-dose xx Min (xx:xx) (xx)	xx.x (xx.x) or NA	xxx (xx)	xxx (xx)	xx (xx)			
			Post-dose x Hours	Post-dose x Hours (xx:xx) (xx) Etc…	xx.x (xx.x) or NA	xxx (xx)	xxx (xx)	xx (xx)			

Unscheduled YYYY-MM-DD (Pxx) Etc…	NA	as appropriate	xx.x (xx.x) or NA	xxx (xx)	xxx (xx)	xx (xx)	xxx	xxx.x	xxx.x

Race: B=Black, W=White, NHPI=Native Hawaiian or other Pacific Islander, AIAN=American Indian or Alaska Native, ANZ=Australia or New Zealand (indigenous), A=Asian, O=Other.
[a] A negative number for study day denotes the number of days prior to the start of study treatment. Pxx = Days after last dose.
[b] For change from baseline, baseline is defined as the average of the pre-dose measurements taken prior to the start of treatment at Day 1 (Visit 4).

Source: advs.sas7bdat

Report generated by program: pt003014/sasdir/programs/statout/l0901.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort by Actual Treatment, Country, Center, Subject ID, Date of Visit, and Nominal Time of Assessment. Show Nominal Window of 'Pre-dose' from dataset as "Pre-dose 60 Min." here in this listing as indicated above.

See Section 3 Tables 3.15.3 and 3.15.4 for listing of potentially clinically significant systolic and diastolic blood pressure values, tachycardia and bradycardia.

Listing 9.2 12-Lead Electrocardiogram (ECG)
Analysis Set: All Subjects Randomized

Subject ID Age (yrs)/ Gender/ Race	Visit Visit Date (Study Day) [a]	Treatment Time (24 hr clock)	Nominal Time of Assessment	Study Time Window (Actual Time) of Assessment (24 hr clock)	Heart Rate (Change) (BPM)	Interval Raw Value (Change From Baseline) [b] RR (ms)	PR (ms)	QRS Axis (ms)	QRS (ms)	QT (ms)	QTcF (ms)	Any Clinically Significant Abnormalities?
Treatment: GFF MDI 14.4/9.6 µg, FF MDI 9.6 µg, GP MDI 14.4 µg, or Placebo MDI												
Country Center # (Investigator): xxxxxxxxxxxxxxxxx Center ### (xxxxxxxxxx)												
Xxxxxx 58/M/W	Visit 1 YYYY-MM-DD (-xx)	NA		NA (NA)	xx.x	xxx	xxx	xx	xxx	xxx	xx	No
	Visit 2 YYYY-MM-DD (-xx)	NA		NA (NA)	xx.x	xxx	xxx	xx	xxx	xxx	xx	No
	Visit 3 YYYY-MM-DD (-xx)	NA		NA (NA)	xx.x	xxx	xxx	xx	xxx	xxx	xx	No
	Day 1 YYYY-MM-DD (1)	NA		NA (NA)	xx.x	xxx	xxx	xx	xxx	xxx	xx	No
	Week xx YYYY-MM-DD (xx)	Hh:mm	Pre-dose xx Min	Pre-dose xx Min (xx:xx)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	No
			Pre-dose xx Min	Pre-dose xx Min (xx:xx)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	No
				Etc…								
	Week xx YYYY-MM-DD (xx)		Post-dose x Hours	Post-dose x Hours(xx:xx)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	Yes
				Etc…								
	Unscheduled YYYY-MM-DD (Pxx)	NA		as appropriate	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	No

Etc…

Race: B=Black, W=White, NHPI=Native Hawaiian or other Pacific Islander, AIAN=American Indian or Alaska Native, ANZ=Australia or New Zealand (indigenous), A=Asian, O=Other.
NA = Not Applicable.
Abnormalities at Screening Visits 1 to 3 and Pre-dose on Day 1 (Visit 4) were noted on the Medical History CRF; abnormalities Post-dose on Day 1 (Visit 4) or afterward were noted on the Adverse Events CRF.
[a] A negative number for study day denotes the number of days prior to the start of study treatment. Pxx = Days after last dose.
[b] For change from baseline, baseline is defined as the average of the pre-dose measurements taken prior to the start of treatment at Day 1 (Visit 4).

Source: eg.sas7bdat

Report generated by program: pt003014/sasdir/programs/statout/l0902.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort by Actual Treatment, Country, Center, Subject ID, Date, and Time of ECG Assessment.

See Section 3 Tables 3.16.3 and 3.16.5 for potentially clinically significant ECG values.

Listing 9.3 Pregnancy Testing After Start of Treatment in the Study
Analysis Set: All Subjects Randomized

Subject ID	Age (yrs) /Gender	Screening Female Reproductive Status	Visit	Visit Date	Pregnancy Test		
					Type of Test	Date	Result
Treatment: GFF MDI 14.4/9.6 µg, FF MDI 9.6 µg, GP MDI 14.4 µg, or Placebo MDI							
Country Center # (Investigator): xxxxxxxxxxxxxxxxx Center ### (xxxxxxxxxx)							
xxxxxx	58/M	NA	Week 12	YYYY-MM-DD	Not Done		
			Week 24	YYYY-MM-DD	Not Done		
xxxxxx	76/F/W	Woman of non-childbearing potential	Week 12	YYYY-MM-DD	Urine Pregnancy Test	YYYY-MM-DD	Negative
			Week 24	YYYY-MM-DD	Serum Pregnancy Test	YYYY-MM-DD	Negative
Etc…							

Race: B=Black, W=White, NHPI=Native Hawaiian or other Pacific Islander, AIAN=American Indian or Alaska Native, ANZ=Australia or New Zealand (indigenous), A=Asian, O=Other.

Source: pg.sas7bdat

Report generated by program: pt003014/sasdir/programs/statout/l0903.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort by Actual Treatment, Country, Center, Subject ID, Visit Date, and Date of Pregnancy Test.

Listing 9.4 Comments
Analysis Set: All Subjects Randomized

Subject ID	Age (yrs)	Gender	Race	Visit	Comment Applies To:	Comments
Treatment: GFF MDI 14.4/9.6 µg, FF MDI 9.6 µg, GP MDI 14.4 µg, or Placebo MDI						
Country Center # (Investigator): xxxxxxxxxxxxxxxxx Center ### (xxxxxxxxxx)						
xxxxx	63	Male	W	Visit 1	Subject Eligibility	xxxxxxxxxxxxxxxxxxxxxxx
				Visit 2	Study Medication	
				...	Adverse Event	
				Follow-up	Visit Scheduling	
				Unscheduled	Other: xxxxxxxxxxxxxxx	

Race: B=Black, W=White, NHPI=Native Hawaiian or other Pacific Islander, AIAN=American Indian or Alaska Native, ANZ=Australia or New Zealand (indigenous), A=Asian, O=Other.

Source: xxxxxxx.sas7bdat

Report generated by program: pt003014/sasdir/programs/statout/l0904.sas Version YYYY-MM-DD xx:xx (Page n of N)

Notes to Programmer: Sort by Actual Treatment, Country, Center, Subject ID, Visit, and category that comment applies to (Subject Eligibility, Study Medication, etc…).

APPENDIX 7 TABLE OF CONTENTS FOR POST-TEXT TLFs IN THE CHINA POPULATION

Number:	PT003014
Investigational Drug and Drug Number:	Glycopyrronium and Formoterol Fumarate Inhalation Aerosol (GFF MDI); PT003 Glycopyrronium Inhalation Aerosol (GP MDI); PT005 Formoterol Fumarate Inhalation Aerosol (FF MDI); PT001
Indication:	COPD
Dosage Form/Strength:	GFF MDI 14.4/9.6 µg ex-actuator BID GP MDI 14.4 µg ex-actuator BID FF MDI 9.6 µg ex-actuator BID

PT003014 Protocol Title: A Randomized, Double-Blind, Chronic Dosing (24 Weeks), Placebo-Controlled, Parallel Group, Multi-Center Study to Assess the Efficacy and Safety of PT003, PT005, and PT001 in Subjects with Moderate to Very Severe COPD, Compared with Placebo

General Instructions for End-of-Text TFLs

The main study mock-ups document for PT003014 provides details regarding the presentation of TLFs (including titling, formatting, page layouts, content, etc.).

TABLE OF CONTENTS FOR END-OF-TEXT TLFs

SHELLS FOR END-OF-TEXT TLFS

1. Subject Disposition, Demographic, Baseline, and Other Summary Tables

Table 1.1.1 Subject Disposition
Analysis Set: All Subjects Randomized

Table 1.1.3 Distribution of Subjects in Analysis Populations, by Center and Treatment
Analysis Set: All Subjects Randomized

Table 1.1.4 Reasons for Subjects Not Randomized
Analysis Set: Non-Randomized Analysis Set

Table 1.1.5 Subjects Excluded From ITT, PP, Rescue Ventolin User, and Safety Populations
Analysis Set: All Subjects Randomized

Table 1.2.2 Reason for Early Discontinuation
Analysis Set: ITT Population

Table 1.3 Reason for Exclusion From the PP Population
Analysis Set: ITT Population

Table 1.4.1 Demographics and Baseline Characteristics Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Table 1.5.1 Severity and Duration of COPD Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Table 1.6.1 Screening Pre- and Post-Bronchodilator and Baseline Spirometry Parameters Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Table 1.7.1 Reversibility to Ventolin HFA Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Table 1.8.1 Reversibility to Atrovent HFA Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Table 1.9.1 Medical/Surgical History
Analysis Set: Safety Population

Table 1.9.2 Cardiovascular Risk Factors of Interest
Analysis Set: Safety Population

Table 1.9.3 History of Moderate or Severe COPD Exacerbations Within Past 12 Months
Analysis Set: ITT Population

Table 1.10.1 Prior Medications - COPD-Related
Analysis Set: Safety Population

Table 1.10.2 Prior Medications - Non-COPD-Related
Analysis Set: Safety Population

Table 1.11.1 Concomitant Medications - COPD Related
Analysis Set: Safety Population

Table 1.11.2 Concomitant Medications - Non-COPD Related
Analysis Set: Safety Population

Table 1.12 Study Treatment Exposure and Compliance
Analysis Set: Safety Population

Table 1.13 Changes in Smoking Status After Start of Treatment
Analysis Set: Safety Population

2. Efficacy Data Summary Tables and Figures, Including HCRU Tables

Change From Baseline in Morning Pre-Dose Trough FEV_1

Table 2.1.1 Morning Pre-Dose Trough FEV_1 (L) at Week 24
Analysis Set: ITT Population

Figure 2.1.1.1 Adjusted Mean Change From Baseline in Morning Pre-Dose Trough FEV_1 (L) ± SE Over Time
Analysis Set: ITT Population

Figure 2.1.1.2 Treatment Differences From Placebo MDI*: Adjusted Mean Change From Baseline (95% CI) in Morning Pre-Dose Trough FEV_1 (L) Over Time
Analysis Set: ITT Population

Table 2.1.2 Morning Pre-Dose Trough FEV_1 (L) at Week 24
Analysis Set: PP Population

Figure 2.1.2 Adjusted Mean Change From Baseline in Morning Pre-Dose Trough FEV_1 (L) ± SE Over Time
Analysis Set: PP Population

Table 2.1.3.1 Missing Data for Change From Baseline in Morning Pre-Dose Trough FEV_1 by Visit and Reason
Analysis Set: ITT Population

Table 2.1.4.1 Sensitivity Analysis: Treatment Comparisons for Change From Baseline in Morning Pre-Dose Trough FEV_1 (L) at Week 24
Analysis Set: ITT Population

Table 2.1.4.4 Cumulative Proportion of Responders Based on Change From Baseline in Morning Pre-dose Trough FEV_1 at Week 24
Analysis Set: ITT Population

Figure 2.1.4.31 Cumulative Proportion of Responders Based on Change From Baseline in Morning Pre-dose Trough FEV_1 at Week 24
Analysis Set: ITT Population

Transition Dyspnea Index (TDI)

Table 2.2.1 TDI Focal Score Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Figure 2.2.1.1.1 Adjusted Mean TDI Focal Score ± SE Over Time
Analysis Set: ITT Population

Figure 2.2.1.1.2 Treatment Differences From Placebo MDI*: Adjusted Mean TDI Focal Score (95% CI) Over Time
Analysis Set: ITT Population

Figure 2.2.1.2.1 Adjusted Mean TDI Focal Score ± SE Over Time: CAT Score Subpopulation of >= 10
Analysis Set: ITT Population

Figure 2.2.1.2.2 Adjusted Mean TDI Focal Score ± SE Over Time: CAT Score Subpopulation of >= 15
Analysis Set: ITT Population

Figure 2.2.1.2.3 Adjusted Mean TDI Focal Score ± SE Over Time: CAT Score Subpopulation of >= 20
Analysis Set: ITT Population

Table 2.2.2.1 TDI Component Scores for Functional Impairment, Magnitude of Task, and Magnitude of Effort Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Table 2.2.3 Response in TDI Focal Score (Achievment of a Minimum Clinically Important Difference Threshold of ≥1 Unit on Average) Over 24 Weeks Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Peak Change From Baseline in FEV_1

Table 2.3.1 Peak Change From Baseline in FEV1 (L) Within 2 Hours Post-Dose
Analysis Set: ITT Population

Figure 2.3.1 Adjusted Mean Peak Change From Baseline in FEV_1 (L) ± SE Within 2 Hours Post-Dose
Analysis Set: ITT Population

St. George Respiratory Questionnaire (SGRQ)

Table 2.4.1 SGRQ Total Score Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Figure 2.4.1.1 Adjusted Mean Change From Baseline in SGRQ Total Score (units) ± SE Over Time
Analysis Set: ITT Population

Figure 2.4.1.2 Adjusted Mean Change From Baseline in SGRQ Total Score (units) ± SE Over Time: CAT Score Subpopulation of >= 10
Analysis Set: ITT Population

Figure 2.4.1.3 Adjusted Mean Change From Baseline in SGRQ Total Score (units) ± SE Over Time: CAT Score Subpopulation of >= 15
Analysis Set: ITT Population

Figure 2.4.1.4 Adjusted Mean Change From Baseline in SGRQ Total Score (units) ± SE Over Time: CAT Score Subpopulation of >= 20
Analysis Set: ITT Population

Table 2.4.2 Total Score of Each SGRQ Domain Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Table 2.4.3 Response in SGRQ Total Score (Achievment of a Minimum Clinically Important Difference Threshold of ≥4 Units on Average) Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Number of Puffs of Rescue Ventolin HFA

Table 2.5.1 Mean Daily, Daytime, and Nighttime Number of Puffs of Rescue Ventolin HFA
Analysis Set: Rescue Ventolin User Population

Figure 2.5.1.1 Adjusted Mean Change From Baseline in Mean Daily Number of Puffs of Rescue Ventolin HFA ± SE Over Time
Analysis Set: Rescue Ventolin User Population

Figure 2.5.1.2 Adjusted Mean Change From Baseline in Mean Daytime Number of Puffs of Rescue Ventolin HFA ± SE Over Time
Analysis Set: Rescue Ventolin User Population

Figure 2.5.1.3 Adjusted Mean Change From Baseline in Mean Nighttime Number of Puffs of Rescue Ventolin HFA± SE Over Time
Analysis Set: Rescue Ventolin User Population

Table 2.5.2 Percentage of Days With No Rescue Ventolin HFA Use Over 24 Weeks
Analysis Set: Rescue Ventolin User Population

Time to Onset of Action Assessed Using FEV_1 on Day 1

Table 2.6.1 FEV_1 (L) by Post-Dose Timepoint on Day 1
Analysis Set: ITT Population

Figure 2.6.1 Adjusted Mean Change From Baseline in FEV_1 (L) ± SE Over the 2 Hour Post-Dose Interval on Day 1
Analysis Set: ITT Population

Other Spirometry Measures Including Percent Responders Analyses for Day 1

Table 2.7 FEV_1 AUC_{0-2} (L)
Analysis Set: ITT Population

Figure 2.7 Adjusted Mean FEV_1 AUC_{0-2} (L) ± SE Over Time
Analysis Set: ITT Population

Table 2.8 FVC AUC_{0-2} (L)
Analysis Set: ITT Population

Figure 2.8 Adjusted Mean FVC AUC_{0-2} (L) ± SE Over Time
Analysis Set: ITT Population

Table 2.9 Peak Change From Baseline in FVC (L) Within 2 Hours Post-Dose
Analysis Set: ITT Population

Figure 2.9 Adjusted Mean Peak Change From Baseline in FVC (L) ± SE Within 2 Hours Post-Dose
Analysis Set: ITT Population

Table 2.10 Morning Pre-Dose Trough FVC (L)
Analysis Set: ITT Population

Figure 2.10 Adjusted Mean Change From Baseline in Morning Pre-Dose Trough FVC (L) ± SE
Analysis Set: ITT Population

Table 2.11.1 Percentage of Subjects With ≥10% Improvement From Baseline in FEV_1 During 2 Hour Post-Dose Interval and by Post-Dose Timepoint on Day 1
Analysis Set: ITT Population

Table 2.11.2 Percentage of Subjects With ≥12% Improvement From Baseline in FEV_1 During 2 Hour Post-Dose Interval and by Post-Dose Timepoint on Day 1
Analysis Set: ITT Population

Table 2.11.3 Percentage of Subjects With ≥100 mL Improvement From Baseline in FEV_1 During 2 Hour Post-Dose Interval and by Post-Dose Timepoint on Day 1
Analysis Set: ITT Population

Table 2.11.4 Percentage of Subjects With ≥200 mL Improvement From Baseline in FEV_1 During 2 Hour Post-Dose Interval and by Post-Dose Timepoint on Day 1
Analysis Set: ITT Population

Table 2.11.5 Percentage of Subjects With Improvement From Baseline in FEV_1 of Both ≥12% and ≥200 mL During 2 Hour Post-Dose Interval and by Post-Dose Timepoint on Day 1
Analysis Set: ITT Population

Table 2.12 FVC (L) Over the 2 Hour Post-Dose Interval on Day 1
Analysis Set: ITT Population

Figure 2.12 Adjusted Mean Change From Baseline in FVC (L) ± SE Over the 2 Hour Post-Dose Interval on Day 1
Analysis Set: ITT Population

Exacerbations

Table 2.13.1 Rate of COPD Exacerbations Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Table 2.13.2 Rate of COPD Exacerbations With Imputation Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Table 2.14 Time to First COPD Exacerbation of Any Severity and Time to First Moderate or Severe COPD Exacerbation
Analysis Set: ITT Population

Figure 2.14.1.x Kaplan-Meier Curves for Time to First COPD Exacerbation of Any Severity Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Figure 2.14.2.x Kaplan-Meier Curves for Time to First Moderate or Severe COPD Exacerbation Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Table 2.15 Time to Treatment Failure Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Figure 2.15 Kaplan-Meier Curves for Time to Treatment Failure Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Table 2.16.1 Time to First Clinically Important Deterioration (CID) Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Figure 2.16.1.x Kaplan-Meier Curves for Time to First CID Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Table 2.16.2 Time to First Clinically Important Deterioration (CID) With Death Overal Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Figure 2.16.2.x Kaplan-Meier Curves for Time to First CID With Death and Time to First Occurrence of Each Component of CID With Death Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Table 2.17 Time to First Sustained Clinically Important Deterioration (CID) and Time to First Occurrence of Each Component of Sustained CID Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Figure 2.17.x Kaplan-Meier Curves for Time to First Sustained CID and Time to First Occurrence of Each Component of Sustained CID Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Symptoms

Table 2.18.1 Mean Daily, Daytime, and Nighttime Total Symptom Scores
Analysis Set: ITT Population

Table 2.18.2 Mean Daily, Daytime, and Nighttime Cough Symptom Scores
Analysis Set: ITT Population

Table 2.18.3 Mean Daily, Daytime, and Nighttime Shortness of Breath Symptom Scores
Analysis Set: ITT Population

Table 2.18.4 Mean Daily, Daytime, and Nighttime Sputum Volume Symptom Scores
Analysis Set: ITT Population

Table 2.18.5 Mean Number of Nighttime Awakenings
Analysis Set: ITT Population

Correlations

Table 2.19.1 Pearson Correlation Matrix of Key Efficacy Endpoints (Excluding Correlations with Efficacy Endpoints Over Weeks 12-24)
Analysis Set: All Available Data

Table 2.19.2 Pearson Correlation Matrix of Key Efficacy Endpoints Over Weeks 12-24 With Other Key Efficacy Endpoints and With Each Other
Analysis Set: All Available Data

Subgroup Analyses

Table 2.22.2 Demographics and Baseline Characteristics by GOLD Category
Analysis Set: ITT Population

Table 2.22.3 Demographics and Baseline Characteristics by GOLD Severity
Analysis Set: ITT Population

Table 2.24.2 Severity and Duration of COPD by GOLD Category
Analysis Set: ITT Population

Table 2.24.3 Severity and Duration of COPD by GOLD Severity
Analysis Set: ITT Population

Table 2.25.2 Reversibility to Ventolin HFA by GOLD Category
Analysis Set: ITT Population

Table 2.25.3 Reversibility to Ventolin HFA by GOLD Severity
Analysis Set: ITT Population

Table 2.26.2 Reversibility to Atrovent HFA by GOLD Category
Analysis Set: ITT Population

Table 2.26.3 Reversibility to Atrovent HFA by GOLD Severity
Analysis Set: ITT Population

Table 2.27.2 Study Treatment Exposure and Compliance by GOLD Category
Analysis Set: Safety Population

Table 2.27.3 Study Treatment Exposure and Compliance by GOLD Severity
Analysis Set: Safety Population

Table 2.28.2 Morning Pre-Dose Trough FEV_1 (L) by GOLD Category
Analysis Set: ITT Population

Figure 2.28.2.1 Forest Plot for Morning Pre-Dose Trough FEV_1 (L) ± SE at Week 24 by GOLD Category
Analysis Set: ITT Population

Table 2.28.3 Morning Pre-Dose Trough FEV_1 (L) by GOLD Severity
Analysis Set: ITT Population

Figure 2.28.3.1 Forest Plot for Morning Pre-Dose Trough FEV_1 (L) ± SE at Week 24 by GOLD Severity
Analysis Set: ITT Population

Table 2.30.2 Peak Change From Baseline in FEV1 (L) Within 2 Hours Post-Dose by GOLD Category
Analysis Set: ITT Population

Figure 2.30.2.1 Forest Plot for Peak FEV_1 (L) ± SE Within 2 Hours Post-Dose at Week 24 by GOLD Category
Analysis Set: ITT Population

Table 2.30.3 Peak Change From Baseline in FEV1 (L) Within 2 Hours Post-Dose by GOLD Severity
Analysis Set: ITT Population

Figure 2.30.3.1 Forest Plot for Peak FEV_1 (L) ± SE Within 2 Hours Post-Dose at Week 24 by GOLD Severity
Analysis Set: ITT Population

Healthcare Resource Utilization

Table 2.37.1 Healthcare Resource Utilization: Number of Days Missed From Work
Analysis Set: Safety Population

Table 2.37.2 Healthcare Resource Utilization by Relationship to COPD and Treatment
Analysis Set: Safety Population

3. Safety

Adverse Events

Table 3.1.1 Overall Summary of Adverse Events
Analysis Set: Safety Population

Table 3.2.1.1.x Adverse Events by MedDRA Primary System Organ Class and Preferred Term
Analysis Set: Safety Population

Table 3.2.1.2.x Adverse Events With Onset After the Last Date of Treatment by MedDRA Primary System Organ Class and Preferred Term
Analysis Set: Safety Population

Table 3.2.2.x Adverse Events Occurring in >=2% of Subjects in a Treatment by Descending Frequency
Analysis Set: Safety Population

Table 3.2.3 Adverse Events in MedDRA SMQs/Groupings of Interest by Term
Analysis Set: Safety Population

Table 3.2.4.x Non-serious Adverse Events Occurring in ≥5% of Subjects in a Treatment by MedDRA Primary System Organ Class and Preferred Term
Analysis Set: Safety Population

Table 3.3.x Rate of Adverse Events Adjusted for Exposure by MedDRA Primary System Organ Class and Preferred Term
Analysis Set: Safety Population

Table 3.4.x Adverse Events Suspected to be Drug-Related by MedDRA Primary System Organ Class and Preferred Term
Analysis Set: Safety Population

Table 3.5.x Adverse Events Causing Study Drug Discontinuation by MedDRA Primary System Organ Class and Preferred Term
Analysis Set: Safety Population

Table 3.6.x Listing of Adverse Events Leading to Permanent Discontinuation of Study Treatment
Analysis Set: All Subjects Randomized

Table 3.7.1.x Serious Adverse Events by MedDRA Primary System Organ Class and Preferred Term
Analysis Set: Safety Population

Table 3.7.2.x Serious Adverse Events With Onset After the Last Date of Treatment by MedDRA Primary System Organ Class and Preferred Term
Analysis Set: Safety Population

Table 3.8.1 Listing of Serious Adverse Events (SAEs)
Analysis Set: All Subjects Screened

Table 3.8.2 Listing of SAE-Specific Report Information
Analysis Set: All Subjects Screened

Table 3.9.x Rate of Serious Adverse Events Adjusted for Exposure, by MedDRA Primary System Organ Class and Preferred Term
Analysis Set: Safety Population

Table 3.10.x Serious Adverse Events Suspected to be Drug-Related by MedDRA Primary System Organ Class and Preferred Term
Analysis Set: Safety Population

Table 3.11.1.x TEAEs by Primary System Organ Class, Preferred Term, and Highest Severity – GFF MDI 14.4/9.6 µg
Analysis Set: Safety Population

Table 3.11.2.x TEAEs by Primary System Organ Class, Preferred Term, and Highest Severity – FF MDI 9.6 µg
Analysis Set: Safety Population

Table 3.11.3.x TEAEs by Primary System Organ Class, Preferred Term, and Highest Severity – GP MDI 14.4 µg
Analysis Set: Safety Population

Table 3.11.4.x TEAEs by Primary System Organ Class, Preferred Term, and Highest Severity – Placebo MDI
Analysis Set: Safety Population

Table 3.12.x Death Events, by MedDRA Primary System Organ Class and Preferred Term
Analysis Set: Safety Population

Table 3.13 Listing of Deaths
Analysis Set: All Subjects Screened

Laboratory Parameters

Table 3.14.1 Laboratory Parameters by Visit and Time of Assessment – Hematology Panel
Analysis Set: Safety Population

Table 3.14.2 Laboratory Parameters by Visit and Time of Assessment – Blood Chemistry Panel
Analysis Set: Safety Population

Table 3.14.3 Laboratory Parameters by Visit and Time of Assessment – Kidney Function
Analysis Set: Safety Population

Table 3.14.4 Laboratory Parameters by Visit and Time of Assessment – Urinalysis pH and Specific Gravity
Analysis Set: Safety Population

Table 3.14.5 Shift Table for Laboratory Hematology Data: NCI-CTC Grading
Analysis Set: Safety Population

Table 3.14.6 Shift Table for Laboratory Chemistry Data: NCI-CTC Grading
Analysis Set: Safety Population

Table 3.14.7 Shift Table for Kidney Function: NCI-CTC Grading
Analysis Set: Safety Population

Table 3.14.8 Post-Baseline Newly Occurring or Worsening Potentially Clinically Significant Laboratory Values Based on CTCAE 4.03 and Other Criteria
Analysis Set: Safety Population

Table 3.14.9 All Potassium Records for Subjects With Newly Occurring or Worsening Potentially Clinically Significant Potassium Values Post-Baseline
Analysis Set: Safety Population

Table 3.14.10 All Glucose Records for Subjects With Newly Occurring or Worsening Potentially Clinically Significant Glucose Values Post-Baseline
Analysis Set: Safety Population

Table 3.14.11 All Records for Subjects With Newly Occurring or Worsening Potentially Clinically Significant Values Post-Baseline Other Than Those for Glucose and Potassium
Analysis Set: Safety Population

Vital Signs

Table 3.15.1 Vital Sign Measurements by Visit and Time of Assessment
Analysis Set: Safety Population

Table 3.15.2 Post-Baseline Potentially Clinically Significant Vital Sign Values
Analysis Set: Safety Population

Table 3.15.3 Listing of Potentially Clinically Significant Systolic and Diastolic Blood Pressure Increases and Decreases
Analysis Set: Safety Population

Table 3.15.4 Listing of Potentially Clinically Significant Tachycardia and Bradycardia Events
Analysis Set: All Subjects Randomized

12-Lead Electrocardiogram (ECG)

Table 3.16.1 ECG Parameters by Visit and Time of Assessment
Analysis Set: Safety Population

Figure 3.16.1a Mean Change From Baseline for QTcF (ms) ± SE Over Time During Treatment
Analysis Set: Safety Population

Figure 3.16.1b Mean Change From Baseline for QTcF (ms) ± SE Over 2 Hours Post-Dose on Day 1
Analysis Set: Safety Population

Figure 3.16.1c Mean Change From Baseline for Heart Rate (bpm) ± SE Over Time During Treatment
Analysis Set: Safety Population

Figure 3.16.1d Mean Change From Baseline for Heart Rate (bpm) ± SE Over 2 Hours Post-Dose on Day 1
Analysis Set: Safety Population

Table 3.16.2 Post-Baseline Potentially Clinically Significant (PCS) ECG Values
Analysis Set: Safety Population

Table 3.16.3 Listing of ECG's Meeting QTcF Interval Prolongation Criteria
Analysis Set: All Subjects Randomized

Table 3.16.4 Listing of PR Interval Increases: Post-Baseline Increases of >50 ms From Baseline
Analysis Set: All Subjects Randomized

Table 3.16.5 Listing of QRS Prolongations: Post-Baseline Prolongations of >40 ms From Baseline
Analysis Set: All Subjects Randomized

4. Subject Data Listings

4.1 Subject Discontinuations/Completions

Listing 1.1 Study Centers
Analysis Set: All Subjects Screened

Listing 1.2 Subject Disposition and Demographic Data
Analysis Set: All Subjects Screened

Listing 1.3 Randomized Treatment, Actual Treatment, and Duration of Treatment
Analysis Set: All Subjects Randomized

Listing 1.4 Reasons Subjects Were Not Randomized
Analysis Set: Non-Randomized Analysis Set

Listing 1.5 Changes in Smoking Status During Study
Analysis Set: All Subjects Randomized

4.2 Protocol Deviations

Listing 2.1 Violation of Inclusion/Exclusion Criteria and Waivers
Analysis Set: All Subjects Randomized

Listing 2.2 Screening Lung Function and Ventolin HFA and Atrovent HFA Reversibility
Analysis Set: All Subjects Randomized

4.3 Subjects Excluded From the ITT, PP, Rescue Ventolin User, and Safety Populations

See Table 1.1.4 in Section 1.

4.4 Baseline Characteristics

Listing 4.1 COPD Diagnosis
Analysis Set: All Subjects Randomized

Listing 4.2 Screening CAT Assessment
Analysis Set: All Subjects Randomized

Listing 4.3 Screening MMRC Scale
Analysis Set: All Subjects Randomized

Listing 4.4 History of Moderate or Severe COPD Exacerbations
Analysis Set: All Subjects Randomized

Listing 4.5.1 Relevant Medical and Surgical History
Analysis Set: All Subjects Randomized

Listing 4.5.2 Cardiovascular Risk Factors of Interest
Analysis Set: All Subjects Randomized

Listing 4.6 Screening Reproductive Status and Pregnancy Test Results
Analysis Set: All Subjects Randomized

Listing 4.7 Prior, Concomitant, and Post-Treatment COPD Medications
Analysis Set: All Subjects Randomized

Listing 4.8 Prior, Concomitant, and Post-Treatment Non-COPD-Related Medications
Analysis Set: All Subjects Randomized

Listing 4.9 Suspect Drug Assessment for SAEs
Analysis Set: All Subjects Randomized

4.5 Dosing and Compliance

Listing 5.1.1 Study Drug Dosing, Dispensing, and Return
Analysis Set: All Subjects Randomized

Listing 5.1.2 Atrovent HFA and Ventolin HFA Dispensing
Analysis Set: All Subjects Randomized

Listing 5.2 Compliance and Exposure to Study Treatment
Analysis Set: All Subjects Randomized

4.6 Individual Efficacy Data and HCRU Data

4.6.1 Efficacy

Listing 6.1.1 Subjects Who Failed Restrictions Prior to Spirometry Assessment
Analysis Set: All Subjects Randomized

Listing 6.1.2 Reason for Missingness Overall and by Visit
Analysis Set: All Subjects Randomized

Listing 6.1.3 Spirometry Measurements
Analysis Set: All Subjects Randomized

Listing 6.1.4 FEV_1 (L) at Each Post-Dose Timepoint Through 2 Hours on a Test Day
Analysis Set: ITT Population

Listing 6.1.5 FVC (L) at Each Post-Dose Timepoint Through 2 Hours on a Test Day
Analysis Set: ITT Population

Listing 6.1.6 Subject Dosing and Symptoms Diary, Including Rescue Medication Use
Analysis Set: All Subjects Randomized

Listing 6.1.7 COPD Exacerbations
Analysis Set: All Subjects Randomized

Listing 6.1.8 Baseline Dyspnea Index (BDI) /Transition Dyspnea Index (TDI)
Analysis Set: All Subjects Randomized

Listing 6.1.9 St. George Respiratory Questionnaire (SGRQ)
Analysis Set: All Subjects Randomized

Listing 6.1.10 Individual Items of the St. George Respiratory Questionnaire (SGRQ)
Analysis Set: All Subjects Randomized

4.6.2 Healthcare Resource Utilization

Listing 6.2 Healthcare Resource Utilization
Analysis Set: Safety Population

4.7 Adverse Event Listings

Listing 7.1 Adverse Events by Primary System Organ Class, Preferred Term, Treatment, Country, Center, Subject ID, and Onset Day
Analysis Set: All Subjects Randomized

Listing 7.2 Glossary of Adverse Event Preferred Terms vs. Investigator's Verbatim

Listing 7.3 Adverse Events by Treatment, Country, Center, Subject ID, and Onset Day
Analysis Set: All Subjects Randomized

4.8 Laboratory Values

Listing 8.1 Laboratory Test Results (Hematology Panel)
Analysis Set: All Subjects Randomized

Listing 8.2 Laboratory Test Results (Morphology)
Analysis Set: All Subjects Randomized

Listing 8.3 Laboratory Test Results (Chemistry Panel and Kidney Function)
Analysis Set: All Subjects Randomized

Listing 8.4 Laboratory Test Results (Urinalysis Panel)
Analysis Set: All Subjects Randomized

Listing 8.5 Laboratory Test Comments
Analysis Set: All Subjects Randomized

4.9 Other Clinical Observations and Measurements

Listing 9.1 Vital Signs, Weight, and Height
Analysis Set: All Subjects Randomized

Listing 9.2 12-Lead Electrocardiogram (ECG)
Analysis Set: All Subjects Randomized

Listing 9.3 Pregnancy Testing After Start of Treatment in the Study
Analysis Set: All Subjects Randomized

APPENDIX 8 TABLE OF CONTENTS FOR POST-TEXT TLFs IN THE ASIA POPULATION

Study Number:	PT003014
Investigational Drug and Drug Number:	Glycopyrronium and Formoterol Fumarate Inhalation Aerosol (GFF MDI); PT003 Glycopyrronium Inhalation Aerosol (GP MDI); PT005 Formoterol Fumarate Inhalation Aerosol (FF MDI); PT001
Indication:	COPD
Dosage Form/Strength:	GFF MDI 14.4/9.6 µg ex-actuator BID GP MDI 14.4 µg ex-actuator BID FF MDI 9.6 µg ex-actuator BID

PT003014 Protocol Title: A Randomized, Double-Blind, Chronic Dosing (24 Weeks), Placebo-Controlled, Parallel Group, Multi-Center Study to Assess the Efficacy and Safety of PT003, PT005, and PT001 in Subjects with Moderate to Very Severe COPD, Compared with Placebo

General Instructions for End-of-Text TFLs

The main study mock-ups document for PT003014 provides details regarding the presentation of TLFs (including titling, formatting, page layouts, content, etc.).

TLFs that are identical in presentation to those outlined in the main PT003014 SAP are listed but not presented.

TABLE OF CONTENTS FOR END-OF-TEXT TLFs

SHELLS FOR END-OF-TEXT TLFS

1. Subject Disposition, Demographic, Baseline, and Other Summary Tables

Table 1.1.1 Subject Disposition
Analysis Set: All Subjects Randomized

Table 1.1.3 Distribution of Subjects in Analysis Populations, by Country, Center, and Treatment
Analysis Set: All Subjects Randomized

Table 1.1.4 Reasons for Subjects Not Randomized
Analysis Set: Non-Randomized Analysis Set

Table 1.1.5 Subjects Excluded From ITT, PP, Rescue Ventolin User, and Safety Populations
Analysis Set: All Subjects Randomized

Table 1.2.2 Reason for Early Discontinuation Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Table 1.3 Reason for Exclusion From the PP Population
Analysis Set: ITT Population

Table 1.4.1 Demographics and Baseline Characteristics Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Table 1.5.1 Severity and Duration of COPD Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Table 1.6.1 Screening Pre- and Post-Bronchodilator and Baseline Spirometry Parameters Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Table 1.7.1 Reversibility to Ventolin HFA Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Table 1.8.1 Reversibility to Atrovent HFA Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Table 1.12 Study Treatment Exposure and Compliance
Analysis Set: Safety Population

Table 1.13 Changes in Smoking Status After Start of Treatment
Analysis Set: Safety Population

2. Efficacy Data Summary Tables

Change From Baseline in Morning Pre-Dose Trough FEV_1

Table 2.1.1 Morning Pre-Dose Trough FEV_1 (L) at Week 24
Analysis Set: ITT Population

Figure 2.1.1.1 Adjusted Mean Change From Baseline in Morning Pre-Dose Trough FEV_1 (L) ± SE Over Time
Analysis Set: ITT Population

Figure 2.1.1.2 Treatment Differences From Placebo MDI*: Adjusted Mean Change From Baseline (95% CI) in Morning Pre-Dose Trough FEV_1 (L) Over Time
Analysis Set: ITT Population

Table 2.1.2 Morning Pre-Dose Trough FEV_1 (L) at Week 24
Analysis Set: PP Population

Figure 2.1.2 Adjusted Mean Change From Baseline in Morning Pre-Dose Trough FEV_1 (L) ± SE Over Time
Analysis Set: PP Population

Table 2.1.4.4 Cumulative Proportion of Responders Based on Change From Baseline in Morning Pre-dose Trough FEV_1 at Week 24
Analysis Set: ITT Population

Figure 2.1.4.31 Cumulative Proportion of Responders Based on Change From Baseline in Morning Pre-dose Trough FEV_1 at Week 24
Analysis Set: ITT Population

Transition Dyspnea Index (TDI)

Table 2.2.1 TDI Focal Score Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

St. George Respiratory Questionnaire (SGRQ)

Table 2.4.1 SGRQ Total Score Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Table 2.4.2 Total Score of Each SGRQ Domain Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Table 2.4.3 Response in SGRQ Total Score (Achievment of a Minimum Clinically Important Difference Threshold of ≥4 Units on Average) Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Number of Puffs of Rescue Ventolin HFA

Table 2.5.1 Mean Daily, Daytime, and Nighttime Number of Puffs of Rescue Ventolin HFA
Analysis Set: Rescue Ventolin User Population

Table 2.5.2 Percentage of Days With No Rescue Ventolin HFA Use Over 24 Weeks
Analysis Set: Rescue Ventolin User Population

Time to Onset of Action Assessed Using FEV_1 on Day 1

Table 2.6.1 FEV_1 (L) by Post-Dose Timepoint on Day 1
Analysis Set: ITT Population

Exacerbations

Table 2.13.1 Rate of COPD Exacerbations Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Table 2.13.2 Rate of COPD Exacerbations With Imputation Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Table 2.14 Time to First COPD Exacerbation of Any Severity and Time to First Moderate or Severe COPD Exacerbation
Analysis Set: ITT Population

Figure 2.14.1.x Kaplan-Meier Curves for Time to First COPD Exacerbation of Any Severity Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Figure 2.14.2.x Kaplan-Meier Curves for Time to First Moderate or Severe COPD Exacerbation Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Table 2.15 Time to Treatment Failure Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

Figure 2.15 Kaplan-Meier Curves for Time to Treatment Failure Overall and by CAT Score Subpopulation
Analysis Set: ITT Population

3. Safety

Adverse Events

Table 3.1.1 Overall Summary of Adverse Events
Analysis Set: Safety Population

Table 3.2.1.1 Adverse Events by MedDRA Primary System Organ Class and Preferred Term
Analysis Set: Safety Population

Table 3.2.1.2 Adverse Events With Onset After the Last Date of Treatment by MedDRA Primary System Organ Class and Preferred Term
Analysis Set: Safety Population

Table 3.2.2 Adverse Events Occurring in >=2% of Subjects in a Treatment by Descending Frequency
Analysis Set: Safety Population

Table 3.2.3 Adverse Events in MedDRA SMQs/Groupings of Interest by Term
Analysis Set: Safety Population

Table 3.2.4 Non-serious Adverse Events Occurring in ≥5% of Subjects in a Treatment by MedDRA Primary System Organ Class and Preferred Term
Analysis Set: Safety Population

Table 3.3 Rate of Adverse Events Adjusted for Exposure by MedDRA Primary System Organ Class and Preferred Term
Analysis Set: Safety Population

Table 3.4 Adverse Events Suspected to be Drug-Related by MedDRA Primary System Organ Class and Preferred Term
Analysis Set: Safety Population

Table 3.5 Adverse Events Causing Study Drug Discontinuation by MedDRA Primary System Organ Class and Preferred Term
Analysis Set: Safety Population

Table 3.6 Listing of Adverse Events Leading to Permanent Discontinuation of Study Treatment
Analysis Set: All Subjects Randomized

Table 3.7.1 Serious Adverse Events by MedDRA Primary System Organ Class and Preferred Term
Analysis Set: Safety Population

Table 3.7.2 Serious Adverse Events With Onset After the Last Date of Treatment by MedDRA Primary System Organ Class and Preferred Term
Analysis Set: Safety Population

Table 3.8.1 Listing of Serious Adverse Events (SAEs)
Analysis Set: All Subjects Screened

Table 3.8.2 Listing of SAE-Specific Report Information
Analysis Set: All Subjects Screened

Table 3.9 Rate of Serious Adverse Events Adjusted for Exposure, by MedDRA Primary System Organ Class and Preferred Term
Analysis Set: Safety Population

Table 3.10 Serious Adverse Events Suspected to be Drug-Related by MedDRA Primary System Organ Class and Preferred Term
Analysis Set: Safety Population

Table 3.11.1 TEAEs by Primary System Organ Class, Preferred Term, and Highest Severity – GFF MDI 14.4/9.6 µg
Analysis Set: Safety Population

Table 3.11.2 TEAEs by Primary System Organ Class, Preferred Term, and Highest Severity – FF MDI 9.6 µg
Analysis Set: Safety Population

Table 3.11.3 TEAEs by Primary System Organ Class, Preferred Term, and Highest Severity – GP MDI 14.4 µg
Analysis Set: Safety Population

Table 3.11.4 TEAEs by Primary System Organ Class, Preferred Term, and Highest Severity – Placebo MDI
Analysis Set: Safety Population

Table 3.12 Death Events, by MedDRA Primary System Organ Class and Preferred Term
Analysis Set: Safety Population

Table 3.13 Listing of Deaths
Analysis Set: All Subjects Screened

4. Subgroup Analyses

Table 2.22.2 Demographics and Baseline Characteristics by GOLD Category
Analysis Set: ITT Population

Table 2.22.3 Demographics and Baseline Characteristics by GOLD Severity
Analysis Set: ITT Population

Table 2.24.2 Severity and Duration of COPD by GOLD Category
Analysis Set: ITT Population

Table 2.24.3 Severity and Duration of COPD by GOLD Severity
Analysis Set: ITT Population

Table 2.25.2 Reversibility to Ventolin HFA by GOLD Category
Analysis Set: ITT Population

Table 2.25.3 Reversibility to Ventolin HFA by GOLD Severity
Analysis Set: ITT Population

Table 2.26.2 Reversibility to Atrovent HFA by GOLD Category
Analysis Set: ITT Population

Table 2.26.3 Reversibility to Atrovent HFA by GOLD Severity
Analysis Set: ITT Population

Table 2.27.2 Study Treatment Exposure and Compliance by GOLD Category
Analysis Set: Safety Population

Table 2.27.3 Study Treatment Exposure and Compliance by GOLD Severity
Analysis Set: Safety Population

Table 2.28.2 Morning Pre-Dose Trough FEV_1 (L) by GOLD Category
Analysis Set: ITT Population

Figure 2.28.2.1 Forest Plot for Morning Pre-Dose Trough FEV_1 (L) ± SE at Week 24 by GOLD Category
Analysis Set: ITT Population

Table 2.28.3 Morning Pre-Dose Trough FEV_1 (L) by GOLD Severity
Analysis Set: ITT Population

Figure 2.28.3.1 Forest Plot for Morning Pre-Dose Trough FEV_1 (L) ± SE at Week 24 by GOLD Severity
Analysis Set: ITT Population

Table 2.30.2 Peak Change From Baseline in FEV1 (L) Within 2 Hours Post-Dose by GOLD Category
Analysis Set: ITT Population

Figure 2.30.2.1 Forest Plot for Peak FEV_1 (L) ± SE Within 2 Hours Post-Dose at Week 24 by GOLD Category
Analysis Set: ITT Population

Table 2.30.3 Peak Change From Baseline in FEV1 (L) Within 2 Hours Post-Dose by GOLD Severity
Analysis Set: ITT Population

Figure 2.30.3.1 Forest Plot for Peak FEV_1 (L) ± SE Within 2 Hours Post-Dose at Week 24 by GOLD Severity
Analysis Set: ITT Population