Tiotropium Bromide Inhalation Solution GSP304-201 A Dose Ranging, Parallel Group, Active (Spiriva® Respimat®) And Placebo Controlled Study To Assess Relative Bioavailability, Pharmacodynamics And Safety Of Three Doses Of Tiotropium Bromide Inhalation Solution In Subjects With Mild To Moderate Chronic Obstructive Pulmonary Disease.

Identifiers NCT03118765

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STATISTICAL ANALYSIS PLAN
PHASE 2

VERSION: 2.0
DATE OF PLAN:

12-SEPT-2017

BASED ON:

GSP304-201 Protocol V3.0 11-APR-2017

STUDY DRUG:

GSP304 (tiotropium bromide) Inhalation Solution

PROTOCOL NUMBER:

GSP304-201

STUDY TITLE:

A DOSE RANGING, PARALLEL GROUP, ACTIVE (SPIRIVA® RESPIMAT®) AND PLACEBO-CONTROLLED STUDY TO ASSESS RELATIVE BIOAVAILABILITY, PHARMACODYNAMICS AND SAFETY OF THREE DOSES OF TIOTROPIUM BROMIDE INHALATION SOLUTION IN SUBJECTS WITH MILD TO MODERATE CHRONIC OBSTRUCTIVE PULMONARY DISEASE

SPONSOR:

Glenmark Specialty SA
Avenue Léopold-Robert 37
2300 La Chaux-de-Fonds
Switzerland

This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

SIGNATURE PAGE

This document has been prepared and reviewed by:

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Signature Sept 12, 2017
Date

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Date

TECHNICAL SUMMARY REPORT (TSR)

Name of Sponsor/Company
Glenmark Specialty SA

Name of Investigational Product:
GSP304 (tiotropium bromide) Inhalation Solution

Name of Active Ingredient:
Tiotropium Bromide

Title Of Study:
A Dose Ranging, Parallel Group, Active (Spiriva® Respimat®) and Placebo-controlled Study to Assess Relative Bioavailability, Pharmacodynamics and Safety of Three Doses of Tiotropium Bromide Inhalation Solution in Subjects With Mild to Moderate Chronic Obstructive Pulmonary Disease

Phase of development: Phase 2

Objectives:

Primary:
To assess the relative bioavailability of GSP304 (tiotropium bromide) Inhalation Solution at dose levels of [redacted] compared with Spiriva® Respimat® inhalation spray (5 µg QD) in subjects with COPD.
To characterize the dose response of GSP304 at dose levels of [redacted] with respect to pharmacodynamics (PD).
Secondary:
To assess the safety and tolerability of GSP304 at dose levels of [redacted]

Methodology:

This is a phase 2, randomized, parallel group, active- and placebo-controlled, 5-arm study to compare the PK profile of 3 blinded doses of GSP304 with open label Spiriva® Respimat®. The study will also evaluate the dose response PD profile of 3 blinded doses of GSP304 compared with blinded GSP304 placebo, using spirometry in subjects with mild to moderate COPD. A total of 155 male and female subjects will be randomized in a 1:1:1:1:1 ratio to 1 of 5 treatment arms. A subject will receive 1 of the 3 double-blind doses of GSP304, or double-blind GSP304 placebo, or open-label Spiriva® Respimat®. The study will include a screening period of up to 2 weeks, followed by a 2 week run-in period, 3 weeks of treatment, and a 2 week post treatment follow up period. The total duration of study participation will be approximately 9 weeks. In this study, PK of tiotropium in plasma and urine will be assessed on Day 1 and Day 21 (at steady state).

Number of Subjects (planned):
A total of 155 subjects will be randomized in this study.

Study Endpoints:

Primary Endpoint

- The PK endpoints for tiotropium in plasma to assess the relative bioavailability are:
- Peak concentrations during the dosing interval at steady-state (C_{maxSS})
- Area under the plasma concentration-time curve over the dosing interval at steady state ($AUC_{0\text{-}tauSS}$)
- Change from baseline (Day 1) at Day 21 (Week 3) in trough FEV_1 response at approximately 24 hours after the last dose (average of 23 hours 15 minutes and 23 hours 45 minutes post-dose measurements), in comparison with GSP304 placebo

Secondary Endpoints

- Amount (A_{etau}) and fraction of dose (F_e) of tiotropium excreted in urine over the dosing interval on Day 1 and Day 21
- Peak concentrations during the dosing interval (C_{max}) on Day 1
- Area under the plasma concentration-time curve over the dosing interval ($AUC_{0\text{-}tau}$) on Day 1
- Time of peak drug concentration over the dosing interval (t_{max}) on Day 1 and Day 21
- Average concentration during a dosing interval at steady state (C_{avSS}) on Day 21
- Accumulation ratio (R_{ac})

- Change from baseline in peak FEV_1 within 12 hours post-dose on Day 1 and Day 21
- Change from baseline (Day 1) at Day 21 (Week 3) in trough FVC response at approximately 24 hours after the last dose (average of 23 hours 15 minutes and 23 hours 45 minutes post-dose measurements), in comparison with GSP304 placebo
- Change from baseline in time-normalized area under the curve for FEV_1 measured over 12 hours on Day 1 and Day 21
- Time to onset of response, defined as at least 12% and 200 mL increase in FEV_1 within 12 hours of dosing on Day 1
- Time to achieving steady state as measured by FEV_1 trough assessments
- Time to achieving steady state as measured by FVC trough assessments

Safety Endpoints

- Vital signs, laboratory parameters, 12-lead electrocardiogram (ECG)
- Incidence of all adverse events (AEs)

Diagnosis and main criteria for inclusion:

Males and females of non-childbearing potential ≥40 and ≤85 years of age with a primary clinical diagnosis of mild to moderate COPD, a FEV_1/FVC ratio of <70% and a baseline FEV_1 of ≥50% of predicted normal value as per the NHANES III predicted normal values at screening

Investigational product, dose and mode of administration:

Name of Investigational Products:
GSP304 (tiotropium bromide) Inhalation Solution, [redacted]
GSP304 (tiotropium bromide) Inhalation Solution, [redacted]
GSP304 (tiotropium bromide) Inhalation Solution, [redacted]
Dosage Form: Inhalation Solution
Dosage: Oral inhalation
Dosage Frequency: [redacted]
Mode of Administration: By oral inhalation using a nebulizer

Comparator, dosage and mode of administration:

Placebo to match GSP304
Dosage Form: Inhalation Solution
Dosage Frequency: [redacted]
Mode of Administration: By oral inhalation using a nebulizer

Reference therapy, dose and mode of administration:

Name of Comparator: Spiriva® Respimat® inhalation spray 2.5 µg per actuation
Dosage Form: Inhalation Spray
Dosage: 5 µg (2 actuations of 2.5 µg each)
Dosage Frequency: Once Daily (QD)
Mode of Administration: By oral inhalation using Respimat® Soft Mist Inhaler

Duration of treatment:

3 weeks (21 days)

Criteria for evaluation :

Efficacy:
Spirometry
FEV_1 and FVC
Refer to 'Pharmacodynamics Assessments' sub-section below.
Pharmacokinetic, Pharmacodynamics, Biomarker, and Pharmacogenomics Assessments:
Pharmacokinetic Assessments
Blood samples (approximately 6 mL) will be collected in dipotassium ethylenediaminetetraacetic acid (EDTA)

coated vacutainers on Day 1 and Day 21 according to the below schedule: Pre-dose (0 hour), and 2, 4, 6, 10, 15, 30, 45, 60, 75, and 90 minutes post-dose, as well as 2, 4, 6, 8, 12, 16, 20 and 24 hours post-dose. The pre-dose sample on Day 1 should be collected within 30 minutes prior to dosing while on Days 7, 14, and 21 the pre-dose sample should be collected within 10 minutes prior to the morning dose. On Day 1 and Day 21, samples will be collected within the following collection windows:
For the 2 minute sample, within a window of ±30 seconds
For the 4, 6, 10, 15, and 30 minute samples, within a window of ± 1 minute
For the 45, 60, 75, 90 minute, and 2.0 hour samples, within a window of ± 2 minutes
For the 4, 6, 8, 12, 16, 20 and 24 hour samples, within a window of ± 5 minutes.

In addition, urine will be collected into pre-weighed containers at pre-dose (within 1 hour prior to dosing), and at the following intervals post-dose from 0-6, 6-12, and 12-24 hours on Day 1 and Day 21.
Collection times and the accurate volume of urine will be noted. In each urine container, approximately 5 mL of 1M citric acid must be added prior to start of collection. Plasma and urine concentrations of tiotropium will be quantified by a validated liquid chromatography-mass spectrometry (LC/MS/MS) method.

Pharmacokinetic Parameters

Plasma:

- $AUC_{0\text{-}tauSS}$
- C_{maxSS}
- C_{minSS}
- C_{avSS}
- C_{max} on Day 1
- t_{max} on Day 1 and Day 21
- $AUC_{0\text{-}tau}$ on Day 1
- R_{ac}

Urine:

- A_{etau}
- $F_e\%$

Additional Pharmacokinetics

Additional parameters may be evaluated depending on the data obtained during the study.

- t_{last} on Day 1 and Day 21

Pharmacodynamics, Biomarker, and Pharmacogenomics Assessments

In addition to screening, pre-dose FEV_1 and FVC will be assessed at -45 minutes and -15 minutes prior to dosing on Day 1, Day 7, Day 14, and Day 21. Trough FEV_1 will be assessed on Day 22 (ie, 24 hours after the Day 21 dose). On Day 1 and Day 21, FEV_1 will be recorded, at the following time points after the morning dose: immediately post-dose at 5 minutes (±3 minutes), 15 minutes (±2 minutes), 30 minutes (±5 minutes), 60 minutes, 90 minutes, and 2 hours (120 minutes); and post-dose at 4, 6, 8, 10, 12, 23 hours15 minutes and 23 hours 45 minutes post dose. The window for 1-hour spirometry and thereafter is ±5 minutes.

Spirometry Effort Start Time is defined as the time of the end of the first effort (Test 1) regardless of whether this is an acceptable effort instead of "start time of first spirometry effort " as described in the protocol.

FEV_1: FEV_1 is the volume of air forcibly exhaled in one second as measured by a spirometer.
Peak FEV_1: It is defined as the maximum FEV_1 over the period of 12 hours post-morning dose.
Trough FEV_1: It is defined as the mean FEV_1 obtained 23 hours 15 minutes and 23 hours 45 minutes post-morning dose of the previous day.
Baseline FEV_1: It is defined as the average of the pre-dose FEV_1 measured at -45 minutes and -15 minutes at Day 1
FVC: FVC is the amount of air which can be forcibly exhaled from the lungs after taking the deepest breath possible.
Baseline FVC: It is defined as the average of the pre-dose FVC measured at -45 minutes and -15 minutes at Day 1.

Safety:

Safety assessments will consist of monitoring and recording all Adverse Events (AEs) and serious adverse events (SAEs) including treatment related AEs and SAEs as well as AEs leading to discontinuation, clinical laboratory measurements, vital signs, 12-lead ECG, and physical examinations.

Analysis Sets

Full Analysis Set (FAS)

This will include all subjects who are randomized, have received at least 1 dose of study medication and have at least 1 post-baseline PD assessment. This analysis set will be the primary analysis set for the PD endpoints.

Safety Analysis Set (SAF)

This will include all subjects who are randomized and received at least 1 dose of study medication. All safety endpoints will use the SAF unless otherwise specified.

Per Protocol Analysis Set (PP)

This will include all subjects who are randomized, received at least 1 dose of study medication, completed the study and do not have exclusionary major protocol deviations. Major and exclusionary protocol deviations will be defined in this SAP and by clinical review prior to unblinding.

PK Analysis Set (PKAS)

This will include all subjects who are randomized, received at least 1 dose of study treatment and have at least 1 quantifiable PK sample and do not have exclusionary major protocol deviations. The PKAS will be used to analyze the PK endpoints unless otherwise specified in the SAP. Major and exclusionary protocol deviations will be defined in this SAP and by clinical review prior to unblinding.

Determination of Sample Size

A sample size of 28 subjects per treatment arm will have 90% power to detect a difference in mean change from baseline in trough FEV_1 of 150 mL between GSP304 and GSP304 placebo assuming a 2-sided alpha of 5% and a standard deviation (SD) of 170 mL. These assumptions are based on available literature from similar studies conducted for Spiriva® Respimat®.

Given the overall 1:1:1:1:1 study treatment allocation ratio, 140 subjects are required for the analysis of the primary endpoint. Assuming a dropout rate of 10%, a total of 155 subjects (31 subjects per treatment arm) will be randomized.

This sample size is also considered to be sufficient for the relative bioavailability endpoint.

Pharmacodynamics Analyses

The PD comparisons will be made between each dose of GSP304 and GSP304 placebo as well as Spiriva and Placebo.

Analysis of Primary Pharmacodynamics Endpoint.

Change from baseline in trough FEV_1 at 24-hours after the last dose of treatment on Day 21 in comparison to GSP304 placebo.The primary endpoint measures the change from baseline (Day 1) at Day 21 (Week 3) in trough FEV_1 response at approximately 24 hours after the last dose (average of 23 hours 15 minutes and 23 hours 45 minutes post-dose measurements). This will be analyzed using a Mixed-effect Model Repeated Measure (MMRM) model to produce treatment differences for each dose of GSP304 vs GSP304 placebo. The MMRM model will include the trough FEV_1 assessment on day 1 and pre-dose data from all visits (Days 7, 14, and 21, which are the trough FEV_1 assessments on days 6, 13 and 20) and fixed terms for treatment, visit, baseline, center, treatment by visit and baseline by visit interactions. The adjusted means for each treatment and the estimated treatment differences for the treatment comparisons will be presented together with 95% confidence intervals (CIs). Multiple imputation-based methods will be considered as a sensitivity analysis for missing data, with further detail provided. The primary endpoint will be analyzed using the FAS and primary inference will be based on Day 21 trough values. A sensitivity analysis will be based on the Full Analysis Set.

Analysis of Secondary Pharmacodynamics Endpoints

Analysis of secondary PD endpoints will be performed on the FAS.

Change from baseline in peak FEV_1 within 12 hours post dose on Day 1 and Day 21: This endpoint measures the peak FEV_1 from the serial readings taken through 12 hours post-dose and then calculates the change from baseline. The change from baseline will be analyzed using MMRM in a similar way to that of the primary endpoint to produce treatment differences for each dose of GSP304 versus GSP304 placebo.

Change from baseline (Day 1) at Day 21 (Week 3) in trough FVC response at approximately 24 hours after the last dose (average of 23 hours 15 minutes and 23 hours 45 minutes post-dose measurements) will be analyzed using MMRM in a similar way to that of the primary endpoint to produce treatment differences for each dose of GSP304 versus GSP304 placebo.

Change from baseline in time-normalized area under the curve for FEV_1 measured over 12 hours on Day 1 and Day 21: The endpoint measures a series of FEV_1 readings taken within 12 hours of dosing.

The trapezoidal rule will be used to calculate $AUC_{0\text{-}12h}$ and then normalized to the length of time. The change from

baseline will be analyzed using MMRM in a similar way to that of the primary endpoint to produce treatment differences for each dose of GSP304 versus GSP304 placebo.
All PD data will also be displayed in summaries and listings.

Time to steady-state: This is the time period from the first dose to two consecutive similar trough FEV_1 or FVC measurements. The trough values will be tabulated and plotted by time for each active dose and placebo.
Time to onset of action (of both a 12% increase and 200 mL increase in FEV_1 within 12 hours of dosing): This is the time period from the first dose to first onset of at least 12 percent and 200 mL improvement in FEV1 over the baseline value. The trough values will be tabulated and plotted by time for each active dose and placebo.

Pharmacokinetic, Pharmacogenomics, and Other Biomarker Analyses

Pharmacokinetic Analyses

Pharmacokinetic analysis will be performed using the PKAS.

Plasma: Individual subject plasma PK parameters will be determined from plasma concentrations using non-compartmental methods for each subject. Actual collection times will be used for the analyses.

Urine: Amount and fraction of dose of tiotropium excreted in urine during the collected time interval in individual subjects will be estimated. Nominal collection times and urine volumes will be used for the estimation.

Additional parameters may be evaluated depending on the data obtained during the study. The derived PK parameters will be listed by treatment, subject and day and summarized by treatment and day. Wherever appropriate, data will be visualized by means of graphical representations. For the summaries, descriptive statistics for all relevant PK parameters will include: n, arithmetic mean, SD, coefficient of variation (%CV), geometric mean, geometric mean %CV, median, minimum and maximum. The plasma concentrations and amount in urine of tiotropium will also be listed by subject, summarized by treatment, and presented graphically as mean plots, and spaghetti plots.

Statistical Analysis of Pharmacokinetic Parameters

An analysis of variance (ANOVA) will be performed on the ln-transformed PK parameters $AUC_{0\text{-}tauSS}$, and C_{maxSS}. The ANOVA model will include treatment as fixed effect. The results from the model will be back-transformed and the adjusted geometrics means for each treatment and the estimated treatment ratios for the treatment comparisons will be presented together with 90% CIs.
The ratios and corresponding 90% CIs will be expressed as a percentage.
The following comparisons will be made:
GSP304 (tiotropium bromide) Inhalation Solution, [redacted]
GSP304 (tiotropium bromide) Inhalation Solution, [redacted]
GSP304 (tiotropium bromide) Inhalation Solution, [redacted]
For GSP304, dose-proportionality of tiotropium C_{maxSS} and $AUC_{0\text{-}tauSS}$ parameters will be assessed using a power model (linear regression relating log-transformed C_{maxSS} and $AUC_{0\text{-}tauSS}$ to the log- transformed dose). Estimates of the mean slopes of log-transformed dose will be reported along with corresponding 90% CIs. Dose proportionality will also be assessed based on amount of tiotropium excreted in urine.

Pharmacogenomics, and Other Biomarker Analyses

Not applicable.

Safety Analyses

All safety analyses will be performed on the SAF and will be presented by the study treatment. Safety data will be summarized descriptively. Data describing quantitative measures will be summarized as mean, SD, median and range (minimum and maximum). Qualitative variables will be presented as counts and percentages.
All safety data will also be displayed in listings.

Other Analyses

Not applicable.

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LIST OF TABLES

1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Term
AE	Adverse Event
AIC	Akaike Information Criteria
ANOVA	Analysis of Variance
AUC	Area Under the Plasma Concentration-time Curve
AR	Auto Regressive
BLQ	Below the Limit Quantification
BMI	Body Mass Index
CI	Confidence Interval
CV	Coefficient Variation
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CS	Compound Symmetry
CSR	Clinical Statistical Report
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
EDC	Electronic Data Collection
eCRF	Electronic Case Report Form
EDTA	Ethylenediaminetetraacetic Acid
FAS	Full Analysis Set
GCP	Good Clinical Practices
GFR	Glomerular filtration rate
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
IRB	Institutional Review Board
J2R	Jump to Reference
LLOQ	Lower Limit of Quantitative
MMRM	Mixed-effect Model Repeated Measure
MedDRA	Medical Dictionary for Regulatory Activities Terminology
PD	Pharmacodynamics
%CV	Coefficient of Variation

PK	Pharmacokinetics
PKAS	Pharmacokinetics Analysis Set
PP	Per-Protocol Population
PT	Preferred Term
QCD	Quantitative Clinical Development
QD	Once Daily
SD	Standard Deviation
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TOEP	Toeplitz
VC	Variance Components

2. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide details of the planned statistical methodology for the analysis of the study data. The SAP also outlines the statistical programming specifications for the tables, listings and figures.

This SAP describes the study endpoints, derived variables, anticipated data transformations and manipulations, and other details of the analyses not provided in the study protocol. This SAP therefore outlines in detail all other aspects pertaining to the planned analyses and presentations for this study.

The following documents were reviewed in preparation of this SAP:

Protocol Revision Chronology:		
Protocol 1.0	11-Oct-2016	Original
Protocol 2.0	05-Jan-2017	Amendment 1
Protocol 3.0	11-Apr-2017	Amendment 2

This SAP was developed in accordance with ICH E9 guideline. All decisions regarding final analysis, as defined in this SAP document, will be made prior to Database Lock (unblinding) of the study data. Further information can be found in the protocol.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Objective

The primary objectives are:

- To assess the relative bioavailability of GSP304 (tiotropium bromide) Inhalation Solution at dose levels of [redacted] compared with Spiriva® Respimat® inhalation spray (5 µg QD) in subjects with COPD.
- To characterize the dose response of GPS304 at dose levels of [redacted] with respective PD.

3.1.2. Secondary Objective

The secondary objective is to assess the safety and tolerability of GSP304 at dose levels of [redacted]

3.2. Study Endpoints

3.2.1. Primary Endpoints

The primary endpoints are:

- The PK endpoints for tiotropium in plasma to assess the relative bioavailability are:
  - Peak concentrations during the dosing interval at steady-state (C_{maxSS})
  - Area under the plasma concentration-time curve over the dosing interval at steady state ($AUC_{0\text{-}tauSS}$)
- Change from baseline (Day 1) at Day 21 (Week 3) in trough FEV_1 response at approximately 24 hours after the last dose (average of 23 hours 15 minutes and 23 hours 45 minutes post-dose measurements), in comparison with GSP304 placebo

3.2.2. Secondary Endpoints

The secondary endpoints are:

- Amount (A_{etau}) and fraction of dose of tiotropium (F_e) excreted in urine over the dosing interval on Day 1 and Day 21
- Peak concentrations during the dosing interval (C_{max}) on Day 1
- Area under the plasma concentration-time curve over the dosing interval ($AUC_{0\text{-}tau}$) on Day 1

- Time of peak drug concentration over the dosing interval (t_{max}) on Day 1 and Day 21
- Average concentration during a dosing interval at steady state (C_{avSS}) on Day 21
- Accumulation ratio (R_{ac})
- Change from baseline in peak FEV_1 within 12 hours post-dose on Day 1 and Day 21
- Change from baseline (Day 1) at Day 21 (Week 3) in trough FEV_1 response at approximately 24 hours after the last dose (average of 23 hours 15 minutes and 23 hours 45 minutes post-dose measurements), in comparison with GSP304 placebo
- Change from baseline in time-normalized area under the curve for FEV_1 measured over 12 hours on Day 1 and Day 21
- Time to onset of response, defined as at least 12% and 200 mL increase in FEV_1 within 12 hours of dosing on Day 1
- Time to achieving steady state as measured by FEV_1 trough assessments
- Time to achieving steady state as measured by FVC trough assessments

3.2.3. Safety Endpoints

The safety endpoints are:

- Vital signs, laboratory parameters, 12-lead ECG
- Incidence of all AEs

4. STUDY DESIGN

4.1. Summary of Study Design

This is a phase 2, randomized, parallel group, active-and placebo-controlled, 5-arm study to compare the PK profile of 3 blinded doses of GSP304 with open label Spiriva® Respimat®. The study will also evaluate the dose response PD profile of 3 blinded doses of GSP304 compared with blinded GSP304 placebo, using spirometry in subjects with mild to moderate COPD.

The study will consist of a screening period of up to 2 weeks, followed by a 2-week run-in period, a 3-week treatment period, and a 2-week post treatment follow-up period. The total duration of study participation will be approximately 9 weeks.

A total of 155 male and female subjects will be randomized in a 1:1:1:1:1 ratio to 1 of 5 treatment arms. A subject will receive 1 of the 3 double-blind doses of GSP304, or double-blind GSP304 placebo, or open-label Spiriva® Respimat®.

4.2. Definition of Study Drugs

Table 2 and Table 3 provide a description of the double-blind GSP304, double-blind GSP304 placebo, and the open label Spiriva® Respimat® comparator to be used in the study.

Table 2: GSP304

Product name:	GSP304	GSP304	GSP304
Dosage Form:	Inhalation solution	Inhalation solution	Inhalation solution
Unit Dose	[redacted]	[redacted]	[redacted]
Route of Administration	Oral inhalation	Oral inhalation	Oral inhalation
Method of Administration	Nebulization	Nebulization	Nebulization
Physical Description	A clear solution in a semitransparent, soft plastic ampule	A clear solution in a semitransparent, soft plastic ampule	A clear solution in a semitransparent, soft plastic ampule

Table 3: Other Study Drugs

	Comparator Product	GSP304 Placebo
Product Name	Spiriva® Respimat®	Matching placebo for GSP304
Dosage Form	Inhalation spray for oral inhalation	Inhalation solution
Unit Dose	2.5 µg	0 µg
Route of Administration	Oral inhalation	Oral inhalation
Method of Administration	Metered spray for inhalation	Nebulization
Physical Description	A clear solution in a green/grey plastic Respimat® inhaler	A clear solution in a semi-transparent, soft plastic ampule
Manufacturer	Boehringer Ingelheim Pharma GmbH & Co	Glenmark or designee

4.3. Sample Size Considerations

4.3.1. Sample Size Justifications

A sample size of 28 subjects per treatment arm will have 90% power to detect a difference in mean change from baseline in trough FEV_1 of 150 mL between GSP304 and GSP304 placebo assuming a 2-sided alpha of 5% and a standard deviation (SD) of 170 mL. These assumptions are based on available literature from similar studies conducted for Spiriva® Respimat® (Caillaud et al., 2007). Given the overall 1:1:1:1:1 study treatment allocation ratio, 140 subjects are required for the analysis of the primary endpoint. Assuming a dropout rate of 10%, a total of 155 subjects (31 subjects per treatment arm) will be randomized.

This sample size is also considered to be sufficient for the relative bioavailability endpoint.

4.3.2. Sample Size Re-estimation

No sample size re-estimation is planned for this study.

4.4. Randomization

Randomization and investigational product (IP) assignment will occur in the morning of Day 1 after all screening procedures have been performed, run-in has been completed and eligibility of the subject for the study confirmed. Randomization numbers will be issued centrally using interactive voice response system (IVRS)/interactive web response system (IWRS). Randomized

subjects who terminate their study participation for any reason, regardless of whether study drug has been taken or not, will retain their randomization number.

Subjects will be assigned in the ratio of 1:1:1:1:1 to receive treatments with either of double-blind GSP304 at 1 of 3 dose levels, open-label Spiriva® Respimat®, or double-blind GSP304 placebo based on a computer-generated randomization scheme that will be reviewed and approved by a statistician. The randomization scheme will be stored within the IVRS/IWRS database until unblinding of this study is requested. The randomization scheme and identification for each subject will be included in the final clinical study report for this study.

4.5. Clinical Assessments

The following clinical assessments will be performed during the study.

1. Vital signs: vital signs will be taken at screening (Day -28 to -15), Day -1, Day 1 (1 hour pre-dose and 1 hour post-dose), Day 2, Day 7, Day 14 (1 hour pre-dose and 1 hour post-dose), Day 20, Day 21 (post-dose), Day 22 (ie 24 hours after Day 21 dose), and Day 35 (±2; ie 2 weeks follow-up after last dose date).
2. Physical Examination: physical examination will be performed at screening (Day -28 to Day -15 (comprehensive physical examination)), Day -1 (ie, 24 hours before Day 1 dose), Day 7 (pre-dose), Day 14 (pre-dose), and Day 20 (pre-dose).
3. 12 Lead Electrocardiogram (ECG): 12 lead ECG will be performed at screening (Day -28 to Day -15), Day 1 (pre-dose) and Day 21 (pre-dose).
4. Laboratory Tests: hematology, biochemistry, and urine analysis tests will be performed at screening (Day -28 to Day -15), Day 7 (pre-dose), Day 14 (pre-dose), Day 21 (pre-dose), and Day 35 (±2; ie 2 weeks follow-up after last dose date). Urine analysis for drugs of abuse and cotinine and blood alcohol tests will be performed on screening (Day -28 to Day -15), Day -1, and Day 20 (pre-dose). Serum pregnancy testing will be performed in all female subjects on screening (Day -28 to Day -15), and urine pregnancy testing will be performed in female subjects on Day -1 and Day 35 (±2).
5. Other safety assessments consisting of monitoring and recording all Adverse Events, serious adverse events (SAEs) and Concomitant Medications will be collected throughout the study.
6. Pharmacodynamics: The spirometry test will be performed at screening (Day -28 to Day -15), Day 1 (pre-dose -45 mins and -15 mins), Day 7 (pre-dose -45 mins and -15 mins), Day 14 (pre-dose -45 mins and -15 mins), Day 21 (pre-dose -45 mins and -15 mins), and Day 22 (ie 24 hours after Day 21 dose). Pre-dose FEV_1 and FVC will be assessed at -45 minutes and -15 minutes prior to dosing on Day 1, Day 7, Day 14, and Day 21. Trough FEV_1 will be assessed on Day 22 (ie 24 hours after Day 21 dose). On Day 1 and Day 21,

FEV_1 will be recorded, at the following time points after the morning dose: immediately post-dose at 5 minutes (±3 minutes), 15 minutes (±2 minutes), 30 minutes (±5 minutes), 60 minutes, 90 minutes, and 2 hours (120 minutes); and post-dose at 4, 6, 8, 10, 12, 23 hours 15 minutes and 23 hours 45 minutes post-dose. All post-dose timings are relative to the end of dosing (ie, end of nebulization of GSP304/GSP304 placebo or after the second actuation of Spiriva®Respimat®). The window for 1-hour spirometry and thereafter is ±5 minutes.

7. Pharmacokinetic Plasma and Urine Concentrations: Blood samples (approximately 6 mL) will be collected in dipotassium ethylenediaminetetraacetic acid (EDTA) coated vacutainers on Day 1 and Day 21 according to the below schedule: Pre-dose (0 hour), and 2, 4, 6, 10, 15, 30, 45, 60, 75, and 90 minutes post-dose, as well as 2, 4, 6, 8, 12, 16, 20 and 24 hours post-dose. All post-dose timings are relative to the end of dosing (ie, end of nebulization of GSP304/GSP304 placebo or after the second actuation of Spiriva®Respimat®). The pre-dose sample on Day 1 should be collected within 30 minutes prior to dosing while on Days 7, 14, and 21 the pre-dose sample should be collected within 10 minutes prior to the morning dose.
   On Day 1 and Day 21, samples will be collected within the following collection windows:

- For the 2 minute sample, within a window of ±30 seconds
- For the 4, 6, 10, 15, and 30 minute samples, within a window of ± 1 minute
- For the 45, 60, 75, 90 minute, and 2.0 hour samples, within a window of ± 2 minutes
- For the 4, 6, 8, 12, 16, 20 and 24 hour samples, within a window of ± 5 minutes.

In addition, urine will be collected into pre-weighed containers at pre-dose (within 1 hour prior to dosing), and at the following intervals post-dose from 0-6, 6-12, and 12-24 hours on Day 1 and Day 21.

Collection times and the accurate volume of urine will be noted. In each urine container, approximately 5 mL of 1M citric acid must be added prior to start of collection. Plasma and urine concentrations of tiotropium will be quantified by a validated liquid chromatography-mass spectrometry method.

Plasma: Plasma PK parameters will be determined from plasma concentrations using non-compartmental methods for each subject. Actual collection times will be used for the analyses.

Urine: Amount and fraction of dose of tiotropium excreted in urine during the collected time interval in individual subjects will be estimated. Nominal collection times and urine volumes will be used for the estimation.

5. PLANNED ANALYSES

5.1. Interim Analyses

No interim analyses are planned for this study.

5.2. Final Analyses

All planned analyses will be carried out once the clinical database lock (DBL) has taken place. Once this has been achieved, unblinding will occur and the analyses will be performed.

6. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

6.1. General Summary Table and Individual Subject Data Listing Consideration

In general, listings will be sorted and presented by treatment and subject number. Subject number when broken down consists of the site number and 4 digits sequential number. Study visits will be labeled as Screening, Baseline (Day 1), Day 2, Day 7, Day 14, Day 20 and Day 21 as well as End of Study (Follow Up) and Unscheduled. When required, the time of the scheduled assessment will be included.

The following treatment levels will be used for all tables, figures, and listings in the order below. Spiriva R will be used for Spiriva® Respimat® in tables, figures and listings for simplicity.

GSP304[redacted]
GSP304[redacted]
GSP304[redacted]
GSP304 Total (AE/SAE-related tables)
GSP304 Placebo
Spiriva R 5 µg

6.2. General Post Text Summary Table and Individual Subject Data Listing Format Considerations

Tables, figures and listings are numbered following the ICH structure. Table headers, variables names and footnotes will be modified as needed following data analyses. Additional tables, figures and listings will be generated, as needed, following the data analysis (post-hoc).

6.3. Data Management

Data from the study will be managed by the Sponsor's Clinical Research Operations group or designee. The Investigator will allow representatives of the Sponsor, regulatory agencies, and their designees to inspect all study documents (including, but not limited to, consent forms, IP accountability forms, IRB/IEC approvals) and pertinent hospital or clinic records for confirmation of data throughout and after completion of the study. Monitoring visits will be

conducted as needed during the course of the study. A complete review of source documentation of key efficacy and safety data will be conducted at each monitoring visit for verification that all information recorded in the CRF/eCRF accurately reflects the data recorded in the subject's source documents.

All data verification, using hospital or clinic records, will be performed respecting subject confidentiality and will be carried out in accordance with SOPs.

All subject data generated during the study will be recorded and transcribed into a database. The final authorization of the CRF/eCRF data is the Investigator Signature Form. This form must be approved by the Principal Investigator to signify that he/she has reviewed the CRF/eCRF, including all laboratory and safety assessments, and that all of the data therein is complete and accurate.

The data will be reviewed to ensure that the forms were completed properly.

Datasets will be prepared using headings from Clinical Data Interchange Consortium (CDISC) Study Data Tabulation Model (SDTM) implementation for human clinical trials and ADaM (Analysis Dataset Model).

All tables, figures and listings will be produced using SAS® statistical software Version 9.3 or a later version, unless otherwise noted in a secure and validated environment. Each output will be provided in PDF format, with all tables and listings also being produced in RTF format.

All analyses will be performed using SAS® Version 9.3 in a secure and validated environment. All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard PAREXEL procedures.

6.4. Data Presentation Conventions

Continuous data will be summarized in terms of the mean, SD, median, minimum, maximum, and number of observations, unless otherwise stated. Continuous data that are expected to be skewed will be presented in terms of the maximum, upper quartile, median, lower quartile, minimum, and number of observations. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile and upper quartile will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Categorical data will be summarized in terms of the number of subjects providing data at the relevant time point (n), frequency counts, and percentages. Any planned collapsing of categories will be detailed in the corresponding sections of this SAP and within the data displays.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts.

Percentages will be calculated using n as the denominator.

Changes from baseline in categorical data will be summarized using shift tables where appropriate.

P-values greater than or equal to 0.001, in general, will be presented to three decimal places. P-values less than 0.001 will be presented as "<0.001" and p-values greater than 0.999 will be presented as ">0.999".

Confidence intervals will be presented to one more decimal place than the raw data.

A table, figure, listing is to be generated for any required item where no data is available or reported, with either a table or listing stating "No Data Available" or "No Data Reported", or print a one line message indicating there was no report data available: "NO DATA AVAILABLE FOR THIS REPORT".

6.5. Analysis Sets

6.5.1. Full Analysis Set (FAS)

This will include all subjects who are randomized, have received at least 1 dose of study medication and have at least 1 post-baseline PD assessment. This analysis set will be the primary analysis set for the PD endpoints.

6.5.2. Safety Set (SAF)

This will include all subjects who are randomized and received at least 1 dose of study medication. All safety endpoints will use the SAF.

6.5.3. Per-Protocol Set (PP)

This will include all subjects who are randomized, received at least 1 dose of study medication, completed the study and do not have exclusionary major protocol deviations. Major and exclusionary protocol deviations will be defined in section 7.3 and by clinical review prior to unblinding.

6.5.4. Pharmacokinetic Set (PKAS)

This will include all subjects who are randomized, received at least 1 dose of study treatment and have at least 1 quantifiable PK sample and do not have exclusionary major protocol deviations. The PKAS will be used to analyze the PK endpoints unless otherwise specified in this SAP. Major and exclusionary protocol deviations will be defined in section 7.3 and by clinical review prior to unblinding.

Subjects or data may be excluded from the PKAS at the discretion of the PK Scientist upon consultation with the sponsor. Any data excluded will be discussed in the CSR. Any excluded subject will have his or her concentration and PK parameter data (if available) listed only. Subjects who receive placebo will not be part of the PKAS. The PKAS will be used for all tables and graphical summaries of the PK data

6.6. Baseline Definition

The Baseline value will be defined as the Visit 3 (Day 1) measurement. If this measurement is not available, the Visit 1 (D-28 to D-15) measurement will be used as the baseline value. Table 4 below contains a list of definitions of PD parameters and baseline of parameters covered in this SAP.

Table 4: Baseline

Parameter	Definition	Baseline
Peak FEV_1	Maximum FEV_1 over the period of 12 hours post-morning dose.	Average of the pre-dose FEV_1 measured at -45 minutes and -15 minutes at Day 1
Trough FEV_1	Mean FEV_1 obtained 23 hours 15 minutes and 23 hours 45 minutes post-morning dose of the previous day.	Average of the pre-dose FEV_1 measured at -45 minutes and -15 minutes at Day 1
Time-normalized Area Under the Curve FEV_1		Average of the pre-dose FEV_1 measured at -45 minutes and -15 minutes at Day 1
FVC	Amount of air which can be forcibly exhaled from the lungs after taking the deepest breath possible Mean FVC obtained 23 hours 15 minutes and 23 hours 45 minutes post-morning dose of the previous day.	The baseline assessment is the average of the pre-dose FVC measured at -45 minutes and -15 minutes at Day 1
Laboratory Parameters (hematology, blood chemistry, liver function and urinalysis)		Screening (Day -28 to Day -15).
Vital Signs		Day 1 (1hr pre-dose)

Parameter	Definition	Baseline
ECG		Day 1 (pre-dose)
Physical Examinations		Day -1

6.7. Derived and Transformed Data

6.7.1. Age

Age is the subject's age in complete years – calculated based on the informed consent date and subject's date of birth.

If the month and day of informed consent is on or after the month and day of birth:

Age = year of informed consent – year of birth

If the month and day of informed consent is before the month and day of birth:

Age = year of informed consent – year of birth – 1

6.7.2. Study Day

If the date of interest occurs on or after the randomization date:

Study day = date of interest – randomization date + 1

If the date of interest occurs before the randomization date:

Study day = date of interest – randomization date

There is no study day 0.

6.7.3. Change from Baseline

Change from baseline will be calculated by subtracting the baseline measurement from the post baseline measurement.

Change from baseline = post baseline measurement – baseline measurement.

6.7.4. Visits

Table 5 contains a list of visits in the study period. Data will be analyzed based on the nominal visit/time.

Table 5: Visits (Days)

Visit	Scheduled Day	Days
Visit 1 (Screening)	-15	-28 to -15
Visit 2 (Run-in)	-14	-14 to -2

Visit 3 (Baseline)	1	-1 to 2*
Visit 4 (Week 1)	7	
Visit 5 (Week 2)	14	
Visit 6 (Week 3)	21	20 to 22*
Visit 7 (Follow-up)	35	33 to 37

*: Subjects will stay in the clinic as in-patients for about 36 to 48 hours at Visit 3 and Visit 6.

6.7.5. Unscheduled Assessments

Unscheduled assessments (laboratory data, ECG or vital signs associated with non-protocol clinical visits or obtained in the course of investigating or managing adverse events) will be included in listings, but not in summaries. If more than one assessment is available for a given visit, the first or most valid observation will be used in summaries presented in listings and other assessments will be classed as unscheduled measurement.

6.7.6. Pharmacokinetic Parameters

Derivation of PK parameters will be the responsibility of Early Phase, Quantitative Clinical Development (QCD), PAREXEL International and will be conducted either with Phoenix WinNonlin® Professional v. 6.3 (or higher) or SAS® v.9.3 (or higher). The PK parameters in Table 6 will be determined for Tiotropium in plasma after administration of the first dose:

Table 6: Plasma Pharmacokinetic Parameters (Day 1)

Parameter	Definition
$AUC_{0\text{-}tau}$	Area under the concentration-time profile over the dosing interval
C_{max}	Peak concentrations during the dosing interval
t_{last}	Time of last quantifiable concentration
t_{max}	Time of peak drug concentration

The PK parameters in Table 7 will be determined for Tiotropium in plasma following multiple dose administration (Day 21). The terminal elimination half-life will be reported only if data permit a reliable estimation.

Table 7: Plasma Pharmacokinetic Parameters (Day 21)

Parameter	Definition
$AUC_{0\text{-}tauSS}$	Area under the concentration-time profile over the dosing interval at steady state
$AUC_{0\text{-}tauSS}$/Dose	Dose normalized area under the concentration-time profile over the dosing interval at steady state
C_{avSS}	Average concentration during a dosing interval at steady state
C_{maxSS}	Peak concentrations during the dosing interval at steady-state
C_{maxSS}/Dose	Dose normalized peak concentration during the dosing interval at steady state

C_{minSS}	Minimum of trough concentrations during the dosing interval at steady-state
R_{ac}	Accumulation ratio for C_{max} and AUC $_{0\text{-}tau}$
$t_{1/2}$	Terminal elimination half-life
t_{last}	Time of last quantifiable concentration
t_{max}	Time of peak drug concentration

The PK parameters in Table 8 will be calculated for Tiotropium Bromide in urine following treatment administration (Day 1 and Day 21):

Table 8: Urine Pharmacokinetic Parameters (Day 1 and Day 21)

Parameter	Definition
A_{etau}	Cumulative amount of unchanged drug excreted into the urine over the dosing interval
A_{etau}/Dose	Dose normalized cumulative amount of unchanged drug excreted into the urine over the dosing interval
Fe%	Fraction of dose (%) excreted into the urine over the dosing interval

6.7.6.1. Handling of Values Below the Limit of Quantification

All plasma/urine concentrations below the lower limit of quantification (LLOQ) or missing data will be labeled as below the limit of quantification (BLQ) or missing, respectively, in the concentration data listings.

Considerations in the handling of BLQ data for the generation of plasma PK Parameters and for plotting of individual plasma PK concentration data

BLQ values will be imputed in the PK concentration dataset used for the derivation of PK parameters. The following rules will be applied:

- BLQs at the beginning of a subject profile (ie before the first incidence of a measurable concentration on the first day of dosing) will be assigned to zero;
- BLQs at the end of a subject profile (ie after the last incidence of a measurable concentration on last day of dosing) will be set to missing;
- Single or consecutive BLQs which fall between measurable concentrations will be set to missing.
- Quantifiable concentrations falling between two BLQ values might be set to missing if considered anomalous by the PK Scientist after consultation with the sponsor.

For linear plots, zero concentration value(s) will be included in the plot while missing values will be ignored. For log-linear plots, zero concentration value(s) will be assigned a ½ LLOQ value with the exception of the pre-dose sample collected on Day 1 while missing concentrations at the end of the profile will be ignored.

Considerations in the handling of BLQ data for summarizing plasma PK concentration data

BLQ values will be imputed for mean concentration-time plots and tabular summaries according to the following rules:

- All BLQ values will be set to zero, except when an individual BLQ falls between two measurable values or one or more BLQs fall at the end of a subject profile, in which case they will be set to missing;
- Mean values will be reported only if calculated on a minimum of 3 quantifiable concentrations. The number of subjects contributing to the calculation of the mean will be specified in a footnote to the mean plots (both in linear and semi-log scales) if lower than the total amount of samples available per time point;

A high proportion of BLQ values may affect derivation of SD; if more than 30% of values at a time-point are imputed, then SD will not be displayed.

Tabular summaries for concentration-time data will report N (number of subjects who received treatment), n (number of subjects with non-missing values) and, if applicable, number imputed (number of subjects with imputed values (ie, BLQ assigned zero concentration).

Considerations in the handling of BLQ data for summarizing urine PK concentration data

- For instances in which the subject did not void during the specified interval and 'NS' is present in the listing, the concentration value will be set to missing.

Considerations in the handling of missing data for the generation of urine PK Parameters

- For instances in which the subject did not void during the specified interval the concentration will be set to zero to allow calculation of urine PK parameters.

6.7.6.2. Pharmacokinetic Parameters Calculation Methods

PK parameters will be calculated by non-compartmental analysis methods from the concentration-time data following these guidelines:

- Actual sampling times relative to dosing rather than nominal times will be used in the calculation of all derived PK parameters;
- There will be no imputation of missing data;
- Any subjects with missing concentration data will be included in the PK analysis set provided that at least C_{maxSS} and/or $AUC_{0\text{-}tauSS}$ can be reliably calculated. A decision will be taken on a case by case basis by the PK Scientist after consultation with the sponsor;
- C_{max} and C_{maxSS} will be obtained directly from the concentration-time data;

- t_{max} is the time at which C_{max} or C_{maxSS} is observed;
- λ_Z will be estimated at terminal phase by linear regression after log-transformation of the concentrations:
    - Only those data points that are judged to describe the terminal log-linear decline will be used in the regression
    - A minimum number of three data points in the terminal phase will be used in calculation λz with the line of regression starting at any post -C_{max} data point (C_{max} should not be part of the regression slope). The adjusted correlation coefficient (R^2 adjusted) in general should be greater than 0.80.
    - The interval used to determine λz should be equal or greater than 1.5-fold the estimated half-life or otherwise flagged and used at the PK scientist's best knowledge and judgment. The corresponding estimated $t_{1/2}$ will need to be flagged or excluded from statistical analysis accordingly.
- $t_{1/2}$ will be calculated as $\ln 2/\lambda_Z$;
- C_{avSS} will be calculated as $AUC_{0\text{-}tauSS}$/tau;
- $AUC_{0\text{-}tau}$ and $AUC_{0\text{-}tauSS}$ will be calculated using the linear up/linear down method;
- C_{minSS} will be obtained directly from the concentration-time data. In the event of a minimum concentration during the dosing interval at steady state (C_{minSS}) not coinciding with the pre-dose concentration at steady state (C_{trough} on day 21), both parameters will be reported;
- R_{ac}(AUC) will be calculated as $AUC_{0\text{-}tauSS}/AUC_{0\text{-}tau}$;
- $R_{ac}(C_{max})$ will be calculated as C_{maxSS}/C_{max};
- A_{etau} is the cumulative amount excreted over the dosing interval and will be calculated as the sum of the products of concentration and urine volume over the appropriate collection intervals. For the calculation of urine PK parameters the protocol time intervals should be used. If a subject urinates into the toilet or a urine sample is lost any other way, or if no urine volume has been recorded for a sampling interval, the cumulative amount excreted starting with this interval cannot be calculated. If, however, a subject is unable to urinate, no amount excreted has been lost and the cumulative amount can continue to be calculated past that collection interval. For the affected time interval, the partial amount will be zero;
- Fe% is the fraction of unchanged drug in urine expressed as a percentage and will be calculated as $Fe\% = (A_{etau}/Dose)*100$.

If t_{last} (last time point with measurable concentration) is before 24 hour post-dose in more than

50% of treated subjects s at any particular dose of GSP 304 or Spiriva® Respimat®, AUC_{last} (area under the plasma concentration time curve from time zero to last time point with measurable concentration) may be estimated and compared between different doses of GSP 304 and Spiriva® Respimat® by ANOVA.

Any inconsistency between plasma and urine PK would be will be further investigated and might be flagged and/or excluded from the analysis at the discretion of the PK Scientist after consultation with the sponsor.

An exploratory PK/ glomerular filtration rate (GFR) analysis of GSP304 in urine and plasma may be performed if deemed appropriate following review of the summary PK and GFR data. The decision to perform this analysis will be made by the Sponsor upon review of the tables, figures and listings produced at the end of the study. If the decision is made not to proceed with the PK/ GFR analysis, this section of the SAP will not be applicable and the outputs described herein will not be presented.

6.7.7. Pharmacodynamics Parameter Calculation: Time-normalized Area under the Curve (AUC) for FEV_1 measured over 12 hours

Time-normalized Area under the Curve (AUC) for FEV_1 measured over 12 hours is defined as the area between baseline FEV_1 and the FEV_1 curve from 0 to 12 hours divided by 12 hours.

12 hour serial spirometry will be performed at Day 1 and Day 21 of each treatment period: spirometry will be performed immediately at 5 minutes (±3 minutes), 15 minutes (±2 minutes), 30 minutes (±5 minutes), 60 minutes, 90 minutes, and 2 hours (120 minutes); and post-dose at 4, 6, 8, 10, 12, 23 hours 15 minutes and 23 hours 45 minutes.

AUC is calculated from zero time to 12 hours ($AUC_{0\text{-}12}$), using the trapezoidal method, divided by 12 hours to give the $AUC_{0\text{-}12/12h}$ values in litres. Non-missing FEV_1 values at the following time points are required in order to calculate the normalised $AUC_{0\text{-}12/12h}$: pre-dose; at least one value between 2 hours and 6 hours post-dose (inclusive); and at least one value after 6 hours post-dose. Otherwise the normalised $AUC_{0\text{-}12/12h}$ will be missing.

$AUC_{0\text{-}12/12h}$ is calculated as follows:

$$\mathrm{AUC}_{0-12/12h} = \frac{1}{t_{11} - t_0} \sum_{i=1}^{11} \frac{(t_i - t_{i-1})(d_i + d_{i-1})}{2}$$

Where d_i is the spirometry value (FEV_1) obtained at time t_i; t_i is the time (in hours) for which d_i is measured: $t_0 = 0$, $t_1 = 0.08$, $t_2 = 0.25$, $t_3 = 0.5$, $t_4 = 1$, $t_5 = 1.5$, $t_6 = 2$, $t_7 = 4$, $t_8 = 6$, $t_9 = 8$, $t_{10} = 10$ and $t_{11} = 12$. d_0 is the mean of the two pre-dose values at Day 1 or Day 21.

6.8. Handling of Missing Data

6.8.1. Missing Pharmacodynamics Endpoints

No explicit imputation for missing pharmacodynamics endpoints will be performed for this study. If either the baseline or the post-baseline result is missing, the change from baseline is set to missing.

Section 9.6.2 describes the sensitivity analyses to be performed for the primary endpoint in handling missing data.

6.8.2. Missing Start and Stop Dates for Prior and Concomitant Medication

For the purpose of inclusion in prior and/or concomitant medication tables, incomplete medication start and stop dates will be imputed as follows:

- If year and month are present and day is missing, then set day to first day of month for start date, and set day to last day of month for end date
- If year and day are present and month is missing, then set month to January for start date, and set month to December for end date
- If year is present and month and day are missing, then set month and day to January 1 for start date, and set month and day to December 31 for end date
- Completely missing date will not be imputed

The partial dates will be provided as such in the subject data listings (with the imputed dates).

When imputing a start date, ensure that the new imputed date is sensible ie is prior to the end date of prior and concomitant medications.

6.8.3. Missing Start and Stop Dates for Adverse Events

Due diligence will be done to obtain accurate AE information. If all planned methods to obtain accurate AE information have failed, missing and partial AE onset and end dates will be imputed. Imputed dates will be flagged in the individual supportive subject listings. Unless otherwise specified, the following conventions will be used:

Missing and Partial AE onset dates

- If onset date is completely missing, then onset date is set to date of first dose
- If onset year is present and
    - month and day are missing:
        - If onset year = year of first dose, then set onset date to date of first dose

        - If onset year < year of first dose, then set onset month and day to December 31st.
        - If onset year > year of first dose, then set onset month and day to January 1st
    - month is missing:
        - If onset year = year of first dose, then set onset date to date of first dose
        - If onset year < year of first dose, then set onset month to December
        - If onset year > year of first dose, then set onset month to January
- If onset month and year are present and day is missing:
    - If onset year = year of first dose and
        - onset month = month of first dose then set onset date to date of first dose
        - onset month < month of first dose then set onset date to last day of month
        - onset month > month of first dose then set onset date to 1st day of month
    - If onset year < year of first dose then set onset date to last day of month
    - If onset year > year of first dose then set onset date to 1st day of month
- For all other cases, set onset date to date of first dose

Missing and Partial AE end dates

- If end date is completely missing, end date is not imputed and the AE is flagged as "ongoing"
- If year is present and
    - month and day are missing
        - If year = year of last dose, then set end date to the date of last dose
        - If year < year of last dose, then set end month and day to December 31st
        - If year > year of last dose, then set end month and day to January 1st
    - month is missing
        - If year = year of last dose, then set end date to date of last dose
        - If year < year of last dose , then set end month to December
        - If year > year of last dose, then set end month to January
- If month and year are present and day is missing:
    - If year = year of last dose and

        - month = month of last dose then set day to day of last dose
        - month < month of last dose then set day to last day of month
        - month > month of last dose then set day to 1st day of month
    - If year < year of last dose, then set end date to last day of the month
    - If year > year of last dose, then set end date to 1st day of month
- For all other cases, set end date to date of last dose

7. STUDY POPULATION

7.1. Overview of Planned Analyses

The analyses will be based on the SAF, unless otherwise specified. Table 9 provides an overview of the planned analyses and the associated study populations.

Table 9: Overview of Planned Analyses and Study Populations Used

Display Type	Data Displays Generated		
	Table	Figure	Listing
Subject disposition			
Total disposition	Y[1]		
Protocol deviations	Y[2]		Y
Summary of subjects in analysis population	Y		
Subjects excluded from each analysis populations			Y
Demographic Characteristics	Y[3]		Y
Baseline Characteristics	Y		Y
Medical History	Y		Y
Summary of Chronic Obstructive Pulmonary Disease History	Y		Y
Exposure	Y[2]		Y
Treatment Compliance	Y[2]		Y
Prior Medications	Y		Y
Concomitant Medications	Y		Y
Rescue Medications	Y		Y

NOTES :

- Y = Yes display generated
- [1]: Data from clinic or database
- [2]: Display will be based on the SAF
- [3]: Display will be based on the SAF and repeated for the FAS, PP and PKAS

7.2. Subjects Disposition

A clear accounting of the disposition of all subjects who enter the study will be provided, from screening to end of study participation. Summaries of subject disposition presented by treatment arm and overall, will be provided as follows:

- Number and percentage of subjects enrolled
- Number and percentage of subjects randomized
- Number and percentage of subjects in each of the SAF, FAS, PP, and PKAS
- Number and percentage of subjects who withdrew early from the study (including reasons for early withdrawal)

By-subject listings of enrollment details, randomization details, visit dates, and withdrawal details (including reason for discontinuation and duration of treatment prior to discontinuation) will also be provided.

7.3. Screen Failures

Number and percentage of subjects who were screened for the study (enrolled subjects, ie, those who signed informed consent) and reasons for screen failure will be summarized.

7.4. Protocol Deviations

Deviations from the protocol including violations of inclusion/exclusion criteria will be assessed as 'minor' or 'major'.

Major deviations will lead to the exclusion of a subject from the PP population and the PKAS. Major deviations may lead to the exclusion of a subject from the PP population and the PKAS. Major protocol deviations and PP exclusions will be identified during the Blinded Data Review Meeting (BDRM) before database lock.

Major protocol deviations may include:

- Subjects who had their blinded randomization code broken.
- Subjects with overall treatment compliance <80% or >120%.
- Subjects who used prohibited medications (prior and/or concomitant) that may have significant influence on efficacy.
- Subjects who did not satisfy the inclusion/exclusion that may have significant influence on efficacy.
- Subjects not treated with the treatment assigned at randomization, but wrongly treated in another treatment group.

A summary of protocol deviations, major protocol deviations and exclusionary major protocol deviations will be produced by treatment arm as well as by type of deviation will be provided. In addition, a by-subject listing of protocol deviations will be provided.

7.5. Demographic Characteristics

The following demographic characteristics will be summarized for subjects in the SAF, FAS, PP and PKAS populations by treatment arm:

- Age (years, as a continuous variable)
- Sex (Male, Female)
- Race

- Ethnicity
- Weight at screening (in kilograms)
- Height at screening (in centimeters)
- BMI at screening (in kg/m^2) calculated at screening
- Smoking Status at baseline
- Chest X-Ray, CT Scan at baseline
- Pregnancy Test at baseline
- COPD Exacerbation in the previous 3 months before screening at baseline

Age will be calculated as the number of complete years between a subject's birth date and the date of informed consent.

Age will also be summarized in the following categories: 40 <=65 years and >65-85 years. All demographic data will be listed by treatment and subject.

7.6. Listing of Subject Inclusion and Exclusion Criteria

Subjects who failed any of the inclusion and exclusion criteria will be listed along with the reason. Any subject withdrawal during the study, along with the reason for withdrawal, will be documented in listings.

Failed inclusion/exclusion criteria and withdrawal data will be listed by treatment and subject.

7.7. Medical History and Medical Conditions Present at Entry

Medical and surgical history, treatment history, current medical conditions and smoking status will be recorded at the Screening visit. Medical history will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA™) Version 18.0 or later. Medical history data will be listed by treatment and subject.

7.8. Prior and Concomitant and Rescue Medication

Any medication (including over-the-counter medications) or therapy administered to the subject during the study (other than the study drug/treatment, starting at the date of informed consent) is considered a concomitant medication. All concomitant medications must be recorded in the EDC system.

Rescue Medication(s)

Albuterol/salbutamol MDI will be permitted throughout the study as rescue medication and will be dispensed to the subjects at Visit 2 or at the start of washout (if the subject requires washout) and at subsequent scheduled visits as required, for self-administration as needed, at home.

Subjects will be trained to abstain from using albuterol/salbutamol MDI, 6 hours prior to start ofeach visit. If this is not possible, the visit will need to be rescheduled. Any rescue medication(s) taken will be recorded in the subject diary and appropriate eCRFs. A summary showing the number of subjects who used rescue mediation at any time post randomization (based on the information reported in the subject diary) and a descriptive summary of the amount of rescue medication used (based on the information reported in the subject diary) will be provided by treatment arm, as change as from baseline in daily and weekly averages. A by-subject listing of all rescue medication used, as reported on the patient diary, will also be provided.

All concomitant medication will be coded using World Health Organization Drug Dictionary (WHO-DD) 1 June 2009.

The following information must be recorded in the EDC system for each concomitant medication: preferred name or trade name, route of administration, start date, stop date, dose level, total daily dose, and indication. Any changes in the dosage or regimen of a concomitant medication must be recorded in the EDC system.

Medications will be assigned to a time period (prior and/or concomitant) as follows:

- If both the start and stop date exist and are before the first dose date of study drug, the medication will be counted as prior.
- If the start date is on or after the first dose date of study drug, the medication will be counted as concomitant.
- If the start date and stop date is on the first dose date of study drug, the medication will be counted as prior.
- If the start date is before the first dose date of study drug and the stop date is after the first dose date of study drug or the medication is continuing, the medication will be counted as prior and concomitant.
- If the start date is missing and the stop date is before the first dose of study drug, the medication will be counted as prior.
- If the start date is missing and the stop date is after the first dose of study drug or the medication is continuing, the medication will be counted as concomitant.
- If the start and stop dates are missing, the medication will be counted as concomitant.

Summaries showing number of subjects and percentage taking each medication will be provided for each preferred medication term by treatment arm. This will be done separately for prior and

for concomitant medications. A by-subject listing of all prior and concomitant medication data will also be provided.

7.9. Total Duration of Therapy, Average Daily Dose, Maximum Daily Dose, Final Daily Dose of Study Medication, and Compliance

The number of subjects exposed to each study treatment will be summarized.

The number of days on treatment and the number of days on study (screening through to end of study/follow-up) will be summarized by study treatment.

Treatment compliance will be calculated (the total number of doses actually taken / total number of doses expected*100). For subjects who have completed the study:

			Compliance Criteria	
Study Period	Duration	Scheduled Doses	Not less than 80% (doses)	Not more than 120% (doses)
Randomized Treatment	21 Days	21	17	25

For subjects who are early terminated, treatment compliance will be determined from their duration in the study, up to the time they are considered early terminated. Subjects taking fewer than 80% or more than 120% of the required doses will be considered non-compliant with dosing.

In addition, treatment compliance will be classified into four categories (<80%, ≥80% - ≤100%, >100% - <120%, ≥120%). Treatment compliance will be summarized by category and study treatment.

8. PHARMACOKINETICS

8.1. Overview of Pharmacokinetic Analyses

The pharmacokinetic analyses will be based on the PKAS, unless otherwise specified. Table 10 provides an overview of the planned pharmacokinetic analyses.

Table 10: Overview of Pharmacokinetic Analyses

	Stats Analysis		Summary		Individual
	T	F	T	F	L
Plasma Concentrations on Day 1 and Day 21			Y	Y[1]	Y
Urine Concentrations on Day 1 and Day 21			Y	Y[1]	Y
Pharmacokinetic Parameters on Day 1 and Day 21			Y		Y
Primary Endpoints -PKAS					
Peak concentrations during the dosing interval at steady-state (C_{maxSS})	Y[2]	Y	Y		
Area under the plasma concentration-time curve over the dosing interval at steady state ($AUC_{0\text{-}tauSS}$)	Y[2]	Y	Y		
Exploratory Analysis	Y[3]	Y[4]			

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TF related to any formal statistical analyses (ie modeling) conducted.
- Summary = Represents TF related to summaries (ie descriptive statistics) of the baseline, post-treatment and change from baseline for the primary pharmacodynamics analyses method.
- Individual = Represents L related to any displays of individual subject observed raw data.
- [1] = mean graph and semi-log graph by treatment on Day 1 and Day 21; A spaghetti plot for plasma concentration
- [2] =ANOVA applied ; [3]= Power Model applied; [4] = Spaghetti plot and dose-proportionality plots for plasma and urine parameters

8.2. Presentation of PK Data, Descriptive Statistics and PK Assessment

Pharmacokinetic plasma and urine concentration data will be listed by treatment, subject, day and actual sampling times relative to dosing for plasma data. Plasma and urine concentrations will be summarized by treatment, day and nominal time point. The following descriptive statistics will be presented for plasma and urine concentrations obtained at each nominal time point: n, arithmetic mean, SD, coefficient of variation (%CV), geometric mean, median, minimum and maximum values, where $\%\text{CV} = 100 \times \text{SD}/\text{mean}$.

Plasma and urine pharmacokinetic parameters will be listed by treatment, subject and day and summarized by treatment and day. Descriptive statistics for calculated PK parameters will include: n, arithmetic mean, SD, %CV, geometric mean, geometric mean %CV, median, minimum and maximum values, where geometric mean %CV is the standard deviation of

logarithm of data expressed in anti-logarithmically as a percent (ie $100 \times \sqrt{\exp(SD^2) - 1}$). For t_{max} and t_{last} , only median, minimum and maximum values will be presented. No descriptive statistics will be determined when fewer than three individual PK parameters are available.

Combined individual plasma concentrations versus actual times will be plotted by treatment and day (spaghetti plots).

For doses of GSP304, the arithmetic mean plasma concentration versus nominal times will be presented overlaid with the arithmetic mean profile of Spiriva®Respimat® by day both on linear and semi-logarithmic scales.

The following rules will be followed with regards to the number of decimal places and presentation of data in the tables and listings of concentration data:

- The individual concentrations will be reported to the same precision as the source data (for example, if the source data is presented to five significant digits, the individual values will be presented to five significant digits);
- The mean, SD, geometric mean and median will be tabulated to one more significant digit compared to the source data, but with a maximum of four significant digits;
- Minimum and maximum values will be tabulated to the same precision as the source data, but with a maximum of four significant digits;
- Coefficient of variation (%CV) and geometric coefficient of variation will be presented to one decimal place.

The following rules will be followed with regards to the number of decimal places and presentation of data in the tables and listings of PK parameters:

- Individual PK parameters will be presented to four significant digits, with the exception of t_{max}, which will be presented to two decimal places. In addition, parameters directly derived from source data (eg C_{max},) shall be reported with the same precision as the source data (if this is not four significant digits);
- The mean, geometric mean, median and SD values will be reported to four significant digits, all other descriptive statistics will be reported to three significant digits except for %CV and the geometric %CV, which will be presented to one decimal place. For tmax the minimum and maximum will be presented to two decimals places and the rest of the descriptive statistics to three decimal places;
- Estimates and confidence intervals in the form of percentages will be presented to two decimal places.

Source data shall be used in all derived PK parameter calculations without prior rounding.

8.3. Statement of the Null and Alternative Hypotheses

No formal hypothesis testing will be conducted for the primary pharmacokinetic endpoints.

8.4. Analysis of the Primary Pharmacokinetic Endpoints

The primary endpoint, $AUC_{0\text{-}tauSS}$, and C_{maxSS}, will be analyzed using an analysis of variance (ANOVA) model. An ANOVA will be performed on the ln-transformed $AUC_{0\text{-}tauSS}$, and C_{maxSS}. The ANOVA model will include treatment as fixed effect. The results from the model will be back-transformed and the adjusted geometric means for each treatment and the estimated treatment ratios for the treatment comparisons will be presented together with 90% CIs. The ratios and corresponding 90% CIs will be expressed as a percentage. The following comparisons will be made:

- GSP304[redacted] vs Spiriva® Respimat®
- GSP304[redacted] vs Spiriva® Respimat®
- GSP304[redacted] vs Spiriva® Respimat®

The statements of a SAS® PROC MIXED analysis would be:

```
PROC GLIMMIX   data=dataset;
  CLASS subject dose;
  MODEL log_normliased_pk_parameter= dose / ddfm=kr link=log;
  RANDOM intercept /subject= subject;
  ESTIMATE  'GSP1  vs  Spiriva' dose 1  0 0  -1 /cl alpha=0.1;
  ESTIMATE  'GSP2  vs Spiriva'  dose 0  1 0 -1  /cl alpha=0.1;
  ESTIMATE  'GSP3  vs Spiriva'  dose 0  0 1 -1  /cl alpha=0.1;
  LSMEANS dose/diff cl ilink alpha=0.10
RUN;
```

The back-transformed and adjusted means for each treatment and the estimated treatment differences for the treatment comparisons will be presented together with 90% confidence intervals for the treatment comparisons. The adjusted means and estimated treatment differences for the treatment comparisons will also be plotted, with corresponding 90% confidence intervals.

8.5. Exploratory Analysis

Dose-proportionality

Dose-proportionality of tiotropium C_{maxSS} and $AUC_{0\text{-}tauSS}$ parameters will be assessed using an ln-transformed power model:

$$\log_e Y_j = \alpha + \beta \log_e \text{dose}_j + \varepsilon_j,$$

where $Y_j = C_{maxSS}$ or $AUC_{0\text{-}tauSS}$ at j^{th} dose level. If β=0, then it implies that the response is independent from the dose and when β=1, dose-proportionality can be declared.

A mixed effect model can be used to fit the Power Model. Estimates of the mean slopes of log-transformed dose will be reported along with corresponding 90% CIs. If the 90% confidence interval for *β* is entirely contained within the *a priori* equivalence region, then dose proportionality is declared. If not, then dose non-proportionality is declared. Dose proportionality will be declared if the estimate of slope lies between 0.5- 2. Dose proportionality will also be assessed based on amount of tiotropium excreted in urine. Finally, dose normalized $AUC_{0\text{-}tauSS}$ and C_{maxSS} will also be evaluated across doses. Dose proportionality will be confirmed if the dose normalized parameters remain substantially constant in the range of explored doses.

The statements of a SAS® PROC MIXED analysis would be:

```
PROC MIXED data=dataset;
        CLASS subject;
        MODEL log_pk_parameter= log_dose/ ddfm=kr;
        RANDOM intercept log_dose /subject=subject type=UN gcorr s;
        ESTIMATE 'Logdose - 1 unit' log_dose 1/cl alpha=0.1;
RUN;
```

Duration of nebulization

Upon review of the tables, figures and listings produced at the end of the study, an exploratory analysis may be performed to evaluate the effect of duration of nebulization on primary and/or secondary out comes if deemed appropriate following review of the summary data and nebulization times. The decision to perform this analysis will be made by the Sponsor. If the decision is made not to proceed, this section of the SAP will not be applicable and the outputs described herein will not be presented.

9. PHARMACODYNAMICS

9.1. Overview of Pharmacodynamics Analyses

The primary analysis of the primary pharmacodynamics endpoint will be performed on both the FAS (primary) and the PP (supportive) population. The secondary analysis of the primary pharmacodynamics endpoint will be performed on the FAS. The analysis of the secondary pharmacodynamics endpoint will be performed on the FAS.

The primary endpoint is the change from baseline (Day 1) at Day 21 (Week 3) in trough FEV_1 response at approximately 24 hours after the last dose (average of 23 hours 15 minutes and 23 hours 45 minutes post-dose measurements), in comparison with GSP304 placebo.

Table 11 provides an overview of the planned primary pharmacodynamics analyses.

Table 11: Overview of Pharmacodynamics Analyses

	Stats Analysis		Summary		Individual
	T	F	T	F	L
Primary Endpoint - FAS					
Change from baseline (Day 1) at Day 21 (Week 3) in trough FEV_1 response at approximately 24 hours after the last dose (average of 23 hours 15 minutes and 23 hours 45 minutes post-dose measurements)	Y[1]	Y	Y		Y
Perform on PP	Y[1]	Y	Y		
Sensitivity Analysis - Pattern-Mixture model	Y				
Sensitivity Analysis - Tipping Point approach	Y				
Exploratory Analysis	Y	Y			
Secondary Endpoints - FAS					
Change from baseline in Peak FEV_1 within 12 hours post-dose on Day 1 and Day 21	Y[1]	Y	Y		
Change from baseline (Day 1) at Day 21 (Week 3) in trough FVC response at approximately 24 hours after the last dose (average of 23 hours 15 minutes and 23 hours 45 minutes post-dose measurements)	Y[1]	Y	Y		
Change from baseline in time-normalized area under the curve for FEV_1 measured over 12 hours on Day 1 and Day 21	Y[1]	Y	Y		
Time to onset of response, defined as at least 12% and 200 mL increase in FEV_1 within 12 hours of dosing on Day 1			Y	Y	
Time to achieving steady state as measured by FEV1 trough assessments			Y	Y	
Time to achieving steady state as measured by FVC trough assessments			Y	Y	

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TF related to any formal statistical analyses (ie modeling) conducted.

- Summary = Represents TF related to summaries (ie descriptive statistics) of the baseline, post-treatment and change from baseline for the primary pharmacodynamics analyses method.
- Individual = Represents L related to any displays of individual subject observed raw data.
- [1]: MMRM method applied

9.2. General Considerations

All tests will be 2-sided and at 5% level of significance unless otherwise stated.

In addition to the analyses described below, all endpoints will be summarized over time, by treatment, as appropriate.

All endpoints will also be listed by treatment and subject. The interpretation of results from statistical tests will be based on the FAS. The PP population will be used to assess the robustness of the results from the statistical tests based on the FAS. Unless otherwise stated, 'treatment' refers to treatment group as randomized, rather than based on the actual treatment received.

9.3. Testing Statistical Assumptions Including Comparability at Baseline

All baseline data will be summarized by treatment group using descriptive statistics. No formal hypothesis testing will be conducted. Differences may occur by chance. If there are any clinically meaningful differences identified, analyses may be adjusted to account for these imbalances through inclusion of additional covariates in the statistical models.

The PD endpoints (FEV_1, FVC) are assumed to be normally distributed and will be analyzed under this assumption. The assumptions of normality and constant variance will be verified using diagnostic plots (normal quantile plots and scatter plots of residuals by treatment group). If assumptions are violated, either an appropriate transformation will be used or data will be analyzed using non-parametric methods. The methods use will be documented in the clinical study report.

9.4. Statement of the Null and Alternate Hypotheses

A significance test will be made for the primary pharmacodynamics endpoint in order to assess for superiority of GSP304 versus GSP304 placebo. Demonstration of superiority for this treatment comparison will be based on a hypothesis testing approach, whereby the null hypothesis is that there is no difference between treatment groups and the alternative hypothesis is that there is a difference between the treatment groups.

A 2-sided 5% risk associated with incorrectly rejecting the null hypothesis (significance level) is considered acceptable for this study.

9.5. Multiple Comparisons and Multiplicity

As this is a phase 2 study, no adjustments for multiplicity are planned. The nominal p-values of all hypothesis tests will not be adjusted for multiplicity.

9.6. Analysis of the Primary Pharmacodynamics Endpoint

9.6.1. Primary Pharmacodynamics Analysis

The primary endpoint, change from baseline (Day 1) at Day 21 (Week 3) in trough FEV_1 response at approximately 24 hours after the last dose (average of 23 hours 15 minutes and 23 hours 45 minutes post-dose measurements) will be analyzed using a mixed-effect repeated measures (MMRM) model. This model will assume that any missing data is Missing at Random (MAR). The model will include trough data from all visits (Days 1, 6, 13, 20 and Day 21),and fixed terms for treatment, visit, center, baseline, treatment by visit and baseline by visit interactions. If an interaction term is significant, further ad-hoc analysis may be conducted. Subject will be included as a random term to account for the correlation between repeated measurements within a subject, and unstructured covariance structure will be used. If the model fails to converge, alternative structures (VC, AR1, TOEP1, and CS) or removing terms will be investigated. The covariance structure that provides the best fit (as determined by the smallest AIC value) will be used.

The statements of a SAS® PROC MIXED analysis would be:

```
PROC MIXED   data=dataset method= REML;
   CLASS subject treatment center visit;
   MODEL change = treatment center visit baseline treatment*visit   baseline*visit /s ddfm=kr;
   REPEATED visit/subject=subject type=UN;
   LSMEANS treatment*visit/at mean cl diff e;
RUN;
```

The adjusted means for each treatment and the estimated treatment differences for the treatment comparisons will be presented together with 95% confidence intervals, along with p-values for the treatment comparisons. The adjusted means and estimated treatment differences for the treatment comparisons (each GSP304 vs placebo, total GSP304 vs placebo, and Spiriva vs placebo) will also be plotted, with corresponding 95% confidence intervals.

9.6.2. Sensitivity Analyses of the Primary Pharmacodynamics Results

Sensitivity analyses will be performed on the FAS only. Subjects with at least one post-baseline assessment will be used in modeling.

9.6.2.1. Pattern-Mixture Model

The Mixed-effect Model Repeated Measure (MMRM) model will be fitted when some of the response values are missing by assuming that they are missing at random (MAR). This will be done computationally using Restricted Maximum-Likelihood (REML). However, this

assumption is unverifiable. It is necessary to perform sensitivity analyses under different assumptions regarding missing data. When the MAR assumptions do not hold, the data are assumed to be Missing Not At Random (MNAR). One possible way forward is to model a separate distribution for each pattern of missingness. A sensitivity analysis for missing data will be conducted based on multiple imputation-based methods with a form of pattern-mixture model (PMM).

PMMs will be fitted based on multiple imputations method. In the multiple imputation approach, a model will be fitted to the incomplete data and a pseudo-independent sample drawn from the posterior distribution of parameters. Each member of the sample leads to a separate imputed dataset, in which the missing values will be replaced by values drawn randomly from their conditional distribution. This distribution is based on the observed data and the covariates for that subject using the imputation model and the sampled parameter values. Each dataset is then analyzed as if these were real data, leading to a series of estimates for a parameter. These are then combined to supply an overall estimate and standard error based on Rubin's classic rules (Rubin, 1987) for combining across imputations.

The primary endpoint will also be analyzed using a Jump to Reference (J2R) approach, that is, all the patterns have the same profile up to withdrawal (that estimated in the parameter estimation model), but after withdrawal the profile jumps to the estimated profile for the reference arm. Thisapproach is a multiple imputation technique and works under the assumption that data is missing not at random (MNAR).

The J2R approach involves three distinct steps:

1. The missing data are filled in *m* times to generate *m* complete data sets (*m* will be selected to provide sufficiently stable and reproducible results).
    - In J2R method, all the patterns have the same profile up to withdrawal (that estimated in the parameter estimation model), but after withdrawal the profile jumps to the estimated profile for the reference arm. A new model is simulated from the posterior predictive distribution of the fitted model and missing values of the variable are imputed based on the new model.
    - The MNAR statement together with a MONOTON statement in PROC MI will be used. The variables that have missing values are imputed sequentially in each imputation. If the missing pattern is arbitrary, first the MCMC method will be used to partially impute data in order to obtain a monotone missing data pattern.
2. The missing data are filled in *m* times to generate *m* complete data sets. The *m* complete data sets are analyzed by using a procedure.
    - ANCOVA analysis for change from baseline in trough FEV_1 is performed using PROC MIXED with LSMEANS statement.
3. Results of the ANCOVA analysis on *m* imputed datasets can be combined to derive an overall result. PROC MIANALYZE in SAS will be used to combine the results.

The adjusted means for each treatment and the estimated treatment differences for the treatment comparisons will be presented together with 95% confidence intervals for the differences and p-values for the treatment comparisons.

9.6.2.2. Tipping Point (Region) Approach

The primary endpoint will also be analyzed using a special application of multiple imputation of missing values known as the tipping point method. The tipping point method assesses the possibility that subjects on active drug with missing values have worse outcomes than subjects on placebo. This sensitivity analysis involves multiple imputations and is also under the MNAR assumption in which one searches for a tipping point (region) that reverses the study conclusion. This approach is iterative in nature which tests how severe departures from MAR must be in order to overturn conclusions from the primary analysis. If these departures from MAR in order to change the results from statistically significance ($p<=0.05$) to statistically insignificance ($p>0.05$) are deemed to be implausible, the results will be said to be robust to the departure from MAR assumption.

The tipping point approach will be applied to the analysis of the primary endpoint using the MMRM. In the MMRM, the dependent variable is change from baseline while the covariates are treatment, site, baseline value and study day as the within-subject effect.

The imputation will be done on the missing cases of change from baseline values for GSP304 treatment and Spiriva. Under the MNAR assumption, the imputed values for observations in the active treatment group and Spiriva, as well as placebo, will be adjusted directly using a shift parameter. Missing values are imputed under the assumption that the distribution of the missing observations has a lower expected value than that of the observed only by a shift parameter value. The maximum shift parameter is set at 80 mL for being about 50% of treatment efficacy when assuming that a difference in mean change from baseline at the end of treatment in trough FEV_1 between GSP304 and GSP304 placebo is 150 mL. The shift parameter will take on the values from -80 mL to 0 with increment of 20 mL as it is assumed that the tipping point that will reverse the study conclusion is those values. If the tipping point is found to be between two increments on the given interval, a subsequent tipping point procedure will be performed using an interval on the neighborhood of the perceived tipping point finer increments for the shift parameter. If no tipping point is found, the shift parameter will be made more stringent and the process repeated.

Implementing the tipping point approach includes the following steps with the first three steps being the standard multiple imputation (MI) steps using SAS:

a) The missing data are filled in *m* times to generate m complete data sets using PROC MI.

b) The *m* complete data sets are analyzed using PROC MIXED.

c) The results from the *m* complete data sets are combined for the inference using PROC MIANALYZE.

d) Repeat the steps (a) to generate multiple imputed data sets with a specified shift parameter that adjusts the imputed values for observations in the active treatment and placebo groups.

e) Repeat the step (b) for the imputed data sets with shift parameter applied.

f) Repeat the step (c) to obtain the p-value to see if the p-value is still <=0.05.

g) If needed, repeat the steps (d)-(f) with more stringent shift parameter applied until the p-value >0.05.

The iteration for each value of the shift parameter will be summarized in a table where the estimated treatment differences for the treatment comparisons will be presented together with 95% confidence intervals for the differences and p-values for the treatment comparisons.

9.6.3. Exploratory Analysis

If appropriate, a dose response model will be fitted to the primary endpoint to estimate the dose response relationship. Dose response models to be evaluated will include E_{max} (3-parameter) and linear models.

The E_{max} model will be fitted as follows:

$$\text{Endpoint} = E_0 + \frac{E_{max}\,\text{Dose}}{\text{Dose} + \text{ED50}} + \varepsilon$$

where E_0 = Response at dose 0, E_{max} = Maximum effect, ED50 = Dose at which 50% of the maximum effect is reached and ε = Residual error.

The linear model will be fitted as follows:

$$\text{Endpoint} = E_0 + \beta\text{Dose} + \varepsilon$$

where E_0 = Response at Dose 0, β = slope and ε = Residual error

Should these models not fit the data appropriately other models may be explored. For all of the models, baseline will be included as a covariate at E_0. However, baseline may be fitted at ED50 or E_{max} for the E_{max} model depending on how the model fits the data best. Other covariates will be explored. Depending upon the adequacy of model fitting some parameters may need to be parameterized on the log scale (e.g. variance, ED50, E_{max}). The most appropriate model will be assessed visually, by evaluating the AIC and by looking at the residuals. To build confidence in the chosen model, the null model:

$$\text{Endpoint} = E_0$$

will also be fitted to the data and the p-value from a likelihood ratio test will be computed; i.e. the change in deviance (-2 Log Likelihood) between the chosen model and the null model will be compared to a chi-squared distribution with degrees of freedom equal to the difference in the number of parameters in the two models.

Dose response model parameter estimates, along with corresponding 95% confidence intervals, from the final dose response model will be presented.

9.7. Analysis of the Secondary Pharmacodynamics Endpoints

The secondary endpoints are:

- Change from baseline in peak FEV_1 within 12 hours post-dose on Day 1 and 21
- Change from baseline (Day 1) at Day 21 (Week 3) in trough FVC response at approximately 24 hours after the last dose (average of 23 hours 15 minutes and 23 hours 45 minutes post-dose measurements)
- Change from baseline in time-normalized area under the curve for FEV_1 measured over 12 hours on Day 1 and 21
- Time to onset of response, defined as at least 12% and 200 mL increase in FEV_1 within 12 hours of dosing on Day 1
- Time to achieving steady state as measured by FEV_1 trough assessments
- Time to achieving steady state as measured by FVC trough assessments

The change from baseline for the secondary pharmacodynamics endpoint of change from baseline (Day 1) at Day 21 (Week 3) in trough FVC response at approximately 24 hours after the last dose (average of 23 hours 15 minutes and 23 hours 45 minutes post-dose measurements) will be analysed using the same model as described above for the anlaysis of the primary endpoint.

The change from baseline for the secondary pharmacodynamics endpoints of; Change from baseline in peak FEV_1 within 12 hours post-dose on Day 1 and 21 and change from baseline in time-normalized area under the curve for FEV_1 measured over 12 hours on Day 1 and 21 will be analyzed using a mixed-effect repeated measures (MMRM) model. This model will assume that any missing data is Missing at Random (MAR). The model will include data from Day 1 and Day 21 and fixed terms for treatment, visit, center, baseline, treatment by visit and baseline by visit interactions. If an interaction term is significant, further ad-hoc analysis may be conducted. Subject will be included as a random term to account for the correlation between repeated measurements within a subject, and unstructured covariance structure will be used. If the model fails to converge, alternative structures (CS) or removing terms will be investigated. The covariance structure that provides the best fit (as determined by the smallest AIC value) will be used. The adjusted means for each treatment and the estimated treatment differences for the

treatment comparisons will be presented together with 95% confidence intervals, along with p-values for the treatment comparisons. The adjusted means and estimated treatment differences for the treatment comparisons (each GSP304 vs placebo, total GSP304 vs placebo, and Spiriva vs placebo) will also be plotted, with corresponding 95% confidence intervals.

For the secondary endpoint of time to onset of response of both a 12% and 200 mL increase from baseline in FEV_1, the unadjusted mean change from baseline and unadjusted percent mean change from baseline will be summarized for day 1. The unadjusted means will also be plotted over time, for day 1. For the secondary endpoints of time to steady state in FEV_1 and FVC, the adjusted means from the MMRM model discussed above will be summarized by day (Days 1, 6, 13, 20 and 21) and also plotted over time.

9.8. Subgroup Analyses

No subgroup analyses are planned for this study.

9.9. Summary of Reasons for Efficacy Non-Evaluability /Exclusion from Efficacy Analyses

The reasons for excluding subjects from the FAS and PP population will be listed by treatment and subject.

10. SAFETY AND TOLERABILITY

10.1. Overall Summary of Tolerability

The safety analyses will be based on the SAF, unless otherwise specified.

Table 12 provides an overview of the planned analyses.

Table 12: Overview of Planned Safety Analyses

Display Type	Data Displays Generated		
	Table	Figure	Listing
Adverse Events			
Overview	Y		
Treatment Emergent AEs	Y[1]		Y
Treatment-Related Emergent AEs	Y		Y
Pre-Treatment Period AEs	Y		Y
AEs Leading to Withdrawal			Y
SAEs	Y		Y
Treatment Emergent SAEs	Y		Y
Treatment-Related SAEs	Y		Y
Laboratory			
Biochemistry	Y[2]		Y
Hematology	Y[2]		Y
Urinalysis	Y[2]		Y
Pregnancy Test Results			Y
Other			
Vital Signs	Y[3]		Y
ECGs	Y[4]		Y
Physical Examination	Y[5]		Y

NOTES :

- Y = Yes display generated.
- [1]: Display will also be produced by severity, by relationship to study treatment and leading to discontinuation
- [2]: Display will be produced separately for overall laboratory assessments (inc. change from baseline), potentially clinically significant laboratory results, and shift tables
- [3]: Display will be produced separately for overall summary (inc. change from baseline), potentially clinically significant results, and shift tables
- [4]: Display will be produced separately for overall summary (inc. change from baseline), potentially clinically significant ECGs, and shift tables
- [5]:Display will be produced separately for overall summary

Safety will be assessed by evaluating AEs, SAEs, treatment related AEs and SAEs, vital signs, laboratory test results, ECG values, and physical examination findings. The extent of exposure in each treatment group will be characterized according to the number of subjects exposed, the duration of exposure, and the dose to which they were exposed. All safety analyses will be performed on the SAF.

10.2. Adverse Event Preferred Term and Body/Organ System Summary Tables

10.2.1. Summaries of Adverse Event for All Subjects

For each AE, the following information is to be recorded; the start date, the stop date (or whether the AE is ongoing at study completion/discontinuation), the severity and the investigator relationship of the AE to study drug, the therapy for the AE, the action taken with study drug, and whether or not the AE is considered serious.

Adverse events will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA™) Version 18.0 or later.

Treatment Emergent AEs (TEAEs) are defined as AEs (identified by PT) that begins or that worsens in severity after at least one dose of study treatment has been administered, and last upto the AE stop date or the follow-up visit or the last study participation day. The number and percentage of subjects reporting at least one occurrence of a TEAE for each unique System Organ Class and Preferred Term will be tabulated by severity, and by the investigator relationship to study drug. For multiple occurrence of the same TEAE with the different severity, the TEAE with the highest severity will be tabulated. For multiple occurrences of the same TEAE with different relationship to study drug (related and not related), the TEAE will be tabulated as related. All TEAEs leading to discontinuation of treatment will also be tabulated. All AEs for all subjects will be presented in a data listing.

Pre-Treatment AEs (PTAEs) are defined as AEs (identified by PT) that begin or that worsen in severity between study Day -14 and study drug administration, and last up to the AE stop date.

The severity of AE is classified as follows:

Mild	The AE is a transient discomfort and does not interfere in a significant manner with the subject. The AE resolves spontaneously or may require minimal therapeutic intervention
Moderate	The AE produces limited impairment of function and may require therapeutic intervention. The AE produces no sequelae.
Severe	The AE results in a marked impairment of function and may lead to temporary inability to resume usual life pattern.
	The AE produces sequelae, which require (prolonged) therapeutic intervention.

The relationship of AEs to study medication is classified as follows:

- Not Related: A causal relationship between the study treatment and the AE is not a reasonable possibility

- Related: A causal relationship between the study treatment and the AE is a reasonable possibility

A COPD exacerbation is defined as worsening of the following 2 or more major symptoms for at least 2 consecutive days: dyspnea, sputum volume, and sputum purulence or a worsening of any 1 major symptom together with an increase in any 1 of the following minor symptoms for at least 2 consecutive days: sore throat, colds (nasal discharge and/or nasal congestion), fever without other cause, and cough. A COPD exacerbation shall be reported as an AE and may be considered serious if it meets the seriousness criteria for SAE reporting.

All serious AEs that occur after administration of the first dose of study drug will be listed by System Organ Class, Preferred Term, and relationship to study drug as assessed by the investigator. In addition to three treatment levels, a GSP 304 total will be presented in AE/SAE-related summary tables.

10.2.2. Missing and Partial AE Onset Dates

Refers to section 6.8.3

10.2.3. Summaries of Serious Adverse Events (SAE), Adverse Event Dropouts, and Death

For SAEs that are considered to be related to study drug, the number and percentage of subjects reporting at least one occurrence of an SAE for each unique System Organ Class will be tabulated. SAEs that lead to study discontinuation will be tabulated by unique System Organ Class, Preferred Term and relationship to study drug. All SAEs resulting in death will also be tabulated.

All SAEs will be presented for individual subjects in data listings, as well as premature discontinuations due to all causality. Deaths of all causes, study-drug related (occurring during study participation and up to 30 days post-treatment) or not, will be presented in a separate listing.

10.3. Concomitant and Other Medications

Concomitant medication will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA™) Version 18.0 or later. Medical history data will be listed by treatment and subject

All concomitant medications taken since screening until the end of the study will be listed by treatment and subject.

10.4. Laboratory Data

Baseline and post-baseline clinical laboratory data (hematology, biochemistry, liver function, and urinalysis), will be summarized for Visit 4 to Visit 7 (the Final Visit). Descriptive statistics (number of subjects, mean, SD, median, minimum and maximum) will be presented for laboratory data as well as change from baseline by treatment and visit. In addition, values outside the respective normal range and values deemed as clinically significant by the Investigator will be listed.

The number of subjects with values of potential clinical significance determined by the investigator will be tabulated by treatment group and visit.

Shift tables will present changes from baseline in laboratory data (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to end of treatment.

All laboratory data will be listed by treatment and subject.

Estimated Glomerular filtration rate (eGFR) will be estimated using the Cockcroft-Gault approach.

10.5. Vital Signs

The subject's baseline and post-baseline vital signs will be recorded (pulse rates, sitting or lying down systolic and diastolic blood pressure) at Visits 3 to Visit 7. Height and weight will also be recorded at Screening Visit (Day -28 to Day -15). Descriptive statistics (number of subjects, mean, SD, median, minimum and maximum) will be used to summarize vital sign results and changes from baseline by treatment group and visit.

Values outside the respective normal range and values deemed as clinically significant by the Investigator will be listed.

The number of subjects with values of potential clinical significance determined by the investigator will be tabulated by treatment group and visit.

All vital sign data will be listed by treatment and subject.

10.6. Electrocardiogram (ECG)

Baseline and post-baseline electrocardiograms (12-lead ECG) will be performed at Visit 3 and Visit 6. The parameters to be reported are Heart Rate, PR Interval, QRS duration, QT interval, and QTc interval (QTcF and QTcB).

Descriptive statistics for ECG parameters and changes from baseline will be presented by treatment group. Shift tables will present changes from baseline to end of treatment in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant).

The number of subjects with values of potential clinical significance determined by the investigator will be tabulated by treatment group and visit.

All ECG data will be listed by treatment and subject.

10.7. Physical Examination

Baseline and post-baseline physical examinations will be performed at Visit 3 to Visit 6.

Descriptive statistics (frequency and percentage) will be used to summarize physical examination results by body system, treatment group and visit. In addition, the number of subjects with values of potential clinical significance determined by the investigator will be tabulated.

All physical examination data will be listed by treatment and subject.

10.8. Study Termination Status

If the Investigator or the Sponsor's Medical Monitor becomes aware of conditions or events that suggest a possible hazard to subjects if the study continues, the study may be terminated after appropriate consultation between the relevant parties. The study may also be terminated early at the Sponsor's discretion in the absence of such a finding.

Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study;
- Failure to enroll subjects at an acceptable rate;
- A decision on the part of the Sponsor to suspend or discontinue development of the drug product.

10.9. Changes from Protocol

The following changes from the protocol were made in the SAP.

1) The definition of the primary endpoint was clarified from change from baseline in trough forced expiratory volume in one second (FEV_1) at 24 hours after the last dose of treatment on Day 21 in comparision with placebo to change from baseline (Day 1) at Day 21 (Week 3) in trough FEV_1 response at approximately 24 hours after the last dose (average of 23 hours 15 minutes and 23 hours 45 minutes post-dose measurements.

2) The language used for definition of the secondary endpoint of change from baseline in trough FVC, and the associated analyses related to this endpoint, was modified to align it with the language that has been used for the primary endpoint.

3) The following secondary endpoints were added;

- Time to onset of response, defined as at least 12% and 200 mL increase in FEV_1 within 12 hours of dosing on Day 1
- Time to achieving steady state as measured by FEV_1 trough assessments
- Time to achieving steady state as measured by FVC trough assessments

4) Spirometry Effort Start Time: will use the first effort (Test 1) regardless of whether this is an acceptable effort or not. Instead of "start time of first spirometry effort" (per protocol), we are using the end time of the first spirometry effort.

11. REFERENCES

Caillaud D, Le Merre C, Martinat Y et al. A dose-ranging study of tiotropium delivered via Respimat Soft Mist Inhaler or HandiHaler in COPD patients. Int J Chron Obstruct Pulmon Dis. 2007; 2(4):559-65

Rubin, DB (1987). Multiple Imputations for Nonresponse in Surveys, New York: John Wiley & Sons.

Smith BP, Vandenhende FR, DeSante KA, Farid NA, Welch PA, Callaghan JT, Forgue ST. (2000). Confidence interval criteria for assessment of dose proportionality, Pharm Res 17:1278–1283

12. APPENDIX

12.1. Table of Contents for Data Display Specifications

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Listings

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12.2. Data Display Specification

Table 14.1.1
Summary of Disposition

All Screened Subjects

Category	GSP304 [redacted] (N_2= xxx) n (.%)	GSP304 [redacted] (N_2=xxx) n (%)	GSP304 [redacted] (N_2=xxx) n (%)	Placebo (N_2=xxx) n (%)	Spiriva R 5 ug (N_2=xxx) n (%)	Total (N_1=xxx; N_2=xxx) n (%)
Total screened	--	--	--	--	--	xxx
Screen Failures [1]	--	--	--	--	--	xx (xx.x)
Reason for Screen Failure [1]						
Adverse Event	--	--	--	--	--	xx (xx.x)
Did not Meet Inclusion/Exclusion Criteria	--	--	--	--	--	xx (xx.x)
Lost to Follow-up	--	--	--	--	--	xx (xx.x)
Physician Decision	--	--	--	--	--	xx (xx.x)
Protocol Deviation	--	--	--	--	--	xx (xx.x)
Withdrawal by Subject	--	--	--	--	--	xx (xx.x)
Other	--	--	--	--	--	xx (xx.x)
Completed Run-In Period [1]	--	--	--	--	--	xx (xx.x)
Randomized [2]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xxx
Completed Study [2]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Terminated Early [2]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reason for Early Termination [2]						
Withdrawal of Consent by the Subject	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Adverse Event	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Investigator's Discretion	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Noncompliance with Study Procedures	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Protocol Deviation	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Violation of Inclusion/Exclusion Criteria	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Withdrawal Criteria	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Informed Consent	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Treatment Administration	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Prohibited Medications	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Randomization Code Broken	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Visit Schedule	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Procedure/Tests	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
AE/SAE	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject suffers from significant inter-current illness or undergoes surgery	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject requires concomitant medication, which may interfere with the PK of study medication	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Unable to comply with the spirometry washout criteria	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
COPD Exacerbation	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lost To Follow-up	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Death	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Pregnancy	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Sponsor Decision	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Non- Compliance with Study Drug	xx (xx.x)	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)	xx (xx.x)

[1] N_1 is the number of screened subjects. Percentages are based on the number of screened subjects; [2] N_2 is the number of randomized subjects. Percentages for all categories are based on the number of randomized subjects. n = Number of subjects with data in the summarized category

Program location/program name.sas/ddmmmyyyy/hh:mm
Source Data: Listing xxxxxxx Database Extract Date: ddmmmyyyy

Programming notes:

Table 14.1.2
Summary of Subjects in Analysis Population

Randomized Subjects

	GSP304				Spiriva R	
	[redacted]	[redacted]	[redacted]	Placebo	5 ug	Total
	(N=xxx)	(N=xxx)	(N=xxx)	(N=xxx)	(N=xxx)	(N=xxx)
Category	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Full Analysis Population	xx (xx.x)	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)	xx (xx.x)
Per-protocol Population	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Pharmacokinetic Population	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Percentages are based on the total number of randomized subjects in each treatment group. N = Number of randomized subjects; n = Number of subjects with data in the summarized category; Full analysis population includes all subjects who are randomized, have received at least 1 dose of study medication and have at least 1 post-baseline PD assessment; Safety population includes all subjects who are randomized and received at least 1 dose of study medication; Per-protocol population includes all subjects who are randomized, received at least 1 dose of study medication, completed the study and do not have exclusionary major protocol deviations; Pharmacokinetic population includes all subjects who are randomized, received at least 1 dose of study treatment and have at least 1 quantifiable PK sample and do not have exclusionary major protocol deviations.

Program location/program name.sas/ddmmmyyyy/hh:mm
Source Data: Listing xxxxxxx Database Extract Date: ddmmmyyyy

Programming notes:

Table 14.1.3
Summary of Protocol Deviations

Safety Set

	GSP304				Spiriva R	
	[redacted] (N=xxx) n (%)	[redacted] (N=xxx) n (%)	[redacted] (N=xxx) n (%)	Placebo (N=xxx) n (%)	5 ug (N=xxx) n (%)	Total (N=xxx) n (%)
Subjects with at least one PD	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with at least one Major PD [1]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Category						
Violation of inclusion/exclusion Criteria	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Withdrawal Criteria	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Informed Consent	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Treatment Administration	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Prohibited Medications	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Randomization Code Broken	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Visit Schedule	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Procedure/Tests	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
AE/SAE	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with at least one Major PD leading to exclusion from PP						
Category						
Violation of inclusion/exclusion Criteria	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Withdrawal Criteria	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Informed Consent	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Treatment Administration	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Prohibited Medications	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Randomization Code Broken	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Visit Schedule	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Procedure/Tests	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
AE/SAE	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

[1] Deviations which require exclusion from per-protocol and/or PKAS population. The final MPD categories and decision on deviations to be decided during the blinded data review process. Subjects may have more than one significant protocol deviation; N = Number of safety sujects; n = Number of subjects with data in the summarized category.

Program location/program name.sas/ddmmmyyyy/hh:mm
Source Data: Listing xxxxxxx Database Extract Date: ddmmmyyyy

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Programming notes:

Repeat for

Table 14.1.4 Summary of Protocol Deviations
PK Analysis Set

Table 14.1.8.1
Summary of Demographic Characteristics

Full Analysis Set

		GSP304				Spiriva R	
		[redacted]	[redacted]	[redacted]	Placebo	5 ug	Total
	Category/Statistics	(N=xxx) n (%)	(N=xxx) n (%)	(N=xxx) n (%)	(N=xxx) n (%)	(N=xxx) n (%)	(N=xxx) n (%)
Age	n	xxx	xxx	xxx	xxx	xxx	xxx
(years)	Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx; xx	xx; xx	xx; xx	xx; xx	xx; xx	xx; xx
Age Category	≥ 40, <65	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
(years)	≥ 65, <85	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Sex	Female	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Male	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Race	n	xxx	xxx	xxx	xxx	xxx	xxx
	Asian	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Black/ African American	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	White	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	American Indian/ Alaska Native	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Native Hawaiian/ other Pacific Islander	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Multiple	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Not Stated	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ethnicity	Hispanic or Latino	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Not Hispanic or Latino	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Not Stated	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

N = Number of full analsyis subjects; n = Number of subjects with data in the summarized category

Program location/program name.sas/ddmmmyyyy/hh:mm

Source Data: Listing xxxxxxx Database Extract Date: ddmmmyyyy

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Programming notes:

Repeat for

Table 14.1.8.2 Summary of Demographic Characteristics

Safety Set
Footnote: N = Number of safety subjects ; n = Number of subjects with data in the summarized category

Table 14.1.8.3 Summary of Demographic Characteristics

Per-Protocol Set
Footnote: N = Number of per-protocol subjects ; n = Number of subjects with data in the summarized category

Table 14.1.8.4 Summary of Demographic Characteristics

PK Analysis Set
Footnote: N = Number of PK analsyis subjects ; n = Number of subjects with data in the summarized category

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Table 14.1.9
Summary of Baseline Characteristics

Full Analysis Set

		GSP304				Spiriva R	
		[redacted]	[redacted]	[redacted]	Placebo	5 ug	Total
	Category/Statistics	(N=xxx) n (%)	(N=xxx) n (%)	(N=xxx) n (%)	(N=xxx) n (%)	(N=xxx) n (%)	(N=xxx) n (%)
Height (cm)	n	xxx	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x(x.xx)	xx.x (x.xx)	xx.x (x.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx; xx	xx; xx	xx; xx	xx; xx	xx; xx	xx; xx
Weight (kg)	n	xxx	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx;xx	xx; xx	xx ;xx	xx; xx	xx; xx	xx; xx
BMI (kg/m^2)	n	xxx	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx; xx	xx;xx	xx; xx	xx; xx	xx; xx	xx; xx
Smoking Status	Yes	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	No	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of Cigarette Pack (years)	n	xxx	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx; xx	xx; xx	xx; xx	xx; xx	xx; xx	xx; xx
Time from COPD Diagnosis (years)	n	xxx	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx; xx	xx; xx	xx; xx	xx; xx	xx ;xx	xx; xx
Any COPD exacerbation in previous 3 months before screening [1]	Yes	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	No	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Number of COPD if [1] =Yes	n	xxx	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx; xx	xx; xx	xx; xx	xx; xx	xx; xx	xx; xx
If [1] =Yes, was there any hospitalization?	Yes	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	No	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

N = Number of full analsyis subjects; n = Number of subjects with data in the summarized category

Program location/program name.sas/ddmmmyyyy/hh:mm
Source Data: Listing xxxxxxx Database Extract Date: ddmmmyyyy

Programming notes:

Table 14.1.10
Summary of Medical History per SOC and PT

Safety Set

System Organ Class Preferred Term	GSP304 [redacted] (N=xxx) n (%) [#]	GSP304 [redacted] (N=xxx) n (%) [#]	GSP304 [redacted] (N=xxx) n (%) [#]	Placebo (N=xxx) n (%) [#]	Spiriva R 5 ug (N=xxx) n (%) [#]	Total (N=xxx) n (%) [#]
Any medical history	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
SOC #1	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
PT #1	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) [#]	xx (xx.x) [#]	xx (xx.x) [#]
SOC #2	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
PT #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) [#]	xx (xx.x) [#]	xx (xx.x) [#]
...						

SOC = System Organ Class; PT = Preferred Term; N = Number of safety subjects; n = Number of subjects reporting at least one medical history in that category; [#] = Number of individual occurrences of the medical history in that category

Program location/program name.sas/ddmmmyyyy/hh:mm
Source Data: Listing xxxxxxx Database Extract Date: ddmmmyyyy

Programming notes:

Ordered in terms of decreasing frequency for SOC, and PT within SOC, in the treatment group, and then alphabetically for SOC, and PT within SOC.

Table 14.1.11
Summary of Treatment Compliance

Safety Set

Category	Statistics	GSP304 [redacted] (N=xxx) n (%)	GSP304 [redacted] (N=xxx) n (%)	GSP304 [redacted] (N=xxx) n (%)	Placebo (N=xxx) n (%)	Spiriva R 5 ug (N=xxx) n (%)	Total (N=xxx) n (%)
Number of Subjects Exposed		xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Average Daily Dose (ug) [1]	n	xxx	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx; xx	xx; xx	xx; xx	xx; xx	xx; xx	xx; xx
Nebulization Time (minute)	n	xxx	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx; xx	xx; xx	xx; xx	xx; xx	xx; xx	xx; xx
Number of Days on Treatment [2]	n	xxx	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx; xx	xx; xx	xx; xx	xx; xx	xx; xx	xx; xx
Number of Days on Study [3]	n	xxx	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx; xx	xx; xx	xx; xx	xx; xx	xx; xx	xx; xx
Compliance Group (%)	<80%	xx (xx.x)	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)	xx (xx.x)
	>100% - <120%	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	≥120%	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Compliance (%)	n	xxx	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx; xx	xx; xx	xx; xx	xx; xx	xx; xx	xx; xx

[1] Average dose = Add up all dose takend by the subject and divided by the number of days in the study ;[2] Total number of dosing days from first to last day of dose; [3] Total number of days from study creening through to end of study/follow-up.
N = Number of safety subjects ; n = Number of subjects with data in the summarized category

Program location/program name.sas/ddmmmyyyy/hh:mm
Source Data: Listing xxxxxxx Database Extract Date: ddmmmyyyy

Programming notes:

SAP section 7.9

Table 14.1.12
Summary of Prior Medication

Safety Set

WHODD September v2015 WHO ATC Class Anatomical Main Group [level 1] Pharmacological Subgroup [Level 3] Preferred Term	GSP304 [redacted] (N=xxx) n (%)	GSP304 [redacted] (N=xxx) n (%)	GSP304 [redacted] (N=xxx) n (%)	Placebo (N=xxx) n (%)	Spiriva R 5 ug (N=xxx) n (%)	Total (N=xxx) n (%)
Any medical history	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
3-OXOANDROSTEN (4) DERIVATIVES, G03BA	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
GENITO URINARY SYSTEM AND SEX HORMONES, G	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
ANDROGENS, G03B	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
TESTOSTERONE	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
...						

N = Number of safety subjects; n = Number of subjects reporting at least one prior medication in that category

Program location/program name.sas/ddmmmyyyy/hh:mm
Source Data: Listing xxxxxxx Database Extract Date: ddmmmyyyy

Programming notes:

Repeat for

Table 14.1.13 Summary of Concomitant Medications

Footnote:

N = Number of safety subjects; n = Number of subjects reporting at least one concomitant medication in that category; [#] = Number of individual occurrences of the concomitant medication in that category

Table 14.1.14
Summary of Rescue Medication Use (Reported in eDiary)

Full Analysis Set

		GSP304				Spiriva R	
		[redacted]	[redacted]	[redacted]	Placebo	5 ug	Total
	Statistics	(N=xxx) n (%)	(N=xxx) n (%)	(N=xxx) n (%)	(N=xxx) n (%)	(N=xxx) n (%)	(N=xxx) n (%)
Any Use		xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of Puffs	n	xxx	xxx	xxx	xxx	xxx	xxx
(years)	Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx; xx	xx; xx	xx; xx	xx; xx	xx; xx	xx; xx

N = Number of full analsyis subjects; n = Number of subjects with data in the summarized category

Program location/program name.sas/ddmmmyyyy/hh:mm
Source Data: Listing xxxxxxx Database Extract Date: ddmmmyyyy

Table 14.2.1.1
Summary of FEV_1 (L) Data by Visit , Time and Treatments

Full Analysis Set

			GSP304				Spiriva R
Visit	Nominal Time	Statistics	[redacted] (N=xxx)	[redacted] (N=xxx)	[redacted] (N=xxx)	Placebo (N=xxx)	5 ug (N=xxx)
Day 1	-45 min	n	xxx	xxx	xxx	xxx	xxx
		Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x	xx.x
		Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
	-15 min	n	xxx	xxx	xxx	xxx	xxx
		Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x	xx.x
		Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
	Baseline [1]	n	xxx	xxx	xxx	xxx	xxx
		Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x	xx.x
		Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
	5 min	n	xxx	xxx	xxx	xxx	xxx
		Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x	xx.x
		Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
	Change from Baseline	n	xxx	xxx	xxx	xxx	xxx
		Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x	xx.x
		Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
	30 min	n	xxx	xxx	xxx	xxx	xxx
		Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x	xx.x
		Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
	Change from Baseline	n	xxx	xxx	xxx	xxx	xxx
		Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)

	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
90 min	n	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
Change from Baseline	n	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
4 hours	n	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
Change from Baseline	n	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
8 hours	n	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
Change from Baseline	n	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
12 hours	n	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
Change from Baseline	n	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)

		Median	xx.x	xx.x	xx.x	xx.x	xx.x
		Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
	23 hours 45 min	n	xxx	xxx	xxx	xxx	xxx
		Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x	xx.x
		Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
	Change from Baseline	n	xxx	xxx	xxx	xxx	xxx
		Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x	xx.x
		Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
Insert Day 7 and Day 14	-45 min; -15 min; Trough [2]						
Day 21	-45 min	n	xxx	xxx	xxx	xxx	xxx
		Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x	xx.x
		Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
	Change from Baseline	n	xxx	xxx	xxx	xxx	xxx
		Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x	xx.x
		Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
	-15 min	n	xxx	xxx	xxx	xxx	xxx
		Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x	xx.x
		Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
	Change from Baseline	n	xxx	xxx	xxx	xxx	xxx
		Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x	xx.x
		Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
	5 min	n	xxx	xxx	xxx	xxx	xxx
		Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x	xx.x
		Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
	Change from Baseline	n	xxx	xxx	xxx	xxx	xxx
		Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x	xx.x
		Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
	15 min	n	xxx	xxx	xxx	xxx	xxx

	Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
Change from Baseline	n	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
30 min	n	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
Change from Baseline	n	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
60 min	n	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
Change from Baseline	n	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
90 min	n	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
Change from Baseline	n	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
2 hours	n	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
Change from Baseline	n	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
4 hours	n	xxx	xxx	xxx	xxx	xxx

	Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
Change from Baseline	n	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
6 hours	n	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
Change from Baseline	n	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
8 hours	n	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
Change from Baseline	n	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
10 hours	n	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
Change from Baseline	n	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
12 hours	n	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
Change from Baseline	n	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
23 hours 15 min	n	xxx	xxx	xxx	xxx	xxx

	Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
Change from Baseline	n	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
23 hours 45 min	n	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
Change from Baseline	n	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
Trough [2]	n	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx
Change from Baseline	n	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx;xx	xx;xx	xx;xx	xx;xx	xx;xx

[1] The baseline assessment for FEV_1 is the average of the pre-dose FEV_1 measured at -45 minutes and -15 minutes at Day 1.
[2] Trough FEV_1 is defined as the average of FEV_1 obtained 23 hours 15 minutes and 23 hours 45 minutes post-morning dose of the previous day.

N = Number of full analysis subjects; n = Number of subjects with data in the summarized category

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Programming notes: Include Day 7 and Day 14 before Day 21

Repeat for

Table 14.2.1.3 Summary of FEV_1 (L) Data byViist , Time and Treatment

(Per-Protocol Set)

Footnote: [1] The baseline assessment for FEV_1 is the average of the pre-dose FEV_1 measured at -45 minutes and -15 minutes at Day 1.
[2] Trough FEV_1 is defined as the average of FEV_1 obtained 23 hours 15 minutes and 23 hours 45 minutes post-morning dose of the previous day.

Table 14.2.2.1 Summary of Peak FEV_1 (L) within 12 Hours Post Dose by Visit and Treatment

(Full Analysis Set)

Footnote: [1] The baseline assessment for Peak FEV_1 is the average of the pre-dose FEV_1 measured at -45 minutes and -15 minutes at Day 1.

Programming note:
Change 'Nominal Time' to 'Assessement' and include 'Actual Value' in second column

Table 14.2.2.3 Summary of FVC (L) Data by Visit , Time and Treatment

(Full Analysis Set)

Footnote: [1] The baseline assessment for FVC is the average of the pre-dose FVC measured at -45 minutes and -15 minutes at Day 1.
[2] Trough FVC is defined as the average of FVC obtained 23 hours 15 minutes and 23 hours 45 minutes post-morning dose of the previous day.

Table 14.2.2.5 Summary of Time-Normalized AUC for FEV_1 (L) Measured over 12 Hours by Visit, Time and Treatment

(Full Analysis Set)

Footnote: [1] The baseline assessment for Time-Normalized AUC for FEV_1 (L) is the average of the pre-dose FEV_1 measured at -45 minutes and -15 minutes at Day 1.
Programming note:
Change 'Nominal Time' to 'Assessement' and include 'Actual Value' in second column

Table 14.2.1.2
Statistical Analysis of Change from Baseline in Day 21 Trough FEV_1 (L)

Full Analysis Set

	GSP304				Spiriva R
Statistics [1]	[redacted] (N=xxx)	[redacted] (N=xxx)	[redacted] (N=xxx)	Placebo (N=xxx)	5 ug (N=xxx)
n	xxx	xxx	xxx	xxx	xxx
LS Mean(SE)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
LSMD (SE)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	-	xx.x (xx.xx)
95% CI for LSMD	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	-	(xx.x, xx.x)
p-value for LSMD	x.xxx	x.xxx	x.xxx	-	x.xxx

Trough FEV_1 is defined as the average of FEV_1 obtained 23 hours 15 minutes and 23 hours 45 minutes post-morning dose of the previous day; N = Number of full analysis subjects; n = Number of subjects with at least one post baseline visit in the summarized category
[1] LSMD = Least Square Mean Difference for each GSP304 vs placebo, and Spiriva vs placebo; The model will include Troug FEV1 from all visits (Days 1, 6, 13, 20 and Day 21) and fixed terms for treatment, visit, center, baseline, treatment by visit and baseline by visit interactions; Unstructured covariance structure is used.

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Programming notes:

Repeat for

Table 14.2.1.4 Statistical Analysis of Change from Baseline in Day 21 Trough FEV_1 (L)

Per-Protocol Set

Footnote: Same as in 14.2.1.2

Table 14.2.2.2 Statistical Analysis of Change from Baseline in Peak FEV_1 (L) within 12 Hours Post Dose on Day 1 and Day 21

Full Analysis Set

Footnote: N = Number of full analysis subjects; n = Number of subjects with at least one post baseline visit in the summarized category
[1] LSMD = Least Square Mean Difference for each GSP304 vs placebo, and Spiriva vs placebo; The model will include Peak FEV1 from Days 1 and 21 and

fixed terms for treatment, visit, center, baseline, treatment by visit and baseline by visit interactions; Unstructured covariance structure is used.

Table 14.2.2.4 Statistical Analysis of Change from Baseline of Trough FVC (L) on Day 1 and Day 21

Full Analysis Set

Footnote: Same as in 14.2.1.2 , but change FEV1 to FVC

Table 14.2.2.6 Statistical Analysis of Change from Baseline in Time-Normalized AUC for FEV_1 (L) Measured over 12 Hours on Day 1 and Day 21

Full Analysis Set

Footnote: N = Number of full analysis subjects; n = Number of subjects with at least one post baseline visit in the summarized category
[1] LSMD = Least Square Mean Difference for each GSP304 vs placebo, and Spiriva vs placebo; The model will include AUC FEV1 from Days 1 and 21 and fixed terms for treatment, visit, center, baseline, treatment by visit and baseline by visit interactions; Unstructured covariance structure is used.

Table 14.2.1.5
Sensitivity Statistical Analysis of Change from Baseline in Day 21Trough FEV_1 (L) :
Pattern Mixture Model

Full Analysis Set

		GSP304				Spiriva R
Model	Statistics	[redacted] (N=xxx)	[redacted] (N=xxx)	[redacted] (N=xxx)	Placebo (N=xxx)	5 ug (N=xxx)
	n	xxx	xxx	xxx	xxx	xxx
MIPMM [1]	LS Mean (SE)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	LSMD (SE)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	-	xx.x (xx.xx)
	95% CI for LSMD	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	-	(xx.x, xx.x)
	p-value for LSMD	x.xxx	x.xxx	x.xxx	-	x.xxx
MIPMM [2]	LS Mean (SE)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	LSMD (SE)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	-	xx.x (xx.xx)
	95% CI for LSMD	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	-	(xx.x, xx.x)
	p-value for LSMD	x.xxx	x.xxx	x.xxx	-	x.xxx

Trough FEV_1 is defined as the average of FEV_1 obtained 23 hours 15 minutes and 23 hours 45 minutes post-morning dose of the previous day; N = Number of full analysis subjects; n = Number of subjects with at least one post baseline visit in the summarized category
[1] Multiple Imputation Pattern Mixture Model (MIPMM) under Missing At Random (MAR)

[2] Multiple Imputation Pattern Mixture Model (MIPMM) under Missing Not At Random (MNAR)(J2R)

LSMD = Least Square Mean Difference for each GSP304 vs placebo, and Spiriva vs placebo; The model will include trough FEV1 from all visits (Days 1, 6, 13, 20 and Day 21), and fixed terms for treatment, visit, center, baseline, treatment by visit and baseline by visit interactions; Unstructured covariance structure is used LSMD = Least Square Mean Difference; N = Number of full analysis subjects;

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Programming notes:

Table 14.2.1.6
Sensitivity Statistical Analysis of Change from Baseline in Day 21Trough FEV_1(L) :
Tipping Point Approach

Full Analysis Set

Shift Parameter [1] for GSP304 xx ug (n=xxx)	Statistics	Shift Parameter for GSP304 Placebo (n=xxx)				
		0 mL	-20 mL	-40 mL	-60 mL	-80 mL
0 mL	LSMD	xx.x	xx.x	xx.x	xx.x	xx.x
	95%CI	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)
	p-value	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
-20 mL	LSMD	xx.x	xx.x	xx.x	xx.x	xx.x
	95%CI	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)
	p-value	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
-40 mL	LSMD	xx.x	xx.x	xx.x	xx.x	xx.x
	95%CI	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)
	p-value	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
-60 mL	LSMD	xx.x	xx.x	xx.x	xx.x	xx.x
	95%CI	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)
	p-value	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
-80 mL	LSMD	xx.x	xx.x	xx.x	xx.x	xx.x
	95%CI	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)
	p-value	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx

Trough FEV_1 is defined as the average of FEV_1 obtained 23 hours 15 minutes and 23 hours 45 minutes post-morning dose of the previous day.; N = Number of full analysis subjects; n = Number of subjects with at least one post baseline visit in the summarized category
[1] LSMD = Least Square Mean Difference for each GSP304 vs GSP304 placebo: Missing values are imputed under the assumption that the distribution of the missing observations has a low expected value than that of the observed only by a shift parameter value; The shift parameter is set at 80 mL for being about 50% of treatment efficacy when assuming that a difference in mean change from baseline at the end of treatment in trough FEV_1 between GSP304 and GSP304 placebo is 150 mL; Increment = 20 mL; If the tipping point is found to be between two increments on the given interval, a subsequent tipping point procedure will be performed using an interval on the neighborhood of the perceived tipping point finer increments for the shift parameter; The model will include trough FEV1 from all visits (Days 1, 6, 13, 20 and Day 21) and fixed terms for treatment, visit, center, baseline, treatment by visit and baseline by visit interactions Unstructured covariance structure is used ;

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Programming notes:

Table 14.2.1.7
Exploratory Statistical Analysis of Change from Baseline in Day 21Trough FEV_1 (L)
Dose Response Modelling (Linear Model)

Full Analysis Set

		GSP304			
	Statistics	[redacted] (N=xxx)	[redacted] (N=xxx)	[redacted] (N=xxx)	Placebo (N=xxx)
Mixed Model [1]	n	xxx	xxx	xxx	xxx
	LS Mean (SE)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	LSMD (SE)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	-
	95% CI for LSMD	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	-
	p-value for LSMD	x.xxx	x.xxx	x.xxx	-
Slope [2]	Estimate(SE)	95% CI	p-value		
	xx.x (xx.xx)	(xx.x, xx.x)	x.xxx		

Trough FEV_1 is defined as the average of FEV_1 obtained 23 hours 15 minutes and 23 hours 45 minutes post-morning dose of the previous day; LSMD = Least Square Mean Difference for each GSP304 vs GSP304 placebo; LSMD = Least Square Mean Difference; N = Number of full analysis subjects; n = Number of subjects with at least one post baseline visit in the summarized category
[1] Change from baseline in FEV_1 is modeled using a categorical dose as an explanatory variable with visit and visit by dose interaction as fixed effects. The model will include trough FEV1 from all visits (Days 1, 6, 13, 20 and Day 21) and fixed terms for treatment, visit, center, baseline, treatment by visit and baseline by visit interactions; Unstructured covariance structure is used.
[2] Change from baseline in FEV_1 is modeled using a continuous dose as an explanatory variable with visit and visit by dose interaction as fixed effects.

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Programming notes:

Table 14.2.1.8
Exploratory Statistical Analysis of Change from Baseline in Day 21Trough FEV_1 (L)
Dose Response Modelling (Non-Linear Model)

Full Analysis Set

	Parameter	Estimate(SE)	CI
E-Max Mode l [1]	Intercept	xx.x (xx.xx)	(xx.x, xx.x)
	Parameter 1	xx.x (xx.xx)	(xx.x, xx.x)
	Parameter 2	xx.x (xx.xx)	(xx.x, xx.x)

[1] Non-linear model using a continuous dose as an exploratory variable on change from baseline in FEV_1 will be analyzed using an E-max model with 3 parameters; n = Number of subjects on Day 21. Trough FEV_1 is defined as the average of FEV_1 obtained 23 hours 15 minutes and 23 hours 45 minutes post-morning dose of the previous day.

Intercept = E0, the response at dose = 0 (placebo response)

parameter 1 = $E_{max,}$ the maximum change in the response compared to placebo

parameter 2 = ED50, the dose at 50% of maximum change in the response compared to placebo (ED50)

The estimate of the ED50, the minimum effective dose has to be chosen close to twice the ED50 to obtain 100% of the maximum change in the response compared to placebo.

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Programming notes:

Table 14.2.3.1
Summary of Plasma Concentration (pg/mL) on Day 1 and Day 21 by Subject

PK Analysis Set
Panel/Day/Treatment Group: <Day 1, Day 21> <treatment group>

Subject ID	pre-dose	2 min	4 min	6 min	10 min	15 min	30 min	45 min	60 min	75 min	90 min
xxx-xxxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
xxx-xxxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
.....											
n	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min; Max	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	xx.x;xx.x	xx.x;xx.x	xx.x;xx.x	xx.x;xx.x
%CV	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
GM	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x

GM = Geometric Mean; n = Number of subjects with data in the summarized category
The pre-dose sample on Day 1 should be collected within 30 minutes prior to dosing.
The pre-dose sample on Day 21 should be collected within 10 minutes prior to the morning dose.

Program location/program name.sas/ddmmmyyyy/hh:mm
Source Data: Listing xxxxxxx Database Extract Date: ddmmmyyyy

Programming notes: Values will be reported to the same decimal place as in raw data (provided by bioanalytical lab); min and max values will be tabulated to the same precision as the source data, but with a maximum of 4 significant digits.

Table 14.2.3.1
Summary of Plasma Concentration (pg/mL) on Day 1 and Day 21 by Subject

PK Analysis Set
Panel/Day/Treatment Group: <Day 1, Day 21> <treatment group>

Subject ID	2 hr	4 hr	6 hr	8 h	12 hr	16 hr	20 hr	24 hr
xxx-xxxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
xxx-xxxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
.....								
n	xx	xx	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min; Max	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	xx.x;xx.x
%CV	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
GM	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x

GM = Geometric Mean; n = Number of subjects with data in the summarized category

Program location/program name.sas/ddmmmyyyy/hh:mm
Source Data: Listing xxxxxxx Database Extract Date: ddmmmyyyy

Programming notes: Values will be reported to the same decimal place as in raw data (provided by bioanalytical lab); min and max values will be tabulated to the same precision as the source data, but with a maximum of 4 significant digits.

Table 14.2.3.2
Summary of Urine Concentration on Day 1 and Day 21 by Subject

PK Analysis Set
Panel/Day/Treatment Group: <Day 1, Day 21> <treatment group>

	predose			0-6h			6-12h		
Subject ID	Conc(pg/mL)	Vol(mL)	Ae(mg)	Conc(pg/mL)	Vol(mL)	Ae(mg)	Conc(pg/mL)	Vol(mL)	Ae(mg)
xxx-xxxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
xxx-xxxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
.....									
n	xx	xx	xx	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min; Max	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	xx.x;xx.x	xx.x;xx.x
%CV	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
GM	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x

GM = Geometric Mean; n = Number of subjects with data in the summarized category

Program location/program name.sas/ddmmmyyyy/hh:mm

Source Data: Listing xxxxxxx Database Extract Date: ddmmmyyyy

Programming notes: Conc and volume (from CRF) would be reported to the same decimal place as in raw data (provided by bioanalytical lab and sites)

Table 14.2.3.2
Summary of Urine Concentration on Day 1 and Day 21 by Subject

PK Analysis Set
Panel/Day/Treatment Group: <Day 1, Day 21> <treatment group>

	12-24h			Cummulative amount 0-24h		
Subject ID	Conc(pg/mL)	Vol(mL)	Ae(mg)	Conc(pg/mL)	Vol(mL)	Ae(mg)
xxx-xxxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
xxx-xxxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
.....						
n	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min; Max	xx.x;xx.x	xx.x;xx.x	xx.x;xx.x	xx.x;xx.x	xx.x;xx.x	xx.x;xx.x
%CV	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
GM	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x

GM = Geometric Mean; n = Number of subjects with data in the summarized category

Program location/program name.sas/ddmmmyyyy/hh:mm
Source Data: Listing xxxxxxx Database Extract Date: ddmmmyyyy

Table 14.2.4.1
Summary of Pharmacokinetics Parameters on Day 1 and Day 21 by Subject

PK Analysis Set
Panel/Treatment Group/ Day: <treatment group> <Day 1 >

Subject ID	C_{maxSS} (pg/mL);	t_{max} (h)	$AUC_{0\text{-}tauSS}$ (pg*hr/mL)	t_{last} (h)	$AUC_{0\text{-}tauSS}$/Dose	C_{maxSS}/Dose
xxx-xxxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
xxx-xxxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
.....						
n	xx	xx	xx	xx	xx	xx
Mean	xx.x	--	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	--	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min; Max	xx.x; xx.x	xx.x; xx.x	xx.x; xx.x	xx.x; xx.x	xx.x; xx.x	xx.x; xx.x
%CV	xx.x	--	xx.x	xx.x	xx.x	xx.x
GM	xx.x	--	xx.x	xx.x	xx.x	xx.x
GM%CV	xx.x	--	xx.x	xx.x	xx.x	xx.x

GM = Geometric Mean; n = Number of subjects with data in the summarized category

Program location/program name.sas/ddmmmyyyy/hh:mm
Source Data: Listing xxxxxxx Database Extract Date: ddmmmyyyy

Programming notes: Values will be reported to the same decimal place as in raw data (provided by bioanalytical lab); min and max values will be tabulated to the same precision as the source data, but with a maximum of 4 significant digits.

Table 14.2.4.1
Summary of Pharmacokinetics Parameters on Day 1 and Day 21 by Subject

PK Analysis Set
Panel/Treatment Group/ Day: <treatment group> <Day 21 >

Subject ID	C_{maxSS} (pg/mL)	t_{max} (h)	$AUC_{0\text{-}tauSS}$ (pg*hr/mL)	t_{last} (h)	$AUC_{0\text{-}tauSS}$/ Dose	C_{maxSS}/ Dose	C_{minSS} (pg/mL)	C_{avSS} (pg/mL)	$t_{½}$ (h)	R_{ac}
xxx-xxxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
xxx-xxxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
.....										
n	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
Mean	xx.x	--	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	--	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min; Max	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	xx.x; xx.x	xx.x; xx.x	xx.x;xx.x
%CV	xx.x	--	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
GM	xx.x	--	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
GM%CV	xx.x	--	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x

GM = Geometric Mean; n = Number of subjects with data in the summarized category

Program location/program name.sas/ddmmmyyyy/hh:mm
Source Data: Listing xxxxxxx Database Extract Date: ddmmmyyyy

Programming notes: Values will be reported to the same decimal place as in raw data (provided by bioanalytical lab); min and max values will be tabulated to the same precision as the source data, but with a maximum of 4 significant digits.

Table 14.2.4.2
Summary of Urine Pharmacokinetics Parameters on Day 1 and Day 21 by Subject

PK Analysis Set
Panel/Treatment Group: <treatment group>

Subject ID	Day 1			Day 21		
	Aetau (pg)	Aeta/Dose	Fe (%)	Aetau (pg)	Aeta/Dose	Fe (%)
xxx-xxxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
xxx-xxxx	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
.....						
n	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min; Max	xx.x; xx.x	xx.x; xx.x	xx.x; xx.x	xx.x; xx.x	xx.x; xx.x	xx.x; xx.x
%CV	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
GM	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
GM%CV	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x

GM = Geometric Mean; n = Number of subjects with data in the summarized category

Program location/program name.sas/ddmmmyyyy/hh:mm
Source Data: Listing xxxxxxx Database Extract Date: ddmmmyyyy

Programming notes: Values will be reported to the same decimal place as in raw data (provided by bioanalytical lab); min and max values will be tabulated to the same precision as the source data, but with a maximum of 4 significant digits.

Table 14.2.5
Relative Bioavailability of GSP304 Comparison to Spiriva

PK Analysis Set

Parameter	Statistics	GSP304 [redacted] (N=xxx)	GSP304 [redacted] (N=xxx)	GSP304 [redacted] (N=xxx)	Spiriva R 5 ug (N=xxx)
C_{maxSS}	n	xxx	xxx	xxx	xxx
	LS Mean (SE)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Ratio[1] (SE)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	
	90% CI for Ratio	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	
$AUC_{0\text{-}tauSS}$	n	xxx	xxx	xxx	xxx
	LS Mean (SE)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Ratio[1] (SE)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	
	90% CI for Ratio	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	

An ANOVA is performed on the ln-transformed AUC $_{0\text{-}tauSS}$, and C_{maxSS} and includes treatment as fixed effect. The results from the model are back-transformed.
[1] Ratio = GSP 304/ Spiriva; N = Number of PK subjects; n = Number of subjects with data in the summarized category

Program location/program name.sas/ddmmmyyyy/hh:mm
Source Data: Listing xxxxxxx Database Extract Date: ddmmmyyyy

Table 14.2.6
Pharmacokinetics - Dose Proportionality Assessments of GSP304

PK Analysis Set

Power Model [1]	Parameter	Estimate(SE)	CI
C_{maxSS}	Intercept	xx.x (xx.xx)	(xx.x, xx.x)
	Slope	xx.x (xx.xx)	(xx.x, xx.x)
$AUC_{0\text{-}tauSS}$	Intercept	xx.x (xx.xx)	(xx.x, xx.x)
	Slope	xx.x (xx.xx)	(xx.x, xx.x)
A_{etau}	Intercept	xx.x (xx.xx)	(xx.x, xx.x)
	Slope	xx.x (xx.xx)	(xx.x, xx.x)

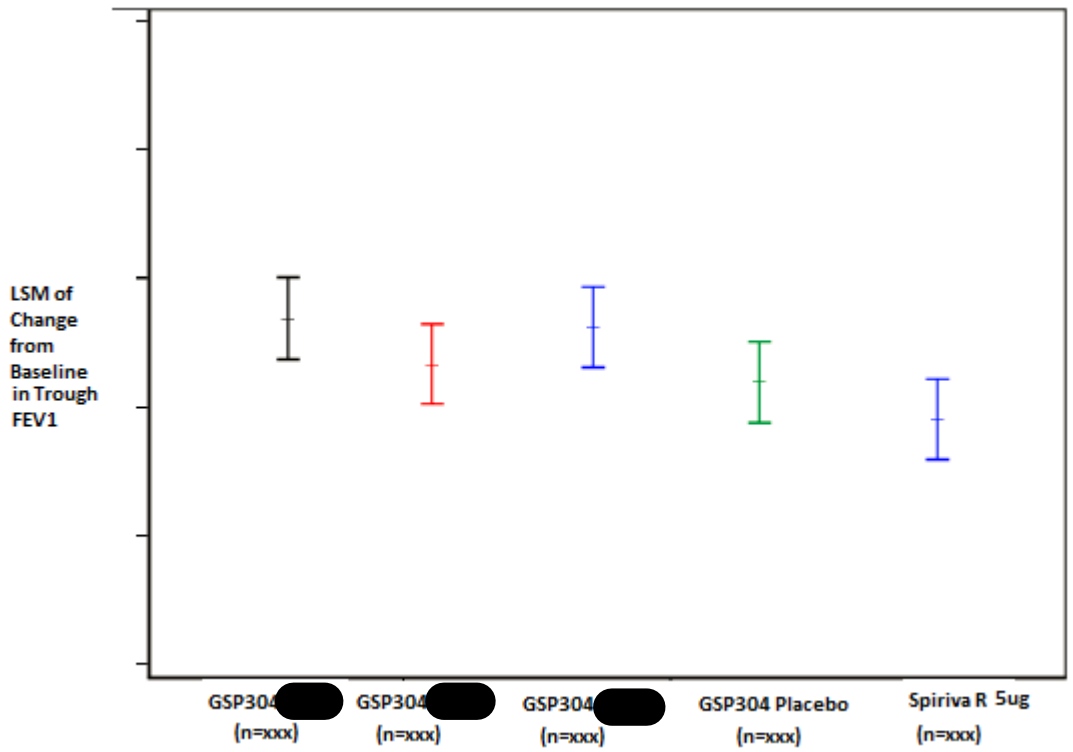
[1] Exploratory Analysis: Dose-proportionality of tiotropium C_{maxSS}, $AUC_{0\text{-}tauSS}$ and A_{etau} parameters is assessed using an ln-transformed power model. Dose proportionality will be declared if the estimate of slope lies between 0.5- 2.

Program location/program name.sas/ddmmmyyyy/hh:mm
Source Data: Listing xxxxxxx Database Extract Date: ddmmmyyyy

Programming notes:

Figure 14.2.1.1
Plot of LS Means of Change from Baseline in Day 21 Trough FEV_1 (L)

Full Analysis Set



Trough FEV_1 is defined as the average of FEV_1 obtained 23 hours 15 minutes and 23 hours 45 minutes post-morning dose of the previous day; LSM = Least Square Mean; n = Number of subjects with at least one post baseline visit in the summarized category; The model will include trough FEV1 from all visits (Days 1, 6, 13, 20 and Day 21) and fixed terms for treatment, visit, center, baseline, treatment by visit and baseline by visit interactions; Unstructured covariance structure is used;

Programming notes: Font for text/label number = 10pt; Only for Day 21

Repeat for

Figure 14.2.1.3. Plot of LS Means of Change from Baseline in Day 21Trough FEV_1(L)

Per-Protocol set
Similar to Figure 14.2.1.1; Only Day 21

Figure 14.2.2.1 Plot of LS Means of Change from Baseline in Peak FEV_1 (L)

Full Analysis Set

Footnote: LSM = Least Square Mean; n = Number of subjects with at least one post baseline visit in the summarized category; The model will include Peak FEV1 from Days 1 and 21 and fixed terms for treatment, visit, center, baseline, treatment by visit and baseline by visit interactions; Unstructured covariance structure is used;

Plots for Day 1and Day 21: overlay with adding different symbols at mean value

Figure 14.2.2.3 Plot of LS Means of Change from Baseline in Day 21 Trough FVC (L)

Full Analysis Set
Footnote: Same as 14.2.1.1

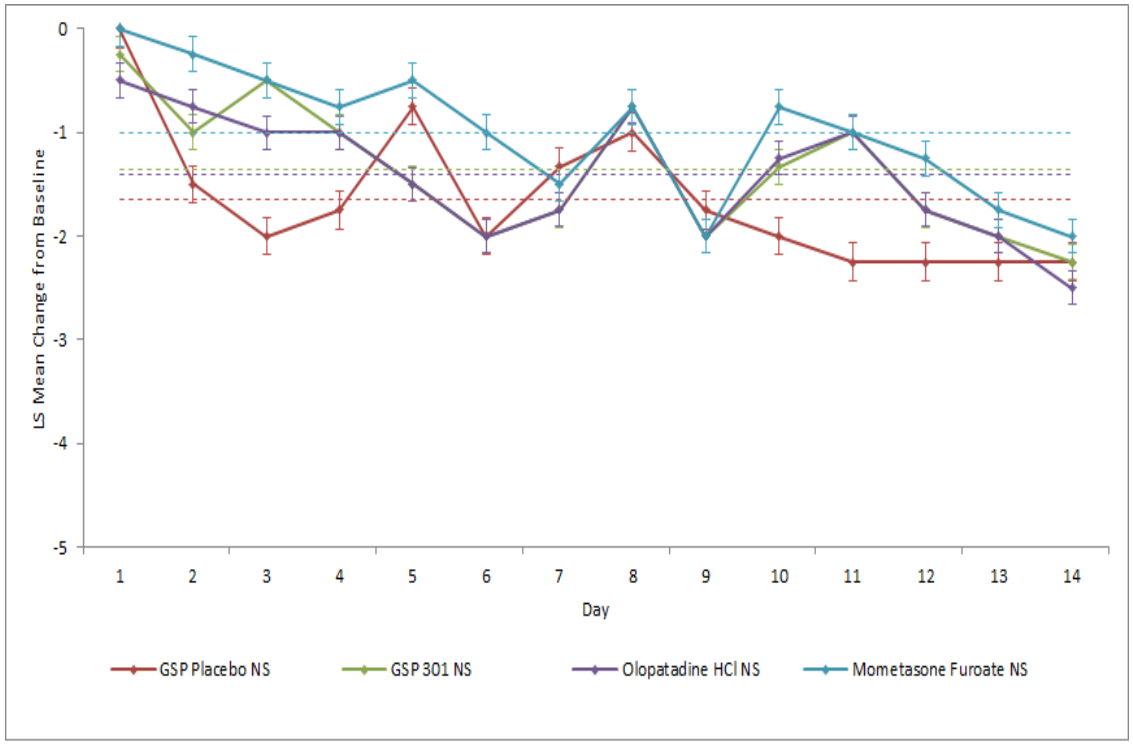
Figure 14.2.2.5 Plot of LS Means of Change from Baseline in Time-Normalized AUC for FEV_1 (L) Measured over 12 Hours

Full Analysis Set
Footnote: LSM = Least Square Mean; n = Number of subjects with at least one post baseline visit in the summarized category; The model will include Time-Normalized AUC for FEV_1 from Days 1 and 21 and fixed terms for treatment, visit, center, baseline, treatment by visit and baseline by visit interactions; Unstructured covariance structure is used;

Plots for Day 1and Day 21: overlay with adding different symbols at mean value

Figure 14.2.1.1.1
Plot of Time to onset of action (Percent change in unadjusted mean FEV_1 (L) on Day 1)

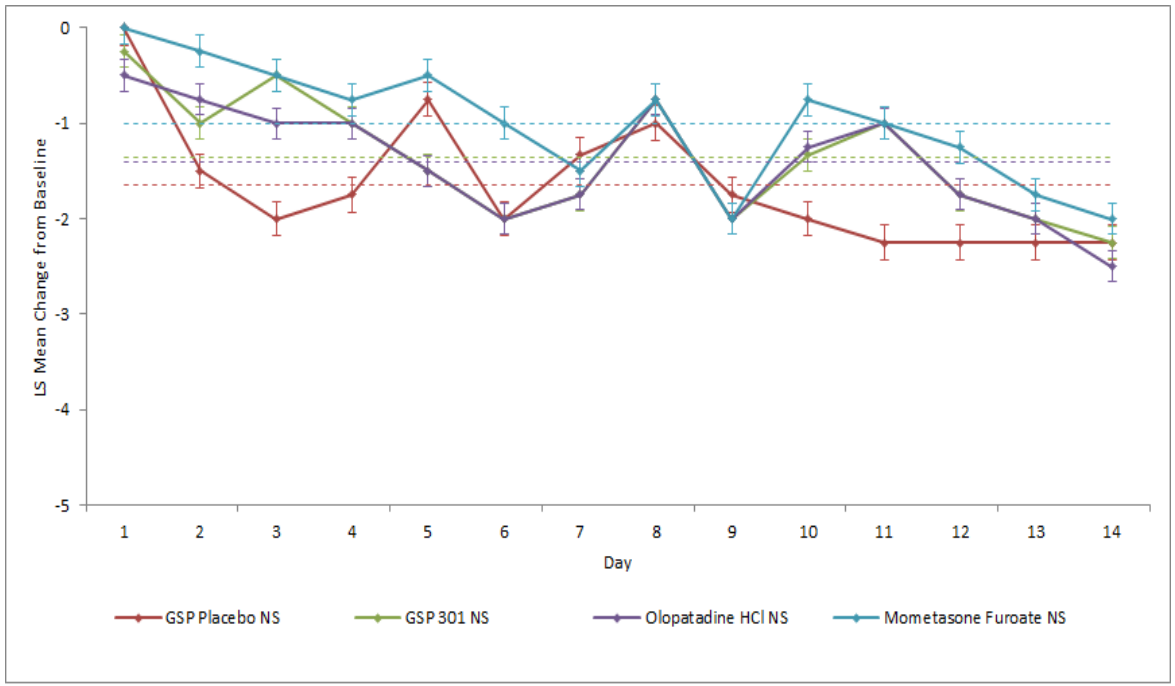
Full Analysis Set



Programming notes: Font for text/label number = 10 pt
Change "Day" with "time" in hours, for the x-axis Add "Mean Percent Change in FEV1" to y-axis title Add a symbol for every point where there is change from baseline of >= 12 %.
Add a horizontal reference line at 12%
Please ensure that line and marker (line graph, means, standard error bars), significance symbols and colors are consistent within this figure and across figures

Figure 14.2.1.1.2
Plot of Time to onset of action (Change in unadjusted mean FEV_1 (L) on Day 1)

Full Analysis Set



Programming notes: Font for text/label number = 10 pt
Change "Day" with "time" in hours, for the x-axis
Add "Mean Change in FEV1" to y-axis title
Add a symbol for every point where there is change from baseline of >= 200mL
Add a horizontal reference line at 200 ml..

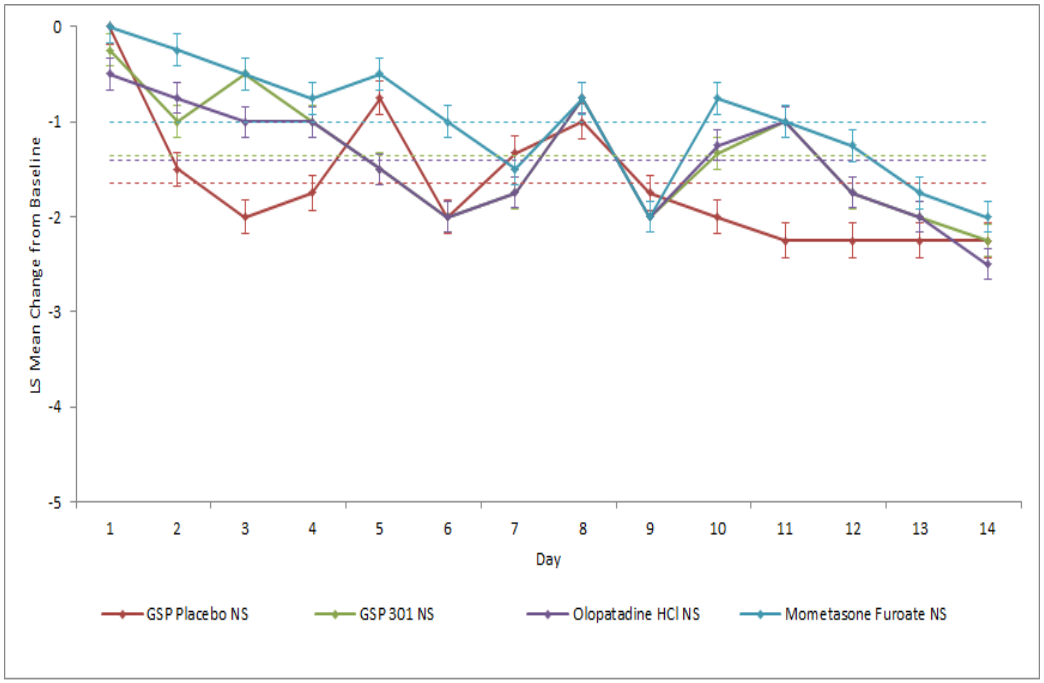
Please ensure that line and marker (line graph, means, standard error bars), significance symbols and colors are consistent within this figure and across figures

Figure 14.2.1.1.3 Plot of Time to onset of action (Percent change in unadjusted mean FEV_1 (L) on Day 1)
Per Protocol Set
Footnote: Same as in 14.2.1.1.1

Figure 14.2.1.1.4 Plot of Time to onset of action (Change in unadjusted mean FEV_1 (L) on Day 1)
Per Protocol Set
Footnote: Same as in 14.2.1.1.1

Figure 14.2.1.2.1
Time to Steady State in Trough FEV1 (L)

Full Analysis Set



Programming notes: Font for text/label number = 10 pt

1. Include Placebo,
2. On the x-axis go from day 0 to day 21, There should be 5 time points (1, 6, 13, 20, 21). Use actual units of time on the x-axis
3. Add " Unadjusted Mean Trough FEV1" to y-axis title

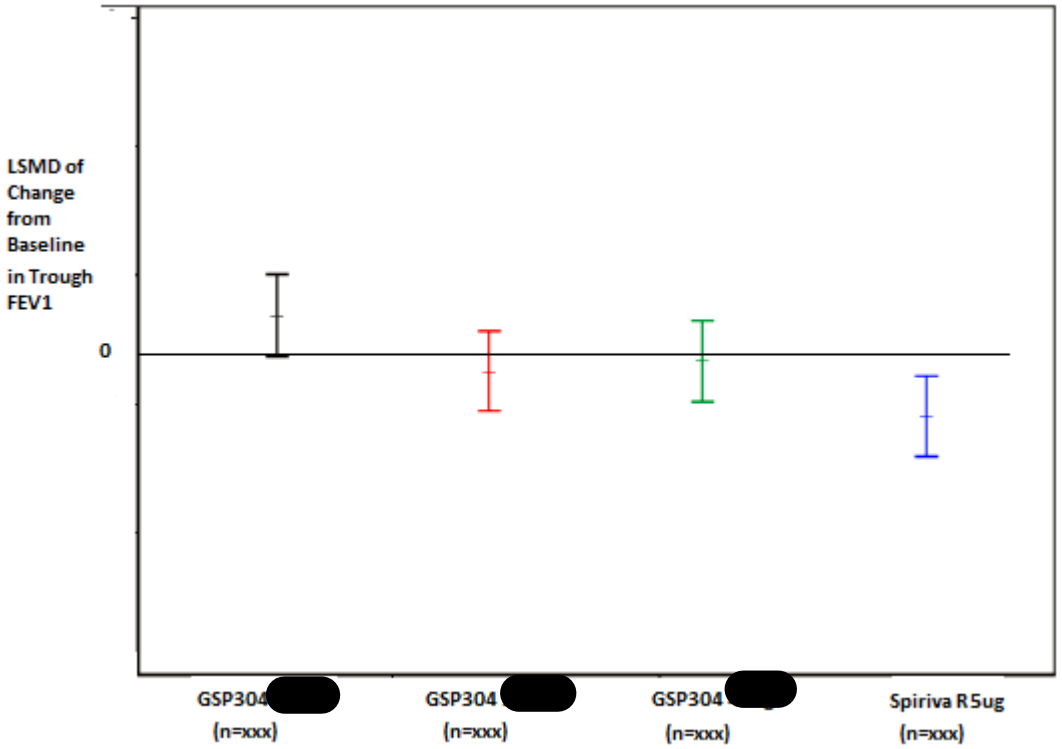
Please ensure that line and marker (line graph, means, standard error bars), significance symbols and colors are consistent within this figure and across figures

Figure 14.2.1.2.2 Time to Steady State in Unadjsuted Trough FEV1(L)
Per Protocol Set
Footnote: Same as in 14.2.1.2.1

Figure 14.2.2.3.1 Time to Steady State in Unadjsuted Trough FVC (L)
Full Analysis Set
Footnote: Same as in 14.2.1.2.1

Figure 14.2.2.3.2 Time to Steady State in Unadjsuted Trough FVC (L)
Per Protocol Set
Footnote: Same as in 14.2.1.2.1

Figure 14.2.1.2
Plot of LS Mean Treatment Differences of Change from Baseline in Day 21 Trough FEV_1 (L) in Comparision with Placebo
Full Analysis Set



Trough FEV_1 is defined as the average of FEV_1 obtained 23 hours 15 minutes and 23 hours 45 minutes post-morning dose of the previous day; LSMD = Least Square Mean Differencefor each GSP304 vs GSP304 placebo, and Spiriva vs GSP304 placebo n = Number of subjects with at least one post baseline visit in the summarized category; The model will include trough FEV1 from all visits (Days 1, 6, 13, 20 and Day 21) and fixed terms for treatment, visit, center, baseline, treatment by visit and baseline by visit interactions; Unstructured covariance structure is used.

Programming notes: Font for text/label number = 10; Only for Day 21

Repeat for

Figure 14.2.1.4 Plot of LS Mean Treatment Differences of Change from Baseline in Day 21 Trough FEV_1 (L) in Comparison with Placebo

Per-Protocol set
Footnote: Same as 14.2.1.2
Similar to Figure 14.2.1.2; Only Day 21

Figure 14.2.2.2 Plot of LS Mean Treatment Differences of Change from Baseline in Peak FEV_1 (L)

Full Analysis Set
Footnote: LSMD = Least Square Mean Differencefor each GSP304 vs GSP304 placebo, and Spiriva vs GSP304 placebo n = Number of subjects with at least one post baseline visit in the summarized category; The model will include peak FEV1 from Days 1 and Day 21 and fixed terms for treatment, visit, center, baseline, treatment by visit and baseline by visit interactions; Unstructured

Plots for Day 1 and Day21: overaly with adding different symbols at mean value

Figure 14.2.2.4 Plot of LS Mean Treatment Differences of Change from Baseline in FVC (L)

Full Analysis Set
Footnote: Trough FEV_1 is defined as the average of FEV_1 obtained 23 hours 15 minutes and 23 hours 45 minutes post-morning dose of the previous day; LSMD = Least Square Mean Differencefor each GSP304 vs GSP304 placebo, and Spiriva vs GSP304 placebo n = Number of subjects with at least one post baseline visit in the summarized category; The model will include trough FEV1 from all visits (Days 1, 6, 13, 20 and Day 21) and fixed terms for treatment, visit, center, baseline, treatment by visit and baseline by visit interactions; Unstructured
Plots for Day 1 and Day21: overlay with adding different symbols at mean value

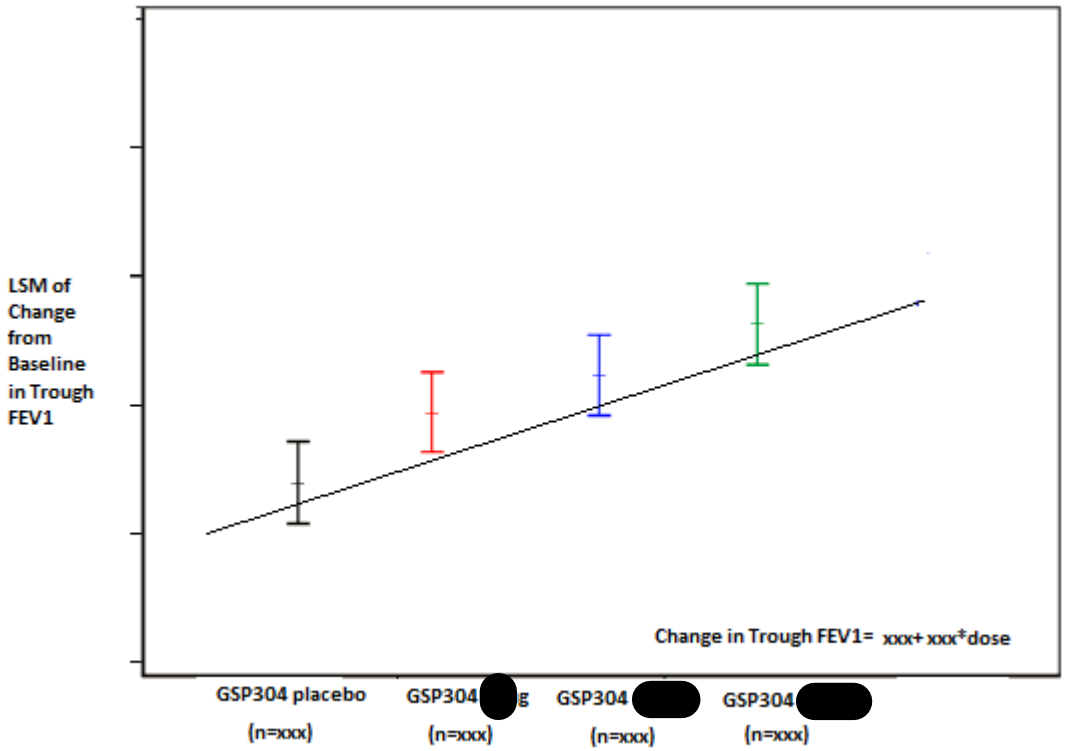
Figure 14.2.2.6 Plot of LS Mean Treatment Differences of Change from Baseline in Time-Normalized AUC for FEV_1 (L) Measured over 12 Hours

Full Analysis Set
Footnote: LSMD = Least Square Mean Differencefor each GSP304 vs GSP304 placebo, and Spiriva vs GSP304 placebo n = Number of subjects with at least one post baseline visit in the summarized category; The model will include time normalized AUC for FEV1 from Days 1 and Day 21 and fixed terms for treatment, visit, center, baseline, treatment by visit and baseline by visit interactions; Unstructured

Plots for Day 1 and Day21: overlay with adding different symbols at mean value

Figure 14.2.1.5
Plot of LS Means of Change from Baseline in Day 21 Trough FEV_1(L) :
Dose Response Modelling (Linear Model)

Full Analysis Set

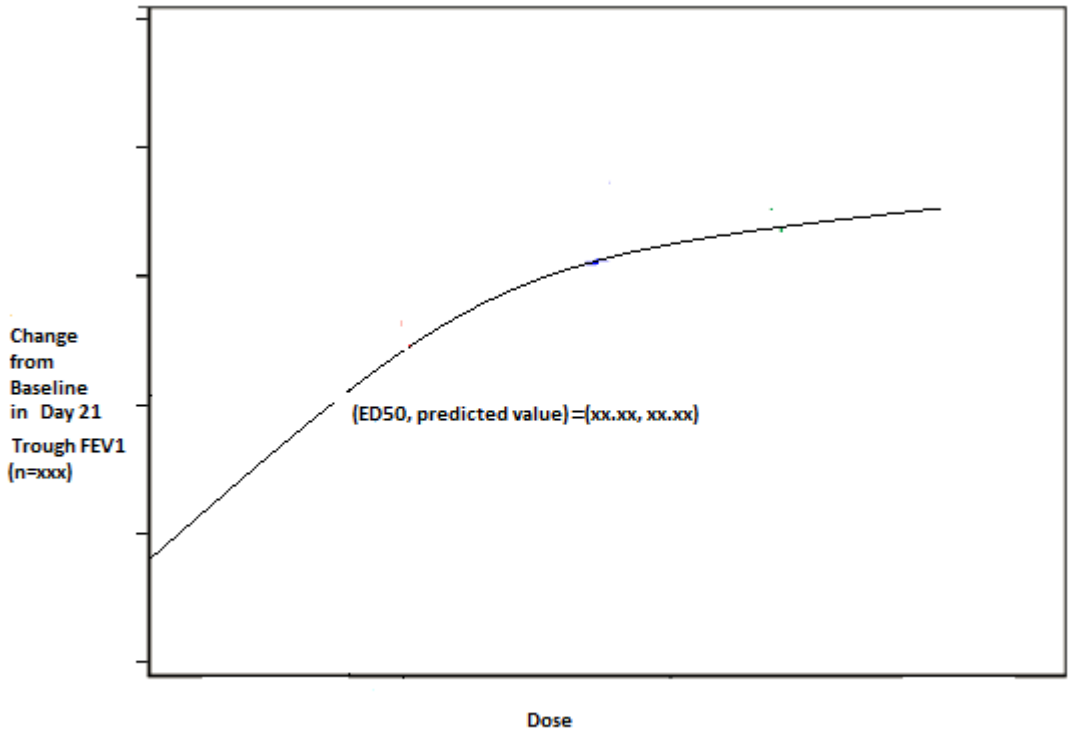


Trough FEV_1 is defined as the average of FEV_1 obtained 23 hours 15 minutes and 23 hours 45 minutes post-morning dose of the previous day; LSM = Least Square Mean; n = Number of subjects with at least one post baseline visit in the summarized category; The model will include trough FEV1 from all visits (Days 1, 6, 13, 20 and Day 21) and fixed terms for treatment, visit, center, baseline, treatment by visit and baseline by visit interactions; Unstructured covariance structure is used.

Programming notes: Font for text/label number = 10 pt;

Figure 14.2.1.6
Plot ofChange from Baseline in Day 21Trough FEV_1 (L)
Dose Response Modelling (Non-Linear Model)

Full Analysis Set

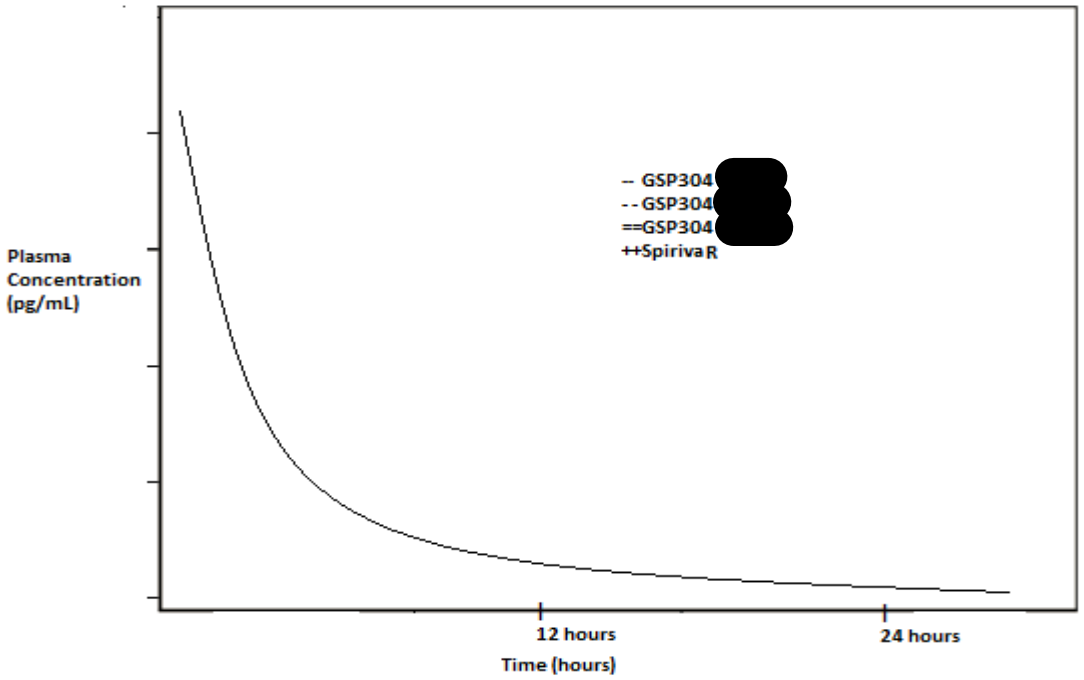


Emax model with 3 parameters is used; n = Number of subjects on Day 21; Trough FEV_1 is defined as the average of FEV_1 obtained 23 hours 15 minutes and 23 hours 45 minutes post-morning dose of the previous day;

Programming notes: Font for text/label number = 10 pt

Figure 14.2.3.1
Plot of Mean Plasma Concentrations by Day (Linear Scale)

PK Analysis Set
Panel/Day: <Day 1, Day 21>



Programming notes: Font for text/label number = 10 pt;

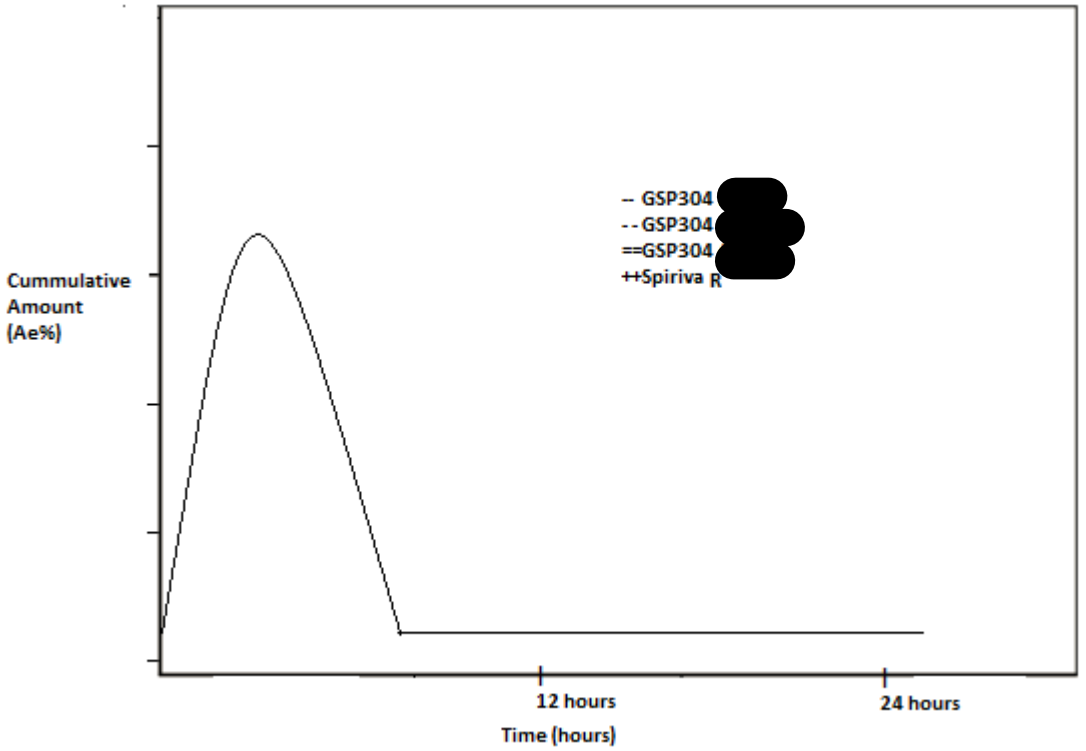
Treatments (4 lines) should be overlaid.

Repeat for

Figure 14.2.3.2 Plot of Mean Plasma Concentrations by Day (Semi-Log Scale)
Similar to Figure 14.4.1.1

Figure 14.2.4.1
Plot of Mean Amount of Urine Excreted by Day (Linear Scale)

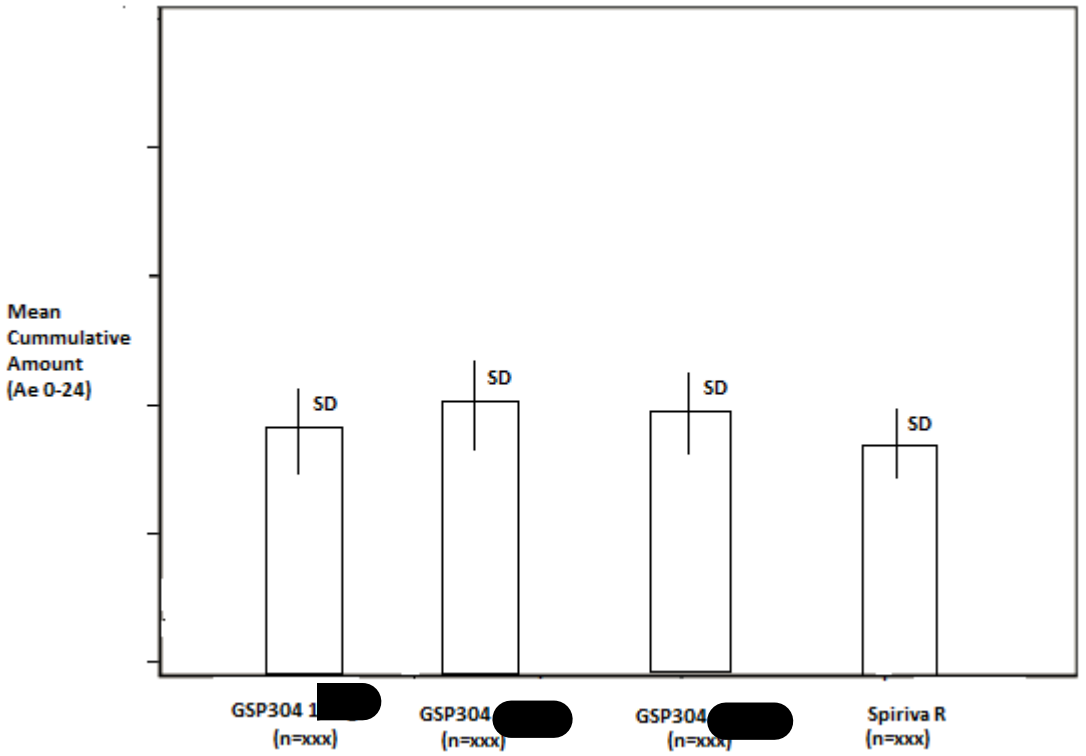
PK Analysis Set
Panel/Day: <Day 1, Day 21>



Programming notes: Font for text/label number = 10 pt; Treatments (4 lines) should be overlaid.

Figure 14.2.4.2
Plot of Mean Amount of Urine Excreted by Day (Linear Scale)

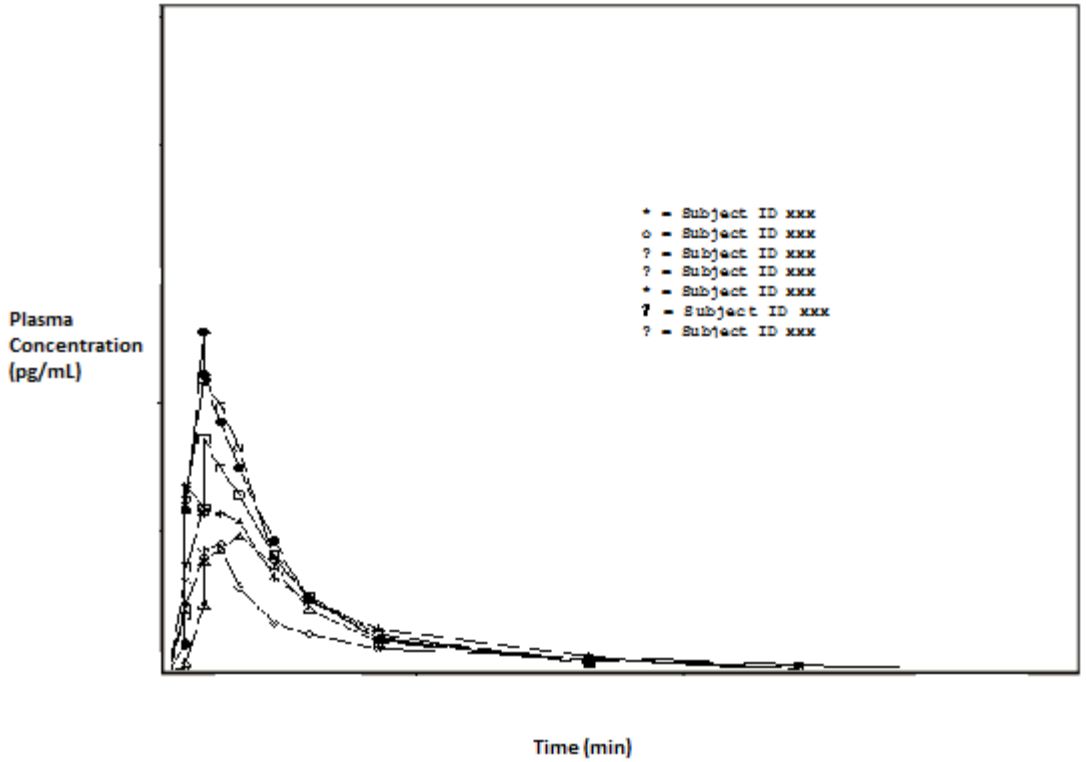
PK Analysis Set
Panel/Day: <Day 1, Day 21>



Programming notes: Font for text/label number = 10 pt;

Figure 14.2.4.2
Plot of Combined Individual Concentrations – Plasma

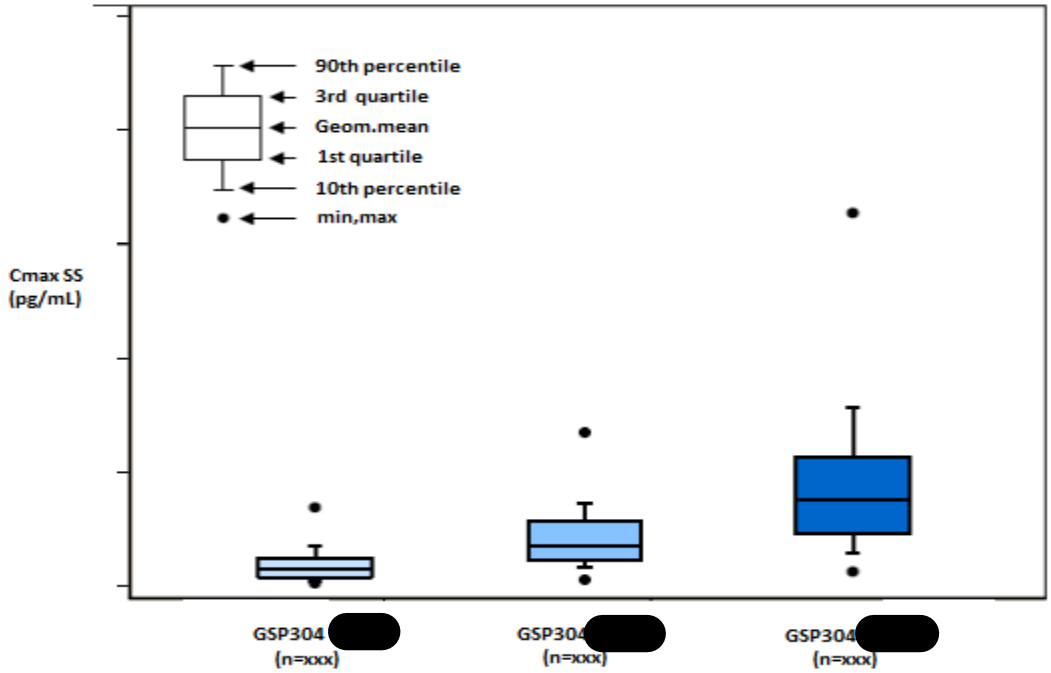
PK Analysis Set
Panel/Day/Treatment Group: <Day 1, Day 21> <treatment group>



Programming notes: Font for text/label number = 10 pt;

Figure 14.2.5.1
Plot of Dose Proportionality - Plasma

Panel/Day/Parameter: <Day 1, Day 21> <parameter>



Programming notes: Font for text/label number = 10 pt;

Y-axis = Parameter (unit) = C_{maxSS} (day 21 only) ; $AUC_{0\text{-}tauSS}$ (day 21 only)

Repeat for

Figure 14.2.5.2 Plot of Dose Proportionality - Urine

Y-axis = Parameter (unit) = A_{etau} (day 1 and day 21)

Table 14.3.1.1
Overall Summary of Adverse Events

Safety Set

	GSP304					Spiriva R	
	[redacted] (N=xxx) n (%) [#]	[redacted] (N=xxx) n (%) [#]	[redacted] (N=xxx) n (%) [#]	Total (N=xxx) n (%) [#]	Placebo (N=xxx) n (%) [#]	5 ug (N=xxx) n (%) [#]	Total (N=xxx) n (%) [#]
TEAEs	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
TEAEs Leading to Discontinuation [1]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
TEAEs Related to Study Drug	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
AEs Leading to Withdrawal [2]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
SAE	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
SAE Seriousness Reasons							
Congenital Anomaly or Bith Defect	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
Persistent or Significant Disability or Incapacity	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
Death	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
Initial or Prolonged Hospitalization	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
Medically Important Event	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
Life Threatening	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
SAEs Related to Study Drug	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]

AE = Adverse Events; SAE = Serious Adverse Events; TEAE = Treatment-Emergent Adverse Events; TEAEs are defined as AEs (identified by PT) that begins or that worsens in severity after at least one dose of study treatment has been administered, up to the last study visit; PT = Preferred Term; n = Number of subjects reporting at least one TEAE in that category; [#] = Number of individual occurrences of the TEAE in that category
[1] counts all TEAEs leading to study discontinuation or treatment discontinuation during treatment period or follow-up period

[2] counts all AE leading to permanent discontinuation of study drug during treatment period or leading to withdrawal (study or drug discontinuation) from study during run-in, treatment period, or follow–up period

Program location/program name.sas/ddmmmyyyy/hh:mm
Source Data: Listing xxxxxxx Database Extract Date: ddmmmyyyy

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Programming notes:

Table 14.3.1.2
Summary of Treatment Emergent Adverse Events per SOC and PT

Safety Set

	GSP304					Spiriva R	
	[redacted] (N=xxx) n (%) [#]	[redacted] (N=xxx) n (%) [#]	[redacted] (N=xxx) n (%) [#]	Total (N=xxx) n (%) [#]	Placebo (N=xxx) n (%) [#]	5 ug (N=xxx) n (%) [#]	Total (N=xxx) n (%) [#]
Any TEAE	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
SOC #1	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
PT #1	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) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
SOC #2	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
PT #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) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
...							

SOC = System Organ Class; PT = Preferred Term; Treatment Emergent AEs (TEAEs) are defined as AEs (identified by PT) that begins or that worsens in severity after at least one dose of study treatment has been administered, up to the last study visit; PT = Preferred Term; N = Number of safety subjects; n = Number of subjects reporting at least one TEAE in that category; [#] = Number of individual occurrences of the TEAE in that category

Program location/program name.sas/ddmmmyyyy/hh:mm
Source Data: Listing xxxxxxx Database Extract Date: ddmmmyyyy

Programming notes:

Ordered in terms of decreasing frequency for SOC, and PT within SOC, in the treatment group, and then alphabetically for SOC, and PT within SOC.

Repeat Table for:

Table 14.3.1.3 Summary of Treatment-Related Emergent Adverse Events per SOC and PT

Programming note: In the first row: Any Treatment-Related AE

Table 14.3.1.4 Summary of Pre-Treatment Adverse Events per SOC and PT
Footnote: Pre-Treatment AEs (PTAEs)are defined as AEs (identified by PT) that begin or that worsen in severity between study Day -14 and study drug

administration, and last up to the AE stop date
Programming note: In the first row: Any Pre-Treatment AE

Table 14.3.1.5 Summary of Serious Adverse Events per SOC and PT
Programming note: In the first row: Any Serious AE

Table 14.3.1.6 Summary of Serious Adverse Events Leading to Study Discontinuation per SOC and PT
Programming note: In the first row: Any Serious AE Leasing to Study Discontinuation

Table 14.3.1.7 Summary of Treatment-Related Emergent Serious Adverse Events per SOC and PT
Programming note: In the first row: Any Treatment-Related Serious AE

Table 14.3.1.8 Summary of Treatment Emergent Adverse Events Leading to Study Discontinuation per SOC and PT
Programming note: In the first row: Any TEAE Leading to Study Discontinuation

Table 14.3.1.9
Summary of Treatment Emergent Adverse Events by Severity per SOC and PC

Safety Set

		GSP304					Spiriva R	
		[redacted] (N=xxx)	[redacted] (N=xxx)	[redacted] (N=xxx)	Total (N=xxx)	Placebo (N=xxx)	5 ug (N=xxx)	Total (N=xxx)
	Category	n (%) [#]	n (%) [#]	n (%) [#]	n (%) [#]	n (%) [#]	n (%) [#]	n (%) [#]
Any TEAE	Any	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
	Mild	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
	Moderate	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
	Severe	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
SOC #1	Any	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
	Mild	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
	Moderate	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
	Severe	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
PT #1	Any	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
	Mild	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
	Moderate	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
	Severe	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
...								
SOC #2	Any	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
	Mild	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
	Moderate	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
	Severe	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
PT #2	Any	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
	Mild	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
	Moderate	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
	Severe	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
...								
...								

SOC = System Organ Class; PT = Preferred Term; TEAE = Treatment-Emergent Adverse Events; TEAEs are defined as AEs (identified by PT) that begins or that worsens in severity after at least one dose of study treatment has been administered, up to the last study visit; PT = Preferred Term; N = Number of safety subjects; n = Number of subjects reporting at least one TEAE in that category;[#] = Number of individual occurrences of the TEAE in that category;

Each subject is counted once within each System Organ Class and Preferred Term according to the maximum intensity for all TEAEs within that System Organ Class, High Level Term or Preferred Term.

Program location/program name.sas/ddmmmyyyy/hh:mm
Source Data: Listing xxxxxxx Database Extract Date: ddmmmyyyy

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Programming notes:

Ordered in terms of decreasing frequency for SOC, and PT within SOC, in the treatment group, and then alphabetically for SOC, and PT within SOC.

Table 14.3.1.10
Summary of Treatment Emergent Adverse Events by Relationship to Study Treatment per SOC and PC

Safety Set

		GSP304					Spiriva R	
		[redacted] (N=xxx)	[redacted] (N=xxx)	[redacted] (N=xxx)	Total (N=xxx)	Placebo (N=xxx)	5 ug (N=xxx)	Total (N=xxx)
	Category	n (%) [#]	n (%) [#]	n (%) [#]	n (%) [#]	n (%) [#]	n (%) [#]	n (%) [#]
Any TEAE	Not Related	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
	Related	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
SOC #1	Not Related	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
	Related	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
PT #1	Not Related	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
	Related	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]	xx (xx.x) [#]
...								

SOC = System Organ Class; PT = Preferred Term; TEAE = Treatment-Emergent Adverse Events; TEAEs are defined as AEs (identified by PT) that begins or that worsens in severity after at least one dose of study treatment has been administered, up to the last study visit; PT = Preferred Term; N = Number of safety subjects; n = Number of subjects reporting at least one TEAE in that category;[#] = Number of individual occurrences of the TEAE in that category

Program location/program name.sas/ddmmmyyyy/hh:mm
Source Data: Listing xxxxxxx Database Extract Date: ddmmmyyyy

Programming notes:

Table 14.3.2
Listing of Deaths for All Causes

All Screened Subjects

Site/Subject ID	Study Period	Treatment	Treatment Start Date	Date of Death	Reason for Death
xxxxxx	Screening	NA	NA	ddmmmyyyy	xxx

NA = Not Applicable

program location/program name.sas/ddmmmyyyy/hh:mm

Programming notes:

Table 14.3.4.1
Summary of Potentially Clinically Significant Laboratory Results - Biochemistry

Safety Set
Panel/Parameter: <parameter>

		GSP304					Spiriva R	
		[redacted]	[redacted]	[redacted]	Total	Placebo	5 ug	Total
		(N=xxx)	(N=xxx)	(N=xxx)	(N=xxx)	(N=xxx)	(N=xxx)	(N=xxx)
Visit	Category	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Baseline[1]	Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	ANCS	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	ACS	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	UE	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Total	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Day 7	Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	ANCS	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	ACS	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	UE	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Total	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Continue for other visits								

[1] Baseline = Screening (Day -28 to Day -15); Percentages are based on the number of subjects with a non-missing measurement for that variable in each corresponding visit; N = Number of safety subjects; n = Number of subjects with data in the summarized category

ANCS = Abnormal, not clinically significant; ACS = Abnormal, clinically significant; UE = Un-evaluable

Program location/program name.sas/ddmmmyyyy/hh:mm
Source Data: Listing xxxxxxx Database Extract Date: ddmmmyyyy

Programming notes:

Parameter = Blood Glucose, Total Protein, Albumin, Albumin to Globulin Ratio, Serum Cholesterol(total), Serum Triglycerides, Serum Creatinine, Blood Urea Nitrogen(BUN), Sodium, Potassium, Bicarbonate

Repeat table for:

Table 14.3.4.2 'Summary of Potentially Clinically Significant Laboratory Result - Hematology'

Panel/Parameter: <Parameter> (<Units>)

Parameter = Erythrocyte Count, Hemoglobin, Packed Cell Volumne, Activated Partial Thromboplastin Time and Prothrombin Time, Mean Corpuscular Volumne, Mean Corpuscular Hemoglobin, Mean Corpuscular Hemoglobin Concentration,Red Cell Distribution Width, Total Leucocyte Count (absolute and percent),Differential Leucocyte Count (absolute and percent), Platelet Count

Table 14.3.4.3 Summary of Potentially Clinically Significant Laboratory Result - Urinalysis

Panel/Parameter: <Parameter> (<Units>)

Parameter = Color, appearance, pH, Microscopy, Specific gravity, Glucose, Protein, Ketones, Blood, Billirubin, Leukocyte Esterase, Nitrite

Table 14.3.6.2 Summary of Potentially Clinically Significant Vital Signs

Panel/Parameter: <Parameter> (<Units>)

Parameter = Systolic Blood Pressure (mmHg), Diastolic Blood Pressure (mmHg), Pulse rate (beats per minute), Respiratory rate (per minute)

Footnote: [1] Baseline = Day 1 (1hr pre-dose); N = Number of safety subjects; ANCS = Abnormal, not clinically significant;

ACS = Abnormal, clinically significant; UE = Un-evaluable.

Pre-dose = within 1 hour before study drug administration in the morning (prior to pre-dose spirometry and PK procedure) on Day1 (Baseline) and Day14;

Post-dose = within 1 hour after study drug administration in the morning; on Day1 and Day14;

Trough = approximately 24 hours after study drug administration in the morning Day1.

Percentages are based on the number of subjects with a non-missing measurement for that variable in each corresponding visit.

Table 14.3.5.1.1
Summary of Laboratory Results - Biochemistry

Safety Set
Panel/Parameter: <Parameter> (<Units>)

		GSP304					Spiriva R	
Visit	Statistic	[redacted] (N=xxx)	[redacted] (N=xxx)	[redacted] (N=xxx)	Total (N=xxx)	Placebo (N=xxx)	5 ug (N=xxx)	Total (N=xxx)
Baseline	n	xxx	xxx	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx; xx	xx; xx	xx; xx	xx; xx	xx; xx	xx; xx	xx; xx
Day 7	n	xxx	xxx	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx; xx	xx; xx	xx; xx	xx; xx	xx; xx	xx; xx	xx; xx
Change from Baseline	n	xxx	xxx	xxx	xxx	xxx	xxx	xxx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min; Max	xx; xx	xx; xx	xx; xx	xx; xx	xx; xx	xx; xx	xx; xx
Continue for other visits								

[1] Baseline = Screening (Day -28 to Day -15) ; N = Number of safety subjects; n = Number of subjects with data in the summarized category

Program location/program name.sas/ddmmmyyyy/hh:mm
Source Data: Listing xxxxxxx Database Extract Date: ddmmmyyyy

Programming notes:

Refer to SAP section 6.1 for Days

Parameter = Blood Glucose, Total Protein, Albumin, Albumin to Globulin Ratio, Serum Cholesterol (total), Serum Triglycerides, Serum Creatinine, Blood Urea

Nitrogen (BUN), Sodium, Potassium, Bicarbonate, GFR

Parameter= AST(SGOT),ALT(SGPT),Gamma-glutamyl transferase, Alkaline Phosphatase, Total Bilirubin,Direct Bilirubin

Repeat table for:

Table 14.3.5.2.1 'Summary of Laboratory Results - Hematology'

Panel/Parameter: <Parameter> (<Units>)

Parameter = Erythrocyte Count, Hemoglobin, Packed Cell Volume, Activated Partial Thromboplastin Time and Prothrombin Time, Mean Corpuscular Volume, Mean Corpuscular Hemoglobin, Mean Corpuscular Hemoglobin Concentration, Red Cell Distribution Width, Total Leucocyte Count (absolute and percent), Differential Leucocyte Count (absolute and percent), Platelet Count

Table 14.3.6.1 Summary of Vital Signs

Panel/Parameter: <Parameter> (<Units>)

Parameter = Systolic Blood Pressure (mmHg), Diastolic Blood Pressure (mmHg), Pulse rate (beats per minute), Respiratory rate (per minute)
Change (next day) to (trough)
Change 'Visit' to 'Visit [1]'

Footnote: [1] Pre-dose = within 1hour before study drug administration in the morning (prior to pre-dose spirometry and PK procedure) on Day 1 (Baseline) and Day 14; Post-dose = within 1 hour after study drug administration in the morning;on Day 1 and Day 21; Trough = approximately 24 hours after study drug administration in the morning on Day 1

Table 14.3.6.4 Summary of Electrocardiogram Results

Panel/Parameter: <Parameter> (<Units>)

Parameter= Heart Rate (beats/minute), PR(msec), QRS(msec), QTcB(msec), QTcF(msec)

Footnote: [1] Baseline = Day 1 (pre-dose); N = Number of safety subjects;n = Number of subjects with data in the summarized category

Table 14.3.5.1.2
Shift Summary from Baseline to Day 21 in Biochemistry

Safety Set

Panel/Treatment Group/Parameter: <Placebo>(<N=xxx>); < Parameter> (<Units>)

	Number of Subjects			Subject Status at Day 21			
	Baseline	Day 21	Day 21 and Baseline	Normal	Abnormal	ANCS	ACS
Baseline [1]	N_1	N_2	N_3	n/N_3 (%)	n/N_3 (%)	n/N_3 (%)	n/N_3 (%)
Total	xx	xx	yy	xx/yy (xx.x) [2]	xx/yy (xx.x)	xx/yy (xx.x)	xx/yy (xx.x)
Normal	xx	xx	yy	xx/yy (xx.x) [3]	xx/yy (xx.x)	xx/yy (xx.x)	xx/yy (xx.x)
Abnormal	xx	xx	yy	xx/yy (xx.x) [4]	xx/yy (xx.x)	xx/yy (xx.x)	xx/yy (xx.x)
ANCS	xx	xx	yy	xx/yy (xx.x)	xx/yy (xx.x)	xx/yy (xx.x)	xx/yy (xx.x)
ACS	xx	xx	yy	xx/yy (xx.x)	xx/yy (xx.x)	xx/yy (xx.x)	xx/yy (xx.x)

[1] Baseline: Screening (Day -28 to Day -15); N_1 = Number of safety subjects with baseline data; N_2 = Number of safety subjects with Date 21 data; N_3 = Number of safety subjects with baseline and Day 21data; n = Number of subjects with data in the summarized category

Percentages are based on the number of subjects with a non-missing measurement for that variable in each corresponding visit.

[2] Percentages are based on total subjects with baseline and Day 21 data

[3] Percentages are based on subjects with normal status at baseline that have Day 21 data

[4] Percentages are based on subjects with abormal status at baseline that have Day 21 data; similar for ANCS, ACS.

ANCS = Abnormal, not clinically significant; ACS = Abnormal, clinically significant

program location/program name.sas/ddmmmyyyy/hh:mm

Source Data: Listing xxxxxxx Database Extract Date: ddmmmyyyy

Programming notes:

For each laboratory parameter, subjects are included only once,

in the maximum post-baseline severity, for that laboratory parameter.

Subjects without any post-baseline results are not included in the shift summary

Parameter = Blood Glucose, Total Protein, Albumin, Albumin to Globulin Ratio, Serum Cholesterol (total), Serum Triglycerides, Serum Creatinine, Blood Urea Nitrogen (BUN), Sodium, Potassium, Bicarbonate

AST(SGOT), ALT(SGPT), Gamma-glutamyl transferase, Alkaline Phosphatase, Total Bilirubin, Direct Bilirubin,

Repeat this table for

Table 14.3.5.2.2 'Shift Summary from Baseline to Day 21 in Hematology'

Panel/Treatment Group/Parameter: <Placebo>(<n=xxx>); < Parameter> (<Units>)

Parameter = Erythrocyte Count, Hemoglobin, Packed Cell Volumne, Activated Partial Thromboplastin Time and Prothrombin Time, Mean Corpuscular Volumne, Mean Corpuscular Hemoglobin, Mean Corpuscular Hemoglobin Concentration, Red Cell Distribution Width, Total Leucocyte Count (absolute and percents), Differential Leucocyte Count (absolute and percents), Platelet Count

Table 14.3.5.3.2 ' Shift Summary from Baseline to Day 21 in Urinalysis'

Panel/Treatment Group/Parameter: <Placebo>(<n=xxx>); < Parameter> (<Units>)

Parameter=Color, appearance, pH, Microscopy, Specific gravity, Glucose, Protein, Ketones, Blood, Billirubin, Leukocyte Esterase, Nitrite

Table 14.3.6.3 ' Shift Summary from Baseline to Day 21 in Vital Signs'

Panel/Treatment Group/Parameter: <Placebo>(<n=xxx>); < Parameter> (<Units>)

Parameter = Systolic Blood Pressure (mmHg), Diastolic Blood Pressure (mmHg), Pulse rate (beats per minute), Respiratory rate (per minute)

Footnote: [1] Baseline = Day 1 (1hr pre-dose)

Table 14.3.6.6 ' Shift Summary from Baseline to Day 21 in ECG Interpretation '

Panel/Treatment Group/Pl acebo (<n=xxx>)

Footnote: [1] Baseline = Day 1 (pre-dose)

Table 14.3.5.3.1
Summary of Laboratory Results - Urinalysis

Safety Set
Panel/Parameter: <Parameter> (<Units>)

		GSP304					Spiriva R	
		[redacted] (N=xxx)	[redacted] (N=xxx)	[redacted] (N=xxx)	Total (N=xxx)	Placebo (N=xxx)	5 ug (N=xxx)	Total (N=xxx)
Visit	Category	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Baseline [1]	None	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Trace	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	+1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	+2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	+3	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	+4	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	+5	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	No Result	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Not Done	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Day 7	None	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Trace	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	+1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	+2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	+3	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	+4	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	+5	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	No Result	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Not Done	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Continue for other visits								

[1] Baseline = Screening (Day -28 to Day -15); N = Number of safety subjects; n = Number of subjects with data in the summarized category;
NEG (negative) = not present or none seen; +(few) = The structure is present but not in all fields examined, a specific structure is occasionally found in a field;
++(moderate) = The structure is present in all fields examined but quantification is still low; +++(many) = The structure is present in all fields examined.
Percentages are based on the number of subjects with a non-missing measurement for that variable in each corresponding visit.

Program location/program name.sas/ddmmmyyyy/hh:mm
Source Data: Listing xxxxxxx Database Extract Date: ddmmmyyyy

---

Programming notes:

Parameter = Color, appearance, pH, Microscopy, Specific gravity, Glucose,

Protein, Ketones, Blood, Billirubin, Leukocyte Esterase, Nitrite

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Table 14.3.5.4
Summary of Laboratory Results - Liver Function Test Elevation and Hy's Law Criteria Summary

Safety Set

Elevation Criteria	GSP304 [redacted] (N=xxx) n (%)	GSP304 [redacted] (N=xxx) n (%)	GSP304 [redacted] (N=xxx) n (%)	GSP304 Total (N=xxx) n (%)	Placebo (N=xxx) n (%)	Spiriva R 5 ug (N=xxx) n (%)	Total (N=xxx) n (%)
Hy's Law[1]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
AST(SGOT)							
2xULN elevations	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
3xULN elevations	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
5xULN elevations	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
10xULN elevations	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
ALT(SGPT)							
2xULN elevations	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
3xULN elevations	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
5xULN elevations	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
10xULN elevations	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Gamma-glutamyl transferase							
2xULN elevations	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
3xULN elevations	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
5xULN elevations	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
10xULN elevations	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Alkaline Phosphatase							
2xULN elevations	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
3xULN elevations	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
5xULN elevations	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
10xULN elevations	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Total Bilirubin							
2xULN elevations	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
3xULN elevations	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
5xULN elevations	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
10xULN elevations	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Direct Bilirubin								
	2xULN elevations	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	3xULN elevations	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	5xULN elevations	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	10xULN elevations	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

[1] Hy's Law criteria are based on the following: ≥2 x ULN elevation of Bilirubin and 3 x ULN elevation of either ALT or AST. In order to meet the above criteria, a subject must experience the elevation in bilirubin and ALT or AST at the same visit. N = Number of safety subjects; n = Number of subjects with data in the summarized category

Program location/program name.sas/ddmmmyyyy/hh:mm
Source Data: Listing xxxxxxx Database Extract Date: ddmmmyyyy

Programming notes:

Table 14.3.6.7
Summary of Physical Examination by Treatment

Safety Set
Panel/Parameter: <Parameter>

Visit	Category	GSP304 [redacted] (N=xxx) n (%)	GSP304 [redacted] (N=xxx) n (%)	GSP304 [redacted] (N=xxx) n (%)	GSP304 Total (N=xxx) n (%)	GSP304 Placebo (N=xxx) n (%)	Spiriva R 5 ug (N=xxx) n (%)	Total (N=xxx) n (%)
Baseline[1]	n	xxx	xxx	xxx	xxx	xxx	xxx	xxx
	Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Abnormal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Not Done	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Day 7	n	xxx	xxx	xxx	xxx	xxx	xxx	xxx
	Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Abnormal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Not Done	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Continue for other visits								

[1] Baseline = Day -1; N = Number of safety subjects; n = Number of subjects with data in the summarized category
Percentages are based on the number of subjects with a non-missing measurement for that variable in each corresponding visit.

Program location/program name.sas/ddmmmyyyy/hh:mm
Source Data: Listing xxxxxxx Database Extract Date: ddmmmyyyy

Programming notes:

Parameter = General Appearance; Skin/subcutaneous Tissue; Head and Neck (including thyroid gland); Eyes, Ears, Nose and Throat; Gastrointestinal System; Lymph Nodes; Musculoskeletal System; Heart/Cardiovascular; Respiratory System; Urogenital System; Ano-rectal; Extremities; Neurological System

Listing 16.2.1.1
Listing of Subject Disposition

All Screened Subjects
Panel/Treatment Group: <GSP304[redacted]
Site/Subject ID/Sex/Age(years)/Race/Baseline Weight(kg): <xxxx/xxxx/M/25/WHITE/75>

Subject Status	Date of Informed Consent/ Date of Randomization	Date of First Study Medication/ Last Study Medication	Date of Early Termination	Reason for Premature Study Termination
Screen Failure	ddmmmyyyy/ddmmmyyyy	ddmmmyyyy/ddmmmyyyy	ddmmmyyyy	Adverse Event

program location/program name.sas/ddmmmyyyy/hh:mm

Programming notes: If the subject status is screen failure, the info past informed consent should show as N/A

Listing 16.2.1.2
Listing of Study Completion/Withdrawal

Safety Set

Site/Subject ID	Treatment	Subject Status	Date of Completion/Withdrawn	Reason for Withdrawn	Study Day
xxxx/xxx-xxxx	xxxx	Complete	ddmmmyyyy/ddmmmyyy	Adverse Event	56

Study day = date of interest – randomization date + 1 if the date of interest occurs on or after the randomization date: Study day = date of interest – randomization date if the date of interest occurs on or before the randomization date

program location/program name.sas/ddmmmyyyy/hh:mm

Programming notes:

Listing 16.2.1.3
Listing of Reason for Early Termination

Safety Set

Site/Subject ID	Treatment	Date of Early Termination	Reason for Early Termination	Failed to Inclusion/Exclusion [#]
xxx/xxx-xxxx	xxxx	ddmmmyyyy	Adverse Event	
xxx/xxx-xxxx	xxxx	ddmmmyyyy		Exclusion [2]

program location/program name.sas/ddmmmyyyy/hh:mm

Programming notes:

Listing 16.2.2
Protocol Deviations

Full Analysis Set

Site/Subject ID	Subject Status	PD Status	Classification	PD Occur Date	Description	Final Decision	Action to be Taken	BDRM Comment
xxx/xxx-xxxx	Completed	Closed	Inc/Excl Criteria	ddmmmyyyy	xxxx	Major	Exclude from PP	xxxx

PD = Protocol Deviation

program location/program name.sas/ddmmmyyyy/hh:mm

Programming notes:

Listing 16.2.3
Listing of Subjects in Analysis Population

Full Analysis Set

Site/Subject ID	FAS	FAS-Exclusion Reason	SAF	SAF Exclusion Reason	PP	PP-Exclusion Reason	PKAS	PKAS-Exclusion Reason	Completed Study	Latest Visit	Protocol Deviation
xxxxxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx

FAS = Full Analysis Set; SAF = Safety Set; PP = Per-Protocol Set; PKAS = Pharmacokinetic Set

FAS will include all subjects who are randomized, have received at least 1 dose of study medication and have at least 1 post-baseline PD assessment; SAF will include all subjects who are randomized and received at least 1 dose of study medication; PP will include all subjects who are randomized, received at least 1 dose of study medication, completed the study and do not have any major protocol deviations; PKAS will include all subjects who are randomized, received at least 1 dose of study treatment and have at least 1 quantifiable PK sample and do not have any major protocol deviations.

program location/program name.sas/ddmmmyyyy/hh:mm

Programming notes:

Listing 16.2.4.1
Listing of Demographic and Baseline Characteristics

Safety Set
Panel/Site/Subject ID/Treatment/Age/Sex/Race/Ethnicity: <xxx/xx-xxxx/Placebo/45/F/Other/WHITE >

Height(cm)	Weight(kg)	BMI(kg/m^2)	Smoking Status (Y/N)	X-Ray Interpretation	Any COPD exacerbation in previous 3 months before screening? (Y/N) [1]	If [1] =Yes, COPD Hosptalization? (Y/N)
xxx	xxx	xxx	Y	xxxx	xxxx	xxxx

Y =Yes; N =No; ANCS = Abnormal, not clinically significant; ACS = Abnormal, clinically significant; UE = Un-evaluable

program location/program name.sas/ddmmmyyyy/hh:mm

Programming notes:

Listing 16.2.4.2
Listing for Medical History

Safety Set

Site/Subject ID	Body System	Medical History Term	LLT/LLT Code	PT/PT Code	HLT	HLT Code	HLGT/HLGT Code	SOC/SOC code
xxxx	xxxx	xxxx	xxx/xxx	xxx/xxx	xxx/xxx	xxx/xxx	xxx/xxx	xxx/xxx

MH = Medical History; LLT = Lowest Term; PT = Preferred Term; HLT =High Level Term; HLGT = High Level Group Term; SOC = System Organ Class
program location/program name.sas/ddmmmyyyy/hh:mm

Programming notes:

Listing 16.2.5.1
Listing of Exposure to Study Medication

Safety Set

Site/Subject ID	Treatment	Date of First Dose	Date of Last Dose	Study Medication Duration (days)
xxx/xxx-xxxx	GSP304[redacted]	ddmmmyyyy	ddmmmyyyy	42

Duration = Last dose date – First dose date +1

program location/program name.sas/ddmmmyyyy/hh:mm

Programming notes:

Listing 16.2.5.2
Listing of Treatment Compliance

Safety Set

Site/Subject ID	Treatment	Number of Received/Number of Expected	Compliance (%)
xxx/xxx-xxxx	Placebo	9/9	100%

program location/program name.sas/ddmmmyyyy/hh:mm

Programming notes:

Listing 16.2.5.3
Listing of Average Daily Dose and Nebulization Time

Safety Set

Site/Subject ID	Visit	Treatment	Average Daily Dose (ug)	Nebulization Time in Miniute
xxx-xxxx	xxxxx	GSP304[redacted]	xxxx	xxx

program location/program name.sas/ddmmmyyyy/hh:mm

Programming notes:

Listing 16.2.5.4
Listing for Prior/Concomitant Medication per Subject

Safety Set
Panel/Site/Subject ID/Sex/Age(years)/Race/Baseline Weight(kg): <xxxx/M/25/WHITE/75>

Treatment	Drug Class/Preferred Term/Medication Reported	Flag	Start Date/End Date	Study Day Start/End	On-going	Dose	Unit	Route	Frequency	Indication
Placebo	xxxxx/xxxx/xxxx	P/C	Ddmmmyyyy/ddmmmyyyy	12/15	Y	xxx	xxxx	xxx	xxxx	xxxx

Study day = date of interest – randomization date + 1 if the date of interest occurs on or after the randomization date: Study day = date of interest – randomization date if the date of interest occurs on or before the randomization date;

Prior and concomitant meditations were coded with the WHO Drug dictionary dated September, 2015; Flag: P = Prior medication if both the start and stop date exist and are before the first dose date of study drug , C = Concomitant medication if the start date is on or after the first dose date of study drug, P/C = if the start date is before the first dose date of study drug and the stop date is after the first dose date of study drug or the medication is continuing,

program location/program name.sas/ddmmmyyyy/hh:mm

Programming notes:

Listing 16.2.5.5
Listing of Study Subjects – Unblinding

Safety Set

Site/Subject ID	Randomization Number	Randomization Date	Treatment Randomized	Treatment Received
xxxx/xxx-xxxx	xxxxxx	ddmmmyyyy	GSP304[redacted]	GSP304[redacted]

program location/program name.sas/ddmmmyyyy/hh:mm

Programming notes:

Listing 16.2.5.6
Listing of Rescue Medication per Subject

Safety Set
Panel/Site/Subject ID/Sex/Age(years)/Race/Baseline Weight(kg): <xxxx/M/25/WHITE/75>

Treatment	Medication Reported
Placebo	xxxx

Rescue meditations were collected on patient eDiarries.

program location/program name.sas/ddmmmyyyy/hh:mm

Note To Programmer: List data as collected/ reported from eDiary. Add columns based on data collected.

Listing 16.2.6.1
Listing of Change from Baseline in Primary and Secondary Pharmacodynamics Endpoints

Safety Set
Panel/Site/Subject ID/Sex/Age(years)/Race/Baseline Weight(kg): <xxxx/M/25/WHITE/75>

Treatment	Endpoints	Value at Baseline	Value at Day 1/Day 21	Change from Baseline at Day 1/Day 21
GSP304[redacted]	[1]	xxxx	xxxx/xxx	xxxxx /xxx

[1] Primary Endpoint: Change from baseline in trough FEV_1 at 24 hours after the last dose of treatment on Day 21
[2] Secondary Endpoint: Change from baseline in peak FEV_1 within 12 hours post dose on Day 1 and Day 21
[3] Secondary Endpoint: Change from baseline in FVC on Day 1 and Day 21
[4] Secondary Endpoint: Change from baseline in time-normalized area under the curve for FEV_1 measured over 12 hours on Day 1 and Day 21

program location/program name.sas/ddmmmyyyy/hh:mm

Programming notes:

Listing 16.2.6.2.1
Listing of Plasma Concentrations

PK Analysis Set

Site/Subject ID	Treatment	Visit	Sample Collection Date	Hour	Nominal Time	Actual Time	Deviations Time	Plasma Concentration (unit)	Comment
xx/xxxx	xxx	xxx	ddmmmyyyy	Pre-dose	xxxx	xxx	xxxx	xxxx	xxxxx

Lower Limit of Quantification (LLOQ) = XX:XX (unit); BLQ = Below the Limit of Quantification; NA = Not Applicable; NS = Not Sampled

program location/program name.sas/ddmmmyyyy/hh:mm

Programming notes: Add comment if sample collected outside of allowed window (reason) and or reason sample excluded

Listing 16.2.6.2.2
Listing of Urine Concentrations on Day1 and Day 21

PK Analysis Set
Panel/ Site/Subject ID /Visit/Study Day: <Day 1/12 >

Treatment	Last Dose Date/Time	Scheduled Time(unit)	Sample Date/Time(start)	Sample Date/Time(end)	Concentration (unit)	Volumne (unit)	Comment
GSP304[redacted]	ddmmmyyyy/hh:mm	hh:mm(sec)	ddmmmyyyy/hh:mm	ddmmmyyyy/hh:mm	xxxx	xxxx	xxxx

Study day = date of interest – randomization date + 1 if the date of interest occurs on or after the randomization date: Study day = date of interest – randomization date if the date of interest occurs on or before the randomization date

Lower Limit of Quantification (LLOQ) = XX (pg/mL); BLQ = Below the Limit of Quantification; NA = Not Applicable; NS = Not Sampled

program location/program name.sas/ddmmmyyyy/hh:mm

Programming notes: Add comment if sample collected outside of allowed window and or reason sample excluded

Listing 16.2.6.2.3
Listing of Pharmacokinetic Parameters

PK Analysis Set
Panel/ Site/Subject ID/Sex/Age(years)/Race/Baseline Weight(kg): <xxxx/xxx-xxx//M/25/WHITE/75>

Treatment	Visit	Hour	Parameter(unit)	Value	Comment
GSP304[redacted]	Day 1	Pre-dose	AUC(ng.h/mL)	xxx	xxxxx

program location/program name.sas/ddmmmyyyy/hh:mm

Programming notes: Add comment if sample collected outside of allowed window and or reason sample excluded

Include all PK parameters

Listing 16.2.6.2.4
Listing of Pharmacokinetic Parameters Excluded from Analysis

PK Analysis Set

Site/Subject ID	Treatment	Visit	Sequence	Period	Parameter(unit)	Value	Reason
xxx-xxxx	GSP304[redacted]	xxx	xxxxx	xxxx	AUC(ng.h/mL)	xxx	Not be determined

program location/program name.sas/ddmmmyyyy/hh:mm

Programming notes:

Listing 16.2.7.1
Listing of Treatment Emergent Adverse Events

Safety Set
Panel/Site/Subject ID/Treatment/AE/Stat Date/End Date/Study Day/Ongoing: <xxxx/xxxx/xxx/xxx/Y/ddmmmyyyy/ddmmmyyyy/xx/Y >

Severity	SAE?	SAE-Seriousness Reasons	Relationship to Study Medication	Action Taken with IP	Outcome	LLT/LLT Code	PT/PT Code	HLT	HLT Code	HLGT/HLGT Code	SOC/SOC code
xxxx	Y	death	xxxx	xxxx	xxxx	xxxx/xxxx	xxxx/xxxx	xxxx/xxxx	xxxx/xxxx	xxxx/xxxx	xxxx/xxxx

Treatment Emergent AEs are defined as AEs (identified by PT) that begins or that worsens in severity after at least one dose of study treatment has been administered, up to the last study visit; AE = Adverse Events; SAE = Serious Adverse Event; LLT = Lowest Term; PT = Preferred Term; HLT =High Level Term; HLGT = High Level Group Term; SOC = System Organ Class; AEs were coded using MedDRA v19.1; Study day = date of interest – randomization date + 1; Treatment Emergent AEs are defined as AEs (identified by PT) that begins or that worsens in severity after at least one dose of study treatment has been administered, up to the last study visit; PT = Preferred Term

program location/program name.sas/ddmmmyyyy/hh:mm

Programming notes:

Repeat for

Table 16.2.7.2 Listing of Pre-Treatment Adverse Events
All Screened Subjects
Footnote: Pre-Treatment AEs (PTAEs)are defined as AEs (identified by PT) that begin or that worsen in severity between study Day -14 and study drug administration, and last up to the AE stop date

Listing 16.2.7.3
Listing of Serious Adverse Events

All Screened Subjects
Panel/Site/Subject ID/Treatment/AE/Stat Date/End Date/Study Day/Ongoing: <xxxx/xxxx/xxx/xxx/Y/ddmmmyyyy/ddmmmyyyy/xx/Y >

Severity	SAE-Seriousness Reasons	Relationship to Study Medication	Action Taken with IP	Outcome	LLT/LLT Code	PT/PT Code	HLT	HLT Code	HLGT/HLGT Code	SOC/SOC code
xxxx	death	xxxx	xxxx	xxxx	xxxx/xxxx	xxxx/xxxx	xxxx/xxxx	xxxx/xxxx	xxxx/xxxx	xxxx/xxxx

Treatment Emergent AEs are defined as AEs (identified by PT) that begins or that worsens in severity after at least one dose of study treatment has been administered, up to the last study visit; SAE = Serious Adverse Event; LLT = Lowest Term; PT = Preferred Term; HLT =High Level Term; HLGT = High Level Group Term; SOC = System Organ Class; AEs were coded using MedDRA v19.1; Study day = date of interest – randomization date + 1; Treatment Emergent AEs are defined as AEs (identified by PT) that begins or that worsens in severity after at least one dose of study treatment has been administered, up to the last study visit; PT = Preferred Term

program location/program name.sas/ddmmmyyyy/hh:mm

Listing 16.2.8.1
Listing of Laboratory Results per Subject - Biochemistry

Safety Set
Panel/Site/Subject ID/Sex/Age(years)/Race/Baseline Weight(kg): <xxxx/M/25/WHITE/75>

Treatment	Parameter(unit)	Normal Range	Day number	Lab Not Done (Y/N)	Scheduled Visit (Y/N)	Data Sample Taken	Lab Result [1]	Change from Baseline [2]
Placebo	Basophil(10^9/L)	xxx-xxx	Day 1	N	Y	ddmmmyyyy	0.2 N	0.06

[1] N = Normal; ANCS = Abnormal, not clinically significant; ACS = Abnormal, clinically significant; UE = Unevaluable; NA = Not Applicable

[2] Baseline = Screening (Day -28 to Day -15)

program location/program name.sas/ddmmmyyyy/hh:mm

Programming notes:

Repeat for

Listing 16.2.8.2 Listing of Laboratory Results per Subject - Hematology
Footnote:
[1] N = Normal; ANCS = Abnormal, not clinically significant; ACS = Abnormal, clinically significant; UE = Unevaluable; NA = Not Applicable
[2] Baseline = Screening (Day -28 to Day -15)

Listing 16.2.8.3 Listing of Laboratory Results per Subject – Urinalysis
Footnote:
[1] N = Normal; ANCS = Abnormal, not clinically significant; ACS = Abnormal, clinically significant; UE = Unevaluable; NA = Not Applicable

[2] Baseline = Screening (Day -28 to Day -15)
NEG(negative) = not present or none seen; +(few) = The structure is present but not in all fields examined. A specific structure is occasionally found in a field; ++(moderate) = The structure is present in all fields examined but quantification is still low.; +++(many) = The structure is present in all fields examined.

Listing 16.2.8.4
Listing of Test Results

Safety Set

Site/Subject ID	Visit	Test	Done?	Results
xxx/xxxxxx	Screening	Pregnancy/xxxx/xxx	Yes	xxxx

program location/program name.sas/ddmmmyyyy/hh:mm

Programming notes: Test = Chest XRay, CT Scan, FSH test and Serum Pregnancy Test, Blood Alcohol Test, Urinalysis, Serology Test
Thyroid stimulating hormone; Follicle stimulating hormone; HBsAg and HCV antibody;
The list should be ordered by Site/Subject ID, then Visit

Listing 16.2.9.1
Listing of Vital Signs Data per Subject

Safety Set
Subject ID/Sex/Age(years)/Race/Baseline Weight(kg): <xxxx/M/25/WHITE/75>

Treatment	Visit	Scheduled Visit (Y/N)	Date	Parameter(unit)	Result	Abnormality	Clinically Significant?
Placebo	Screening	xxxx	ddmmmyyyy	Heart Rate (bpm)	xxxx	No	No

program location/program name.sas/ddmmmyyyy/hh:mm

Programming notes:

Repeat for

Listing 16.2.9.2 Listing of 12-Lead ECG Measurement per Subject

Listing 16.2.9.3 Listing of Physical Examinations per Subject