Verona Pharma plc

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A Phase 2b, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy, Safety, and Pharmacokinetics of Glycopyrrolate Inhalation Solution Over 1 Week in Subjects with COPD

03Feb2025

Statistical Analysis Plan

FINAL Version *1.1*

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Date

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Date

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Summary of Changes

Statistical Analysis Plan Revision History

Version	Date	Summary of Changes
Version 1.0	31Dec2024	Original version
Version 1.1	03Feb2025	Initial version had an incorrect year of 2024 instead of 2025, calendar year is updated in this version.

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List of Abbreviations

AE	adverse event
AESI	adverse events of special interest
AST	aspartate amino transferase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ATC	Anatomical Therapeutic Chemical
ATS	American Thoracic Society
AUC	area under the curve
AUC_{0-4h}	area under the curve over the 4-hour dosing interval
AUC_{0-12h}	area under the curve over the 12-hour dosing interval
AUC_{0-last}	area under the curve from time 0 to the last measurable observed concentration
ACS	abnormal, clinically significant
ANCS	abnormal, not clinically significant
BTR	best test review
BMI	body mass index
BID	twice daily
BUN	Urea nitrogen
BLQ	below the limit of quantification
CAS	Completers Analysis Set
CI	confidence interval
CK	Creatine phosphokinase
COPD	Chronic obstructive pulmonary disease
C_{avg}	average plasma concentration
C_{max}	maximum observed concentration
C_{trough}	trough concentration
CXR	chest x-ray
CL/F	apparent total body clearance
CT	computed tomography
CRF	case report form
DBP	diastolic blood pressure
DBL	database lock
DN	dose normalized
ECG	electrocardiogram
EDC	electronic data capture
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
FAS	Full Analysis Set
FDC	Fixed Dose Combination
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
Ho	null hypothesis
Ha	alternative hypothesis
ICH	International Conference on Harmonization

ITT	intent-to-treat
ICS	inhaled corticosteroid(s)
IRT	interactive response technology
LABA	long-acting β2-agonist
LAMA	long-acting muscarinic antagonist
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
n	number of non-missing observations
N	number of subjects
PR	pulse rate
PK	pharmacokinetic(s)
PKAS	Pharmacokinetic Analysis Set
PKPAS	Pharmacokinetic Parameter Analysis Set
PPS	Per Protocol Set
PT	preferred term
Q1	1st quartile
Q3	3rd quartile
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
QT interval	The portion of an electrocardiogram between the onset of the Q wave and the end of the T wave
RR interval	The time elapsed between two successive R-waves of the QRS signal
SAS	Statistical Analysis System
SAP	statistical analysis plan
SAF	Safety Analysis Set
SAE	serious adverse event
SBP	systolic blood pressure
SOC	system organ class
SD	standard deviation
SE	standard error
t_{max}	time to maximum serum drug concentration
ULN	upper limit of normal
USA	United States of America
TEAE	treatment-emergent adverse events
WHO	World Health Organization
WHODD	WHO Drug Dictionary

1. Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by progressive airflow obstruction which is largely irreversible. Current therapies in the COPD market are typically used in combination to optimize treatment effects in patients. There is a need for nebulized combination maintenance therapies for COPD patients, as none are currently available or in development. A fixed dose combination (FDC) product with ensifentrine and another bronchodilator could provide a single nebulized product with pharmacology equivalent to 2 bronchodilator mechanisms and a non-steroidal anti-inflammatory mechanism. This current study is the first of 3 planned Phase 2 studies investigating inhaled nebulized ensifentrine and glycopyrrolate FDC as a novel therapy for the maintenance treatment of COPD.

The purpose of this Statistical Analysis Plan (SAP) is to define the planned statistical methods consistent with the study objectives. The SAP addresses the primary and secondary objectives and associated outcome measures, as well as a subset of exploratory objectives and associated outcome measures that may be included in primary manuscripts of the study. This plan should be read in conjunction with the study protocol, Version 3.0 (dated 14 October 2024) and the case report forms (CRFs) Version 2.0 and with the understanding that spirometry, laboratory, and ECG data are obtained from external resources. The SAP may be amended, as necessary, to accommodate a protocol amendment(s) and the amended SAP will be finalized and signed off prior to database lock (DBL) for the final analysis.

2. Objectives

2.1. Primary Objective

The primary objective of this study is to evaluate the bronchodilator effect of twice daily (BID) inhaled glycopyrrolate solution in the proposed FDC formulation over a dose range administered by standard jet nebulizer in subjects with COPD in terms of morning trough FEV_1 on Day 7.

2.2. Secondary Objectives

The secondary objectives of this study are to:

- Evaluate the bronchodilator effect of BID inhaled glycopyrrolate solution in the proposed FDC formulation on Day 7 in terms of:
    - Peak forced expiratory volume in 1 second (FEV_1) over 4 hours
    - Average FEV_1 area under the curve (AUC) versus time from time 0 to 4 hours (AUC_{0-4h})
    - Average FEV_1 AUC_{0-12h}
    - Evening trough FEV_1

- Evaluate the bronchodilator effect of a single dose of inhaled glycopyrrolate solution in the proposed FDC formulation on Day 1:
    - Peak FEV_1 (over 4 hours)
    - FEV_1 $AUC_{0\text{-}4h}$

2.3. Exploratory Objectives

The exploratory objective of this study is to assess the dose response of BID inhaled glycopyrrolate solution in the proposed FDC formulation on Day 7:

- Peak FEV_1
- Average FEV_1 $AUC_{0\text{-}12h}$
- Morning trough FEV_1

2.4. Safety Objective

The safety objective of this study is to evaluate the safety and tolerability of inhaled glycopyrrolate solution in the proposed FDC formulation in subjects with COPD.

2.5. Pharmacokinetics Objective

The pharmacokinetics (PK) objective of this study is to assess the PK profile of multiple doses of inhaled glycopyrrolate solution in the proposed FDC formulation in subjects with COPD on Day 7.

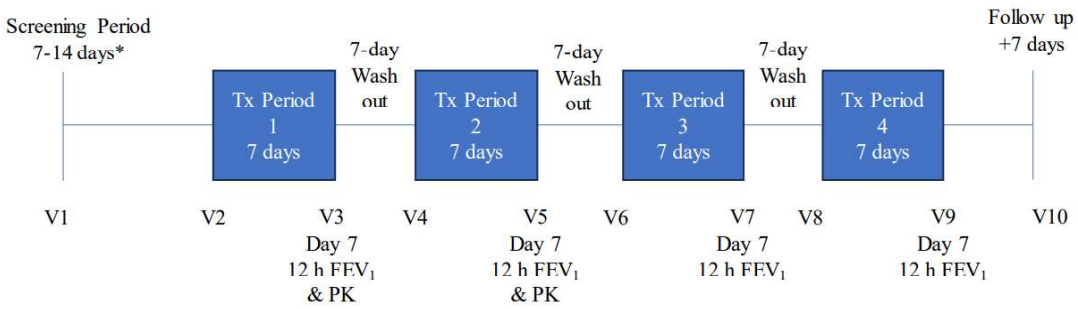
3. Investigational Plan

3.1. Overall Study Design and Plan

This study is a multicenter, randomized, double blind, placebo-controlled, 4-period cross-over study to evaluate glycopyrrolate dose-levels administered BID by a standard jet nebulizer in the proposed FDC formulation: 0 (placebo), 14 µg, 42.5 µg, and 85 µg glycopyrrolate.

Approximately 40 eligible subjects meeting all inclusion, and no exclusion criteria will be dosed for 4 consecutive 7-day treatment periods. The last dose in each treatment period will be the morning of the Day 7 clinic visit, and the treatment periods will be separated by a 7-day washout period. A study design schematic is depicted in Figure 3-1.

Figure 3-1: Study Schematic



*All long-acting bronchodilators should be washed out for 24 or 48 h prior to screening spirometry. Consent must be obtained prior to any study procedures including washouts.
Abbreviations: FEV_1 = forced expiratory volume over 1 second; h = hour; PK = pharmacokinetic; Tx = treatment; V = visit.

Each subject will take 4 dose levels (A-D) of blinded study medication, with one dose level taken during each of the treatment periods as depicted in Table 3-1. Subjects will be randomly assigned to treatment sequences 1 to 4 in a 1:1:1:1 ratio to receive the 4 dose levels in the following sequences as shown in Table 3-2. Each subject is expected to complete all 4 treatment periods. Subjects who do not complete at least 2 Treatment Periods may be replaced.

Table 3-1 Treatment Sequence Allocation

Dose Level	Treatment
A	glycopyrrolate (85 µg) BID
B	glycopyrrolate (42.5 µg) BID
C	glycopyrrolate (14 µg) BID
D	placebo BID

Table 3-2 Dose Levels

Treatment Sequence	Dose Levels Administer in Each Treatment Period			
	Treatment Period 1 (N=40)	Treatment Period 2 (N=40)	Treatment Period 3 (N=40)	Treatment Period 4 (N=40)
Sequence 1 (N= ~10)	A	D	B	C
Sequence 2 (N= ~10)	B	A	C	D
Sequence 3 (N= ~10)	C	B	D	A
Sequence 4 (N= ~10)	D	C	A	B

Spirometry will be assessed pre- and post-dose on Days 1 and 7, as described below. Pharmacokinetic (PK) sampling will take place on Day 7 in treatment periods 1 and 2 only following any ECG or lung function assessments, as described below.

The pre-dose average FEV_1 on Day 1 of treatment periods 2 to 4 (i.e., Visits 4, 6, and 8) should be within ± 20% of the pre-dose average FEV_1 at Day 1 of treatment period 1 (Visit 2) to ensure a consistent baseline FEV_1 for each treatment period. If the FEV_1 varies by more than 20%, the start of the treatment period must be rescheduled to occur within 7 days.

COPD medications are prohibited for the time periods described in the protocol.

Prohibited Medications/Therapy

Medication	Time Interval
Oral Therapies for COPD (e.g., oral steroids, theophylline, and roflumilast). Oral mucolytics are allowed.	6 months prior to Screening and prohibited during the study.
Terbutaline	24 hours prior to Screening and prohibited during the study.
LAMAs 1. Once-daily LAMAs 2. BID LAMAs	1. 48 hours prior to Screening and prohibited during the study 2. 24 hours prior to Screening and prohibited during the study
Non-BID LABAs	Any LABAs that are not dosed BID (e.g., once daily) must be discontinued ≥ 7 days prior to Randomization and are prohibited during the study.

Stable use of BID LABA ± BID inhaled corticosteroids (ICS) at a maintenance dose is permitted during the study. Permitted rescue medications and prohibited medications and therapies are described in the protocol.

Permitted Rescue and Background Medications

Medication	Condition
Albuterol	Used as rescue medication as needed during the study. Must be withheld for at least 4 hours prior to spirometry.[1] Should be withheld for at least 4 hours prior to ECGs.
BID LABA ± ICS	Stable use of BID LABA ± ICS is permitted ONLY IF the subject: 1. Has been taking LABA ± ICS at any dosing frequency at a stable dose for at least 4 weeks prior to Screening AND 2. If on a non-BID LABA ± ICS therapy, can transition, to a BID LABA ± ICS ≥ 7 days prior to randomization for use for remaining duration of the study AND 3. Can withhold use of the BID LABA ± ICS for approximately 24 h prior to any clinic visit where spirometry will be performed (i.e., Visits 1 through 9).[1] BID LABA ± ICS use should not be initiated, dose modified, or discontinued during the study after randomization. ICS monotherapy and high dose ICS (e.g., > 1000 µg of fluticasone propionate or equivalent) is not allowed.
[1]If the withholding periods are not met the visit should be rescheduled (Protocol Section 6.1.1). Abbreviations: ECG = electrocardiogram; ICS = inhaled corticosteroids.	

Subjects will withhold LABA medications for at least 24 hours and rescue medication use for 4 hours prior to spirometry at all required visits. If this withholding period is not met, the subject should be rescheduled.

All sites will use standardized spirometry and ECG equipment provided by a central vendor, and all spirometry and ECGs will be over-read by the blinded central vendor. Data provided for use in reporting and analyses will follow conventions agreed upon in detailed transfer specifications.

Subjects will be screened for eligibility between 7 and 14 days before the first dose of blinded study medication.

During each treatment period, subjects will complete all assessments and procedures as outlined in the clinical protocol Section 1.3.

To protect the integrity of spirometry testing subjects will receive a phone call reminder on Day 6 of each treatment period to remind them to take their evening dose of blinded study medication approximately 12 hours prior to the anticipated arrival time to the clinic on Day 7, to note the time of the Day 6 evening dose was taken, to report that time to site staff at the Day 7 visit, to withhold the Day 7 morning dose until at the clinic, to withhold

albuterol within 4 hours of their Day 7 visit, and to bring their unused study medication to the clinic visit the next day.

Subjects who permanently discontinue double-blind study medication will be withdrawn from the study.

All subjects will complete a Follow-up Phone Call 7 ± 1 days after either the Visit 9 or the Early Withdrawal/Termination Visit.

3.2. Study Endpoints

Primary and secondary endpoints will be derived from FEV1 measurements if at least 3 measurements have best test review (BTR) grades of "Acceptable" or "Borderline Acceptable". The best measurement (e.g., best time) for each parameter will be included in analysis.

Primary and secondary spirometry endpoints are derived as change from the average patient baseline FEV_1.

Each treatment Period will have an average baseline FEV_1 value derived for each patient from best measurements (described above). Average baseline is defined as the pre-dose mean FEV_1 from two separate timepoints within 40 min prior to dosing on Day 1. If only 1 timepoint has a pre-dose measurement available, then that value will be used as the average baseline FEV_1.

As this is a four-period cross-over study, study endpoints are measured in each study Period. Average baseline, change from average baseline, and treatment correspond to the study Period where a specific treatment was administered.

3.2.1. Primary Endpoint

The primary endpoint is the change from average baseline in morning trough FEV_1 measured on Day 7.

3.2.2. Secondary Endpoints

The following are the secondary endpoints:

- Change from average baseline FEV_1 to peak FEV_1 measured over 4 hours post-dose on Day 7
- Change from average baseline FEV_1 to average FEV_1 $AUC_{0\text{-}4h}$ on Day 7
- Change from average baseline FEV_1 to average FEV_1 $AUC_{0\text{-}12h}$ on Day 7
- Change from average baseline FEV_1 to evening trough FEV_1 on Day 7
- Change from average baseline FEV_1 to peak FEV_1 measured over 4 hours after first dose on Day 1

- Change from average baseline FEV_1 to average FEV_1 AUC_{0-4h} measured after first dose on Day 1

3.2.3. Exploratory Endpoints

The exploratory endpoints are the association between glycopyrrolate dose level and Day 7

- Peak FEV_1
- Average FEV_1 AUC_{0-12h} after morning dose
- Morning trough FEV_1 prior to the last dose

3.2.4. Safety Endpoints

The safety endpoints are:

- Incidence of adverse events (AEs)
- Change from baseline in laboratory safety tests (hematology and blood chemistry)
- Markedly abnormal changes in laboratory safety tests (hematology and blood chemistry)
- Shifts in laboratory safety tests (hematology and blood chemistry) classified as marked abnormalities.
- Change from baseline in 12-lead electrocardiogram (ECG) (including QT interval corrected for heart rate using Fridericia's formula [QTcF] and heart rate).
- Shifts in 12-lead ECG (including QTcF and heart rate) from normal to abnormal.
- Change from baseline in vital signs (blood pressure and pulse rate).
- Shifts in vital signs (blood pressure and pulse rate) classified as marked abnormalities.

3.2.5. Pharmacokinetics Endpoints

The PK endpoints are the glycopyrronium free base multiple dose PK parameters and are defined in Section 10.3.

3.3. Treatments

Subjects will be randomly assigned to 1 of 4 dosing sequences which prescribe the specific order for treatment with each of the glycopyrrolate doses and placebo as outlined in Table 3-2. Subjects will receive double-blind study medication (either glycopyrrolate or placebo) in the proposed FDC formulation administered by inhalation via a standard jet nebulizer supplied by the Sponsor. To account for visit windows, sufficient drug supply will be dispensed for up to 11 days of treatment for each treatment period.

Following Visit 2, subjects will self-administer their daily morning and evening doses at home at approximately the same times, approximately 12 hours apart, each day for the duration of the treatment period, except for clinic visits on Days 1 and 7 of each treatment period when subjects will have their doses administered in the clinic. Subjects should note

the time of their evening dose on Day 6 for each treatment period and report that time to the clinic site staff at the Day 7 Visit. The study supplied nebulizer and a study supplied compressor should be used only for the administration of blinded study medication.

3.4. Dose Adjustment/Modifications

There are no planned dose modifications.

Decisions regarding dose interruptions will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

4. General Statistical Considerations

All data recorded in the electronic case report form (eCRF) and provided by external sources will be displayed in patient listings and sorted by treatment sequence, patient number, and visit (where applicable). Data from participants excluded from an analysis set will be included in the applicable data listings but not included in the calculation of summary statistics for that analysis set. All statistical analyses described in this SAP will be conducted using SAS® (SAS Institute Inc, Cary, North Carolina; Version 9.4 or higher).

In general, descriptive statistics, including the number of non-missing observations, arithmetic mean, standard deviation (SD), median, minimum, and maximum, with 95% confidence interval (CI) (where applicable), will be presented by treatment for continuous variables. Frequencies, percentages, and 95% CIs (where applicable) will be presented by treatment for categorical variables.

Spirometry parameters will be analyzed as change from average treatment Period baseline FEV_1 on Day 7 and separately for Day 1, depending on the efficacy endpoint. Similar summaries by treatment and Day will be generated. A summary table of pre-dose average FEV1, endpoint parameters, and change from pre-dose average FEV_1 values at Day 1 and Day 7 will be created.

For spirometry data we will present outputs for values in liters to 3 decimal places with mean/median/Q1/Q3/CI in liters presented to 4 decimal places, standard deviation presented to 5 decimal places and minimum/maximum presented to 3 decimal places. Values in milliliters will be presented to 0 decimal places, mean/median/Q1/Q3/CI in liters presented to 1 decimal place, standard deviation presented to 2 decimal places, and minimum/maximum presented to 0 decimal places. Percentage values (if required) will be presented to 1 decimal place, mean/median/Q1/Q3/CI in liters presented to 2 decimal places, standard deviation presented to 3 decimal places, and minimum/maximum to 1 decimal place. P-values will be presented to 4 decimal places.

For non-spirometry assessments, baseline will be defined as the last non-missing evaluation prior to randomization or the first dose of study medication in Treatment Period 1 (Visit 2), and change from baseline will be derived as the value at the post-baseline visit minus the value at the baseline visit.

Summaries of absolute and change values, means/medians/Q1/Q3 will be displayed to one level of precision greater than the data collected. Standard deviation (SD) and standard error (SE) will be displayed to two levels of precision greater than the data collected, and absolute values and changes, minimum and maximum will be displayed at the level reported.

In the event a variable has values with infinite decimal places, values/minimum/maximum will be reported to 1 decimal place, means/medians/Q1/Q3 reported to 2 decimal places, standard deviations reported to 3 decimal places.

Number and percentage values will be presented as xx (xx.x). If the percentage is 100, no decimal is required. If it is between 0 and 0.1, it will be reported as "< 0.1". P-values will be presented to 4 decimal places. If a p-value is less than 0.0001, it will be reported as "< 0.0001". If a p-value is greater than 0.9999, it will be reported as "> 0.9999". All CIs and statistical hypothesis tests will be two-sided alternative hypotheses with a 5% significance level (i.e., p-value $\leq$0.05). Percentages will be suppressed when the count is zero, in order to draw attention to the non-zero counts. The denominator for all percentages will be the number of participants for that sequence or treatment with available data within the analysis set summarized, unless otherwise specified.

All subject data collected at scheduled and unscheduled visits will be presented in individual subject data listings, including spirometric efforts and triplicate ECG measurements performed as deemed necessary by the study investigator. When no data are available for a table or listing, an empty page with the title will be produced with suitable text (e.g., "There are no records for this table/listing.").

Additional assessments scheduled as necessary to ensure the safety and well-being of participants during the study will be documented in the source documents and Unscheduled Visit eCRF and included in subject listings.

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events.

Reference start date is defined as the day of the first dose of study medication (Day 1 is the day of the first dose of study medication in Period 1) and will appear in every listing where an assessment date or event date appears.

- If the date of the event is on or after the reference start date, then: Study Day = (date of event – reference start date) + 1.
- If the date of the event is prior to the reference start date, then: Study Day = (date of event – reference start date).

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings.

Reference end date is defined as the date of the last dose of study medication.

Study Period will be assigned to post-treatment assessments if the first dose of study medication (Day 1 in that Period) is administered, and the corresponding Period will appear in listings where an assessment date or event date appears. For other assessments Period will not be assigned.

4.1. Study Unblinding

Once the study unblinds, the patient's actual treatment will be assigned based on the assigned sequence. As this is a dose-ranging study, if the subject receives a treatment not prescribed by the sequence that treatment will be utilized in analyses and summaries, and the discrepancy will be reported in Clinical Study Report as well as footnoted in summary tables and figures. Assigned and actual treatment will appear in subject listings.

The external vendor will provide the Material List document after confirmation of a DBL. This document will contain the kit numbers, which will be merged with the site data to obtain the treatment that was dispensed at each visit

4.2. Repeat/Unscheduled Visits

Multiple visits within the same window will be dealt with for all Sets as follows:

- The values from the repeated Screening visit will be used for all subjects re-screened.
- In case the unscheduled visit was performed on or before the treatment, so they can be considered to calculate the baseline value (excluding ECG and spirometry), the following rules will be applied:

- If dates of visits (scheduled and/or unscheduled) are known and different, then the data point closest to study treatment will be taken.
- If the unscheduled visit was performed after the study treatment, the following rules will be applied:For early withdrawals all unscheduled visit records will be considered in worst-case analysis and end of study summary tables. Early termination data will be mapped to the appropriate (next available or end of study) visit. For by-visit summaries, unscheduled visits will not be included in the summary tables. Subject listings will include data from scheduled and unscheduled visits, subject re-testing, and early discontinuation visits.

4.3. Sample Size

Assuming the standard deviation for the differences (SDD) equal to 0.153 L, a sample size of 36 subjects provides 85% statistical power to detect a between-group difference with placebo in trough FEV_1 at Day 7 of at least 81 mL. The sample size provides adequate statistical power for statistical comparisons of each secondary endpoint. Subjects who withdraw prior to completing 2 treatment periods may be replaced. Assuming approximately 10% of early withdrawals, approximately 40 subjects will be enrolled.

4.4. Randomization and Unblinding

Subjects will be randomized to a sequence which prescribes the order they will receive each glycopyrrolate dose and placebo dose over each treatment period using an electronic Interactive Response Technology (IRT). The IRT will not indicate the treatment sequence during the randomization process but will indicate the unique kit numbers to be dispensed to the subject at Visits 2, 4, 6, and 8. Site staff will only have access to blinded reports within the IRT. All subjects should receive all dosing arms, and no stratification is included in the study.

A subject who does not meet the randomization criteria from the protocol should not be randomized, and will be considered a screen failure, and may be eligible for rescreening. If a subject who does not meet the randomization criteria is inadvertently randomized and receives blinded study medication, the Medical Monitor must be contacted and will consult with the Sponsor to determine the appropriate action.

The blind will be broken only if specific emergency treatment would require knowing the treatment status of the subject. If the blind needs to be broken, the Investigator will contact the Sponsor or Medical Monitor as soon as feasible. The Investigator may unblind the blinded study medication immediately if he/she feels it is necessary prior to contacting the Sponsor or Medical Monitor. However, the Investigator should promptly document and explain any premature unblinding to the Sponsor and Medical Monitor. Otherwise, all blinding will be maintained until all queries are resolved and the database is locked. Unblinding that occurs for any other reason, including unintentional unblinding, will be documented and promptly reported to the Sponsor and Medical Monitor.

4.5. Analysis Sets

4.5.1. Enrolled Set

The enrolled set will contain all patients who provide informed consent for this study. Patients will be classified according to randomized treatment with patients not randomized presented in a separate category.

4.5.2. Randomized Set

The Randomized Set will consist of all randomized subjects.

4.5.3. Safety Analysis Set (SAF)

The Safety Analysis Set (SAF) will consist of all randomized subjects who took at least one dose of double-blind study treatment. Safety analysis will be by actual treatment taken.

4.5.4. Full Analysis Set (FAS)

The Full Analysis Set (FAS) will consist of all randomized subjects that took at least one dose of double-blind study treatment with a non-missing average baseline FEV_1 and that have at least one non-missing post dose spirometry parameter value from at least two periods. Analyses will utilize the actual treatment taken.

4.5.5. Completers Analysis Set (CAS)

The Completers Analysis Set (CAS) will consist of all subjects in the FAS that complete all visits and that do not have missing values for primary and secondary spirometry efficacy parameters. Analyses will utilize the actual treatment taken.

4.5.6. Per Protocol Set (PPS)

The Per Protocol Set (PPS) will consist of all subjects in the CAS that did not have significant protocol deviations or events with the potential to affect efficacy evaluations. Reasons for exclusion will be specified prior to DBL and may include violations of inclusion/exclusion criteria, violations of withdrawal criteria, incorrect randomization, use of prohibited medication, and non-compliance.

4.5.7. PK Analysis Set (PKAS)

The PK Analysis Set (PKAS) will consist of all randomized subjects with blood sampling performed after at least one dose of glycopyrrolate and have at least one quantifiable glycopyrronium free base concentrations without significant protocol deviations and/or events with the potential to affect the PK concentrations. Analyses will be performed according to the actual treatment taken.

4.5.8. PK Parameter Analysis Set (PKPAS)

The PK Parameter Analysis Set (PKPAS) will consist of all subjects in the PKAS with data sufficient to calculate at least one PK parameter without significant protocol deviations and/or events with the potential to affect the PK results. Analyses will be performed according to the actual treatment taken.

4.6. Imputation of Incomplete Data

As discontinuation of study medication will result in subject withdrawal, data collected after treatment withdrawal missing data will not be imputed for spirometric analyses.

Data collected after treatment withdrawal will be included in safety analyses, considered in disposition summaries, and included in subject listings.

Incomplete dates reported during the study will undergo query and be resolved prior to database lock and will not require imputation. Missing and partial dates will be imputed for prior and concomitant medications and medical/surgical history as described below.

<u>Prior and Concomitant Medications</u>

- Missing or partial concomitant medication start date and started prior to study treatment:
    - If only Day is missing, use the first day of the month.
    - If Day and Month are both missing, use the first day of the year.

- Missing or partial concomitant medication start date and not started prior to study treatment:
    - Use the study Day 1 (dosing date from Period 1).

- Missing or partial concomitant medication stop date:
    - If only Day is missing, use the last day of the month.
    - If Day and Month are both missing, use the last day of the year.
    - If Day, Month, and Year are all missing, assign 'continuing' status to stop date.

<u>Medical/Surgical History and COPD history</u>

- Missing or partial start date or diagnosis date:
    - If only Day is missing, use the first day of the month.
    - If Day and Month are both missing, use the first day of the year.
    - Otherwise set to missing.

- Missing or partial stop date:
  - If only Day is missing, use the last day of the month.
  - If Day and Month are both missing, use the last day of the year.
  - Otherwise, set to missing.

Imputation of missing glycopyrronium concentration is discussed in Section 10.

5. Subject Disposition

5.1. Disposition

Subject disposition will be summarized overall as the number of subjects who were enrolled, started each treatment Period, who completed treatment, and who completed the study for the Enrolled Set.

Disposition will also be summarized for the Enrolled Set by treatment sequence and overall using frequency counts and percentages. Summaries will include the number of subjects who started study, completed study follow-up, started study treatment, completed study treatment, and the (primary) reason for early discontinuation. Subjects that did not undergo dosing on Day 1 of a Period will not be included the corresponding summary for Period.

Primary reasons for in summaries of discontinuation may include any of the following reasons:

Treatment Discontinuation	Study Discontinuation
Randomized by Mistake with Study Treatment Adverse Event $\geqslant$ 1 Moderate Exacerbation Death Pregnancy Used Prohibited Medication Protocol Deviation Non-Compliance with Study Schedule Non-Compliance with Study Drug Physician Decision Withdrawal by Subject Sponsor Request Study Terminated by Sponsor Site Terminated by Sponsor Lost to Follow-up Other	Screen Failure Randomized by Mistake without Study Treatment Treatment Adverse Event Death Lost to Follow-up Other

Analysis sets that include Enrolled Set, Randomized Set, Safety Analysis Set, Full Analysis Set, Completers Analysis Set, Per Protocol Set, PKAS, and PKAPAS will also be summarized using frequency counts and percentages by treatment sequence and overall.

Exclusions from Analysis Sets will be provided in subject listings. Subject screened and not included in the Randomized Set, subjects in the Randomized Set not included in SAF, subjects in Randomized Set not included in FAS and reason for exclusion will be listed by subject ID and (when applicable) by treatment sequence.

5.2. Randomization

A by-subject listing of randomization information (including date of informed consent, date of randomization, treatment sequence, randomization number and kit numbers) as well as assigned, and actual treatment for all randomized subjects will be produced using the Randomized Set.
The number and percentage of subjects randomized will be summarized by analysis set for the FAS, CAS, PPS, SAF, PKAS, and PKPAS by treatment sequence and overall. All the percentages will be based on the number of subjects in the Randomized Set.

5.3. Protocol Deviations

Protocol deviations will be identified and confirmed prior to database lock and summarized by the deviation categories shown in protocol deviation rules document.

A significant protocol deviation that affects primary efficacy and/or pharmacokinetic assessments (as applicable), or the scientific value of the trial will be further identified. The significant exclusionary protocol deviations that are identified as biasing analyses of spirometric endpoints will result in subject exclusion from Per Protocol Set and/or PK Parameter Analysis Set. There will be no exclusions from the Safety Analysis Set.

The number of subjects with at least 1 significant deviation will be presented by category of violation by treatment sequence and overall for all subjects in the Randomized Set. In addition, the number of subjects with at least 1 significant exclusionary protocol deviation leading to exclusion from Per Protocol Set and, separately, from the PK Analysis Set will be presented by category of violation, type of deviation, by treatment sequence and overall for all subjects in the Randomized Set.

A listing of all protocol deviations will also be provided by sequence for Randomized Set. Listings will include the date and Day of the deviation, Period. intended treatment, actual treatment, and flags (Y/N) to denote a significant deviation, exclusion from the FAS, and exclusion from the PKAS.

6. Demographics and Baseline Characteristics

6.1. Demographic and Baseline Characteristics

A summary of demographic and baseline characteristics will be presented by treatment sequence and overall for Randomized Set and Safety Analysis Set.

The demographic characteristics consist of age (years, provided by the IRT system), sex (male, female), ethnicity (Hispanic or Latino, Non-Hispanic or Latino, Not Reported), and race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Multiple, Not Reported, and Other).

Baseline characteristics consist of Child-Bearing Potential (Yes/No), height (cm), weight (kg), and body mass index (BMI) (kg/m²). Body mass index is derived within the EDC system as (body weight in kilograms)/(height in meters)^2.

Age (years), baseline height (cm), baseline weight (kg), and baseline BMI (kg/m²) will be summarized using descriptive statistics.

The number and percentage of subjects for Child-Bearing Potential (Yes, No), sex (Male, Female), ethnicity (Hispanic or Latino, Not Reported), and race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Mutiple, Not Reported, and Other) will also be reported.

Subject demographic and baseline characteristics will be presented in a listing by treatment sequence for all subjects in the Randomized Set. Ethnicity for non-Hispanic or non-Latino will report the actual ethnicity (African American/African Heritage, Asian-Central/South Asian Heritage, Asian-Southeast Asian Heritage, Asian-East Asian Heritage, White-White/Caucasian/European Heritage).

6.2. Disease Characteristics

A summary of the method used to confirm COPD (chest X-ray, CT scan) will be presented by sequence and overall, for Randomized Set and Safety Analysis Set.

Disease characteristics are defined as:

- FEV_1 reversibility at screening (yes, no) - s defined as (≥12% and ≥200mL increase in FEV1)
- Pre- and post-bronchodilator FEV_1 (both in liters and in percentage of predicted normal)
- Pre- and post-bronchodilator FVC (both in liters and in percentage of predicted normal)

- Post-bronchodilator FEV_1/forced vital capacity (FEV1/FVC)
- Background medication use [yes LABA, yes LABA/ICS, no] –actual
- Known to have Chronic Bronchitis (yes, no)
- Known to have Emphysema (yes, no)
- Smoking status (current, former) –actual recorded in the eCRF
- Number of cigarettes per day, Number of years smoking, Number of Pack Years
- COPD severity based on post-bronchodilator FEV_1 (Mild ≥80%), Moderate (50% ≤ to <80%), Severe (30% ≤ to <50%), Very severe (<30%))
- Time since initial diagnosis of COPD = (date of consent – date first diagnosed+1)/365.25
- Pack Years (EDC) = number of pack years = (number of cigarettes per day / 20) × number of years smoked

Reversibility status is calculated based on pre-bronchodilator and post-bronchodilator FEV_1 values taken at Screening. If patient has increase of ≥12% and ≥200mL then patient is reversible, else patient is non-reversible.

Pack Years is automatically calculated in the eCRF and this value will be used in the summaries.

6.3. Medical History

6.3.1. General Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 27.0 or higher. The subject's medical history will be summarized by treatment sequence and overall, by system organ class (SOC) and preferred term (PT) using the Safety Analysis Set.

Percentages will be calculated based on the number of subjects in the SAF. Patient medical history data including specific details will be presented in a listing.

6.4. Inclusion and Exclusion Criteria

The details of the inclusion and exclusion criteria can be found in Sections 5.1 and 5.2 of the study protocol. Patient status of eligibility criteria met, inclusion criteria not met, and exclusion criteria met as well as corresponding details will be listed for the Enrolled Set.

7. Treatments and Medications

7.1. Medications

Information on prior and concomitant medications taken by subjects are recorded in the eCRF. Prior and concomitant medication will be coded according to World Health Organization Anatomical Therapeutic Chemical (ATC) Classification and the latest World Health Organization drug dictionary (WHODD March 2023 or later). Both prior and concomitant therapies will be presented in one listing.

7.1.1. Prior Medications

Prior medications are defined as medications used prior to the first dose of study drug independent of whether the medication was stopped at randomization or not.

Prior medications will be summarized by Anatomical Therapeutic Clinical Classification System (ATC).

The total number of prior medications and the number and percentage of subjects with at least one prior medication will be summarized. The number and percentage of all prior medications will be presented by ATC levels 1, 2, 4 and preferred drug name. All summaries will be generated by sequence and overall using the SAF.

7.1.2. Concomitant Medications

Concomitant medications are defined as medications started prior to the first dose of study medication but continuing after the first dose or medications started at or after the first dose of study medication.

Concomitant medications will be summarized by Anatomical Therapeutic Clinical Classification System (ATC).

The number and percentage of subjects using concomitant medications will be tabulated by ATC levels 1, 2, 4, and preferred name. At each level of summarization (e.g., ATC class or preferred drug name), a subject is counted once if they reported one or more medications at the particular level.

Concomitant medications will be summarized by treatment sequence and overall and, separately, by treatment and overall using the SAF.

7.1.3. Concomitant Procedures

Concomitant procedures are defined as procedures occurring after the first dose of study medication over the course of the study.

Concomitant procedures will not undergo Medical Dictionary for Regulatory Activities (MedDRA) coding, and data including specific details will be presented in a listing.

7.2. Study Treatments

7.2.1. Extent of Exposure and Treatment Compliance

Compliance to blinded study medication will be calculated where study medication was administered on Day 1, and both dispensed and returned. Percent compliance will be calculated as 100 * (total number of ampules dispensed - unused ampules returned)/number of ampules prescribed).

Ampules prescribed are 2 ampules for Day 1 through Day 6 and 1 ampule for Day 7 for each Period. The prescribed number will take into account rescheduling of a Day 7 visit. The number prescribed will be calculated as [2* ((return date – dispense date)+1)] -1. Study compliance (full) will be derived as 100 times the ratio of the sum of the numerators and the sum of the denominators across treatment Periods Duration of exposure will be derived as return date – dispense date+1. Non-compliance will be defined as a compliance value less than 70% over the full study.

Study treatment compliance and duration of exposure will be summarized for all subjects in the SAF population with descriptive statistics by treatment and overall. Additionally, the number and percentages of subjects who completed treatment per protocol and in each compliance category (<70%, ≥70% to ≤100%) will be also presented by treatment and overall.

A by-patient listing of study drug administration, drug accountability, and compliance will be provided by sequence and Period.

8. Efficacy Analysis

The aim of this study is to quantify the treatment effect of each glycopyrrolate dose over placebo in efficacy as mean change from average baseline for spirometry. Average baseline is derived as the average of the two pre-treatment FEV1 values on Day 1 of each study period that are assessed within 40 minutes prior to dosing. If two values are not available, then a single assessment will be used as average baseline. If not assessed, baseline is set to missing and change from average baseline will not be derived.

The null hypotheses to be tested for each primary and secondary efficacy endpoint will be (H_O) that there is no difference in change from average baseline between glycopyrrolate and placebo for each glycopyrrolate dose, against the alternative hypothesis (H_A) that change differs between that glycopyrrolate dose and placebo. In this study, average baseline is derived for each patient at each Period using values prior to Day 1 dosing.

The null hypotheses to be tested for separate comparisons of a single glycopyrrolate dose with each lower dose in exploratory efficacy endpoints will be (H_O) that there is no difference in change from baseline between that glycopyrrolate and the lower dose compared, against the alternative hypothesis (H_A) that change differs between that glycopyrrolate dose and the lower glycopyrrolate dose compared.

Treatments will be characterized and, the efficacy endpoint comparisons between glycopyrrolate dose and placebo will be made using estimates obtained from Analysis of Covariance (ANCOVA). Models will include terms for treatment, period, subject, and include baseline as a covariate. A separate model will be fit for each efficacy endpoint by study Day. Spirometry measurements will be presented in data listings and summarized by treatment and time point.

For primary and secondary analyses, a summary table will present results for each endpoint by study Day. Results will be presented for:

- Average baseline value pre-dose on Day 1 for each treatment using descriptive statistics.
- Change from average baseline values for each treatment using descriptive statistics.
- Least Squares (LS) Mean estimates for each treatment along with the corresponding standard errors (SE) and 95% CIs.
- Differences in Least Squares (LS) Mean differences for each active treatment comparison, along with the corresponding standards (SE), 95% CIs, and p-values

For exploratory analyses, a summary table will present results for each endpoint at study Day 7. Results will be presented for:

- Least Squares (LS) Mean differences for each active treatment and all lower doses of each active treatment comparison, along with the corresponding standards (SE), 95% CIs, and p-values

Spirometry parameters will be analyzed as change from average baseline FEV1 and will not be transformed prior to analysis.
In analysis of each parameter, change from average baseline and average baseline for each treatment will be combined across Periods, and undergo analysis for a specific study Day and analysis set (FAS, PP).

Standardized residual values from each primary and secondary analysis will be evaluated from each fitted ANCOVA model for the influential values (e.g., outliers). Outliers will be defined as values below the 25th percentile minus 3 times the interquartile range (IQR), or beyond the 75th percentile plus 3*IQR. If extreme values are identified, then analyses may be repeated with outliers excluded. If re-analysis with exclusion is performed, the corresponding exploratory analysis will also be re-analyzed with exclusions.

Spirometry Data Exclusions
Issues which may affect spirometry will be evaluated by the study team on a case-by-case basis and may lead to exclusion from treatment summaries for a given treatment period or the PPS as applicable. All exclusions will be documented throughout the affected data listings.

These issues will include deviations or events that are expected to alter the spirometry analyses, and not all issues may be a due to protocol deviations. Examples that may lead to exclusion of the subject's spirometry results from treatment summaries for a given treatment period and/or the PPS are provided below. This list is not all inclusive:

- <70% compliance for a given treatment period will result in the exclusion of that subject from a given treatment period for the analysis of peak, trough, and AUC FEV1.
- Spirometry performed within 4 hours after the use of a rescue bronchodilator (albuterol) will not be utilized in calculations of peak, trough, or AUC FEV1.

8.1. Primary Efficacy Analysis

Change from average baseline to morning trough FEV1 measured on Day 7 will be summarized. The morning trough FEV1 is measured approximately 12 hours following the prior evening dose, and prior to study medication dosing in the clinic on Day 7.

Primary efficacy analysis will be based on the FAS. Analyses will be repeated for Per-Protocol set.

Primary analysis will be performed for change from average baseline in morning trough measured on Day 7. Primary hypotheses, analysis, comparisons, and reporting will follow conventions described in Section 8.

8.2. Secondary Efficacy Endpoints

Secondary efficacy analysis will be based on the FAS. The secondary endpoints are listed in Section 3.2.2. Analyses will be repeated for PPS set.

Secondary analyses will be performed for:

Change from average baseline to peak FEV1 measured over 4 hours post-dose on Day 7.
Change from average baseline to average FEV1 measured $AUC_{0\text{-}4h}$ on Day 7.
Change from average baseline to average FEV1 measured $AUC_{0\text{-}12h}$ on Day 7.
Change from average baseline to evening trough FEV1 on Day7.
Change from average baseline to average peak FEV1 measured over 4 hours post-dose on Day1.
Change from average baseline to average FEV1 measured $AUC_{0\text{-}4h}$ on Day 1.

Secondary hypotheses, analysis, comparisons, and reporting will follow conventions described in Section 8.

8.3. Derivation of FEV1 AUC0-12h/ AUC0-4h

FEV_1 $AUC_{0\text{-}12h}$ denotes the area under the FEV_1 curve over the 12-hour dosing interval following the morning dose on Day 7. Cumulative FEV_1 expressed as AUC over 12 hours from the time after first dose on Day 7.

The average effect will be calculated as the AUC divided by the actual length of the time interval of interest (for example, 12 hours for $AUC_{0\text{-}12h}$ or 4 hours for $AUC_{0\text{-}4h}$). AUC will be calculated using the trapezoidal method, as follows:

$$\mathrm{AUC} = \frac{1}{2}\sum_{i=1}^{n-1}(T_{i+1} - T_i)(C_{i+1} + C_i)$$

Where Ti is the ith time value, Ci is the ith effect value, n is the number of time values. The change from the baseline FEV_1 to average FEV_1 (AUC) will be summarized and analyzed.

If two last data points are missing, then the AUC is set to missing, that is for $AUC_{0\text{-}12h}$ we require at least up to 8 hours of assessments and for $AUC_{0\text{-}4h}$ we require at least up to 2 hours of assessments. For example, if there are only 8 hours of assessments, then we calculate $AUC_{0\text{-}8h}$, however we label as $AUC_{0\text{-}12h}$.

If there is no pre-dose measurement available for the calculation of the AUC, then the AUC will not be calculated.

The pre-dose measurement used in the calculation of AUC will be the last value measured within 40 minutes pre-dose. The pre-dose value will be used as time 0 when computing $AUC_{0\text{-}T}$.

8.4. Derivation of other Spirometric Endpoints

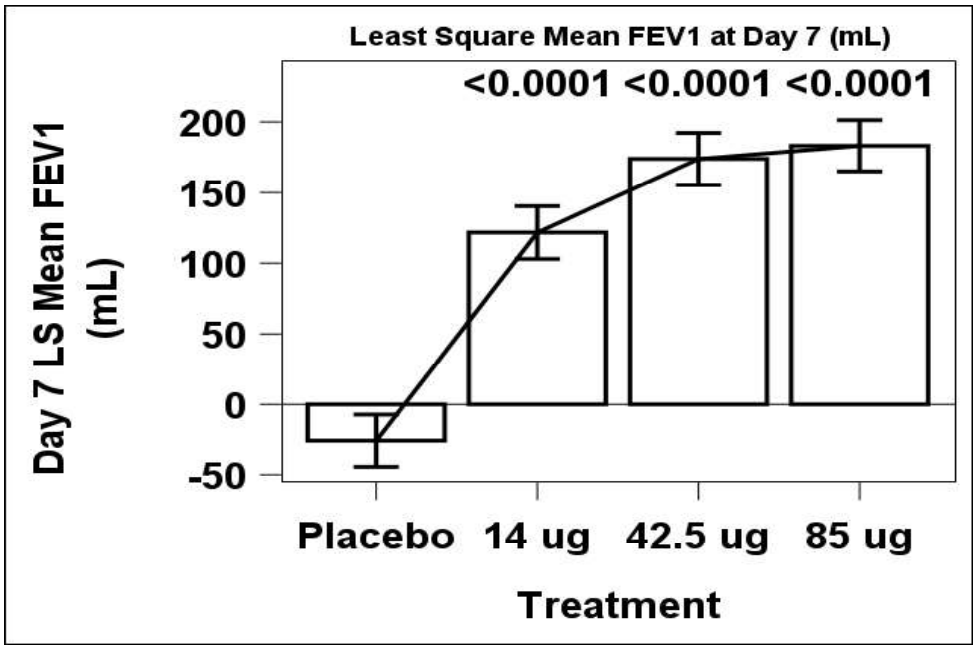
Peak FEV1 will be computed as the maximum value in the 4 hours after dosing (4 timepoints after dosing: 30 minutes, 1 hour, 2 hours and 4 hours).

Morning trough FEV1 is the last value collected prior to the morning dose.
Evening trough FEV1 on Day 7 is 12 hour post-dose assessment value in the clinic on Day 7.

8.5. Graphical Displays

Histograms will be created for each primary and secondary endpoint which present the estimated LS mean (histobar height) for each treatment with 95% confidence intervals (in order of glycoplyrrolate dose, left to right, beginning with placebo placebo) see example below. The LS Mean difference between the glycopyrrolate dose and placebo and an asterisk indicating a p-value ≤ 0.05 for the difference will be annotated above the 95% upper confidence limit for each glycopyrrolate dose. A solid line will be overlaid to connect the treatments at the midpoint of each histobar. See example below. Histobars will be outlined, but not filled-in. Glycopyrrolate dose will be displayed on the x-axis with 0 used to represent the placebo dose.

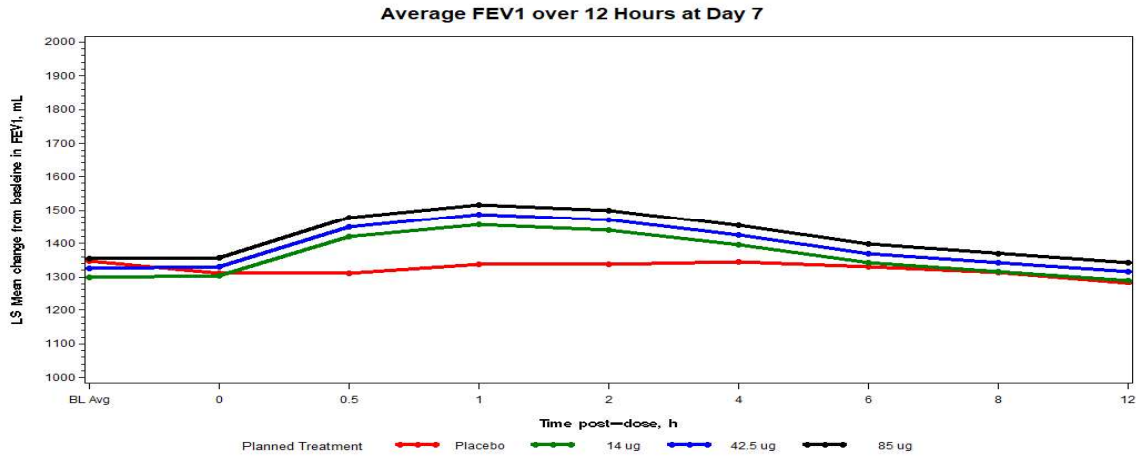
Histogram Example



Treatment average FEV1 values will also be graphically displayed for each period (overlays of treatment average profiles) at each evaluation time for Day 7 over 12 hours (including the baseline average) and for Day 1 over 4 hours. An additional graphical

display of treatment average FEV1 values will also be generated for each treatment (overlays of period average profiles) at each evaluation time for Day 7 over 12 hours (including the baseline average) and for Day 1 over 4 hours.

See example below



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8.6. Exploratory Efficacy Endpoints

The exploratory endpoints are described in Section 3.2.3. The null hypotheses and alternate hypothesis for the exploratory efficacy endpoint are as follows:

Exploratory analyses will present comparisons of the LS Mean corresponding to a given dose of glycopyrrolate to each LS Mean for all lower glycopyrrolate doses on Day 7 beginning at the highest glycopyrrolate dose. The ANCOVA models described for peak FEV1, average FEV1 AUC0-12h, and morning trough FEV1 on Day 7 will be used to make comparisons. Exploratory hypotheses, analysis, comparisons, and reporting will follow conventions described in Section 8. If outliers are identified in primary and secondary analyses, then comparisons may be regenerated with the exclusion of outliers.

9. Safety Analysis

All safety data will be summarized by actual treatment received unless otherwise specified. Safety analysis will be performed using the SAF. Safety endpoints include adverse events (AEs), clinical laboratory assessments, vital signs, electrocardiogram (ECG). In safety analyses, the assigned treatment will extend to the earliest of the first dose of subsequent treatment or end of study visit.

9.1. Adverse Events

An AE is any untoward medical occurrence in a subject, temporally associated with the use of blinded study medication, whether considered related to the blinded study medication.

Any partial date or date that is equal to the initial dose date will be queried to confirm if on or after dose. If the reported AE is found to be prior to dosing, then that AE will not be considered as treatment related and will be reported in Medical History.

A treatment-emergent AE (TEAE) is defined as any AE that meets any of the following conditions, based on the actual AE dates:

- begins on or after the first dose date of treatment;
- begins before the first dose date of treatment and increases in severity on or after the first dose date of treatment;
- is completely missing a start date and the stop date;
- is completely missing a start date and the stop date is on or after the first dose of trial medication.

AEs and TEAEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA Version 27.0 or higher). AEs and TEAEs will be analyzed using quantitative and qualitative measures. TEAEs will be summarized by System Organ Class (SOC) and preferred term (PT) for each treatment.

9.1.1. Incidence of Adverse Events

An overview of TEAEs, including the number and percentage of subjects who experienced at least one TEAE, as well as the total number of TEAEs, will be presented for all glycopyrrolate treatments combined and by treatment. This tabulation will be repeated for the TEAE categories as follow:

- TEAEs
- Treatment Related TEAEs
- TEAEs by Maximum severity (Mild, Moderate, Severe)
- Treatment Related Severe TEAEs
- TEAEs leading to study treatment discontinuation
- TEAE's leading to study discontinuation
- TEAEs leading to death
- TEAEs of Special Interest
- Treatment emergent SAEs
- Treatment emergent related SAEs

All TEAEs will also be presented in a summary table by SOC and PT through end of study participation. A subject may have more than 1 TEAE for an SOC or PT. A subject with 2

or more TEAEs within the same level of summarization will be counted only once in that level. The summary of TEAEs will be presented in descending order from the SOC with the highest total incidence to the SOC to the lowest total incidence. If the total incidence for any 2 or more SOCs are equal, the SOCs will be presented in alphabetical order. The PTs within each SOC will be presented in alphabetical order.

9.1.2. Relationship of Adverse Events to Study Drug

A summary of TEAEs by relationship to study treatment will be presented in a table by incidence of occurrence. The investigator will provide an assessment of the relationship of the event to the study treatment. The possible relationships are Reasonable Possibility and No Reasonable Possibility. If relationship is missing from a TEAE then Reasonable Possibility will be assigned.

All TEAEs assigned Reasonable Possibility will be presented in a summary table for each treatment and total by SOC, PT. If a subject has 2 or more TEAEs in the same SOC (or with the same PT) with a different relationship to study treatment, then the subject will be counted as Reasonable Possibility. If the relationship information is missing, the TEAE will be considered assigned Reasonable Possibility in the summary but will be presented as missing in a separate data listing of Related TEAEs.

9.1.3. Severity of Adverse Event

Adverse events will be evaluated and documented according to intensity assessed by the investigator:

- Mild indicates a mild event
- Moderate indicates a moderate event
- Severe indicates a severe event

In the TEAE severity table, if a patient reported multiple occurrences of the same TEAE, only the most severe will be presented. TEAEs that are missing severity will be presented in tables as severe but all TEAEs will be presented in the data listing with a non-imputed severity. All TEAEs will be presented in a summary table for each treatment and for all glycopyrrolate treatments combined by SOC, PT, and severity. Severe TEAEs will be presented in a separate data listing.

9.1.4. Serious Adverse Events

All SAEs are indicated on the Adverse Events page of the eCRF as Serious Adverse events with a status of Yes. SAEs will be presented in a summary table for each treatment and for

all glycopyrrolate treatments combined by SOC and PT regardless of whether they are judged to be related to the study treatment. SAEs will be presented in a separate data listing.

9.1.5. Adverse Events of Special Interest (AESIs)

AEs of special interest (AESIs) that have been identified for glycopyrrolate include paradoxical bronchospasm (bronchospasm, bronchospasm paradoxical), immediate hypersensitivity reactions (hypersensitivity, anaphylactic reaction), worsening of narrow-angle glaucoma (glaucoma, vision blurred, eye pain), and worsening of urinary retention (urinary retention). All AESIs will be presented in a summary table for each AESI for each treatment and for all glycopyrrolate treatments combined by SOC and PT. Each AESI will be presented in a separate data listing.

9.1.6. Adverse Events of Liver Safety Event

Liver safety event will be collected from liver safety event CRF. ALL liver safety events will be presented in a spearate data listing.

Liver chemistry stopping criteria include:

- ALT result >=8 x ULN
- ALT result >=5 x ULN but <8 x ULN that persists for >=2 weeks
- ALT result >=3 x ULN and a total bilirubin value >=2 x ULN (>35% direct bilirubin) or ALT result >=3 x ULN and PT-INR > 1.5, if PT-INR measured
- ALT or AST >= 3 x ULN associated with symptoms (new or worsening) believed to be related to hepatitis (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia)
- ALT >= 5 x ULN but < 8 x ULN and cannot be monitored weekly for >= 2 weeks

9.1.7. Adverse Events Leading to Treatment Discontinuation

All TEAEs leading to treatment discontinuation are indicated on the Adverse Events page of the eCRF as Drug Withdrawn will be presented in a summary table for each treatment and for all glycopyrrolate treatments combined by SOC and PT. All TEAEs leading to treatment discontinuation will be presented in a separate data listing.

9.1.8. Adverse Events Leading to Study Discontinuation

All TEAEs leading to study discontinuation will be presented in a summary table for each treatment and overall by SOC and PT. All TEAEs leading to study discontinuation will be presented in a separate data listing.

9.1.9. Death

All TEAEs leading to death as indicated on the Adverse Events page of the eCRF as Death (as a fatal outcome or serious criteria of death) will be presented in a summary table for each treatment and for all glycopyrrolate treatments combined by SOC and PT. All TEAEs leading to death will be presented in a separate data listing.

9.2. Clinical Laboratory Evaluations

Laboratory assessments will be performed by a central laboratory and will be performed as outlined in the Schedule of Study Procedures (Table 14-1). All summaries will be based on conventional units.

Descriptive statistics will be presented by visit and by treatment for observed values and changes from the Screening value (for quantitative measurements) in the SAF. Marked abnormalities will correspond to values that exceed laboratory upper normal range limits or fall below lower normal range limits. The incidence of markedly abnormal for each parameter will be summarized for each treatment and for all glycopyrroate treatments combined, and , (with normal included) will be similarly summarized using shift tables. The shift tables including reference ranges and thresholds will be based on the Central Laboratory.

A by-patient listing for laboratory test results and changes will be provided by treatment in chronological order for clinical laboratory tests. Values falling outside of the relevant reference range (low, high) will be flagged in the data listings, as appropriate.

9.2.1. Hematology

The laboratory tests included in hematology are described in Table 14-4. Summary tables and listings will be presented as described in Section 9.2.

9.2.2. Serum Chemistry

The laboratory tests included in serum chemistry are described in Table 14-4. Summary tables and data listings will be presented as described in Section 9.2. Evaluation dates that associated with abnormal liver events are flagged in the data listings.

9.2.3. Viral Serology

The laboratory tests included in Viral Serology are described in Table 14-4. Viral serology results will be presented in subject data listings as described in Section 9.2.

9.2.4. Pregnancy

Women who are pregnant or breastfeeding are not eligible to participate. Pregnancy testing will be conducted in women of childbearing potential at Screening and over the course of the study.
A serum pregnancy test will be performed on females of childbearing potential at Screening (Visit 1). A urine pregnancy test will be conducted at the Day 1 visit for each of the treatment period. A subject listing will be presented for pregnancy report and pregnancy test results as described in Section 9.2.

9.3. Vital Sign Measurements

Systolic blood pressure (SBP) (mmHg), diastolic blood pressure (DBP) (mmHg), pulse rate (PR) (beats/min), and weight (kg) measurements will be collected with a completely automated device. Manual techniques will be used only if an automated device is not available.

Supine blood pressure and pulse measurements should be obtained after the subject has been at rest for at least 5 minutes in the supine position and located in a quiet setting without distractions (e.g., television, cell phones).

Vital signs will be summarized for each treatment and for all glycopyrrolate treatments combined, including change from baseline for the SAF population. Change from baseline values outside pre-specified ranges (low, high) that exceed markedly abnormal limits will be summarized and also summarized using shift tables for each treatment and for all glycopyrrolate treatments combined for each parameter. The number of normal, and markedly abnormal values will be summarized for each treatment and for all glycopyrroate treatments combined using shift tables. Vital signs performed in triplicate will use the average in summaries. Individual measurements and average values will be reported in listings.

Table 7-1 Criteria of Abnormal Post-Baseline Vital Signs

Variable	Unit	Abnormally Low	Abnormally High
SBP	mmHg	-A decrease from Baseline of ≥40 - Value ≤90	– An increase from Baseline of ≥40 – Value ≥180
DBP	mmHg	– A decrease from Baseline of ≥20 – Value ≤50	– An increase from Baseline of ≥20 – Value ≥105

Pulse rate	Bpm	– A decrease from Baseline of ≥30 – Value ≤50	– An increase from Baseline of ≥30 – Value ≥110

A by-patient listing for all vital sign results will be presented in a listing. Listings will include changes and flags to identify markedly abnormal values.

9.4. Electrocardiogram

The following ECG parameters will be reported for this study:

- RR Interval (msec)
- PR Interval (msec)
- QRS Duration (msec)
- QT Interval (msec)
- QTcF Interval (msec)
- QTcB Interval (msec)
- Heart Rate (beats per minute [bpm])
- Overall assessment of ECG (Investigator's judgment):
    - Normal
    - Abnormal, Clinically Significant (ACS)
    - Abnormal, Not Clinically Significant (ANCS)
    - Incomplete Analysis
    - Uninterpretable

Markedly abnormal quantitative ECG measurements will be identified in accordance with the following predefined markedly abnormal criteria:

- Absolute values for QT interval, QTcB interval and QTcF interval will be classified as:
- > 450 msec
- > 480 msec
- > 500 msec

Change from Baseline for QT interval, QTcB interval and QTcF will be classified as:

- >30 msec increase from baseline
- >60 msec increase from baseline

Descriptive statistics for ECG parameter at each assessment visit will be presented for the observed and change from baseline values. Additionally, the investigator ECG

interpretation categorized as ‘Normal’, ‘Abnormal Clinically Significant’, ‘Abnormal not Clinically Significant’, ‘Uninterpretable’ will also be provided for each scheduled assessment visit via the eCRF and upon review (note: ECG interpretations of ‘Abnormal Clinically Significant’ would be recorded as AEs or Medical History).

Continuous parameters from the ECGs will be summarized for each treatment and for all glycopyrrolate treatments combined, including change from baseline for the SAF population. Values that exceed pre-specified marked abnormality limits will be summarized for each MA criterion with number and percentage of subjects that met each markedly abnormal threshold at each time of assessment for each treatment and overall. Shifts from baseline in investigator interpretation will be summarized for each treatment and overall, at each time of assessment.

All ECG data will be presented in a listing and values outside markedly abnormal limits will be flagged.

10. Pharmacokinetics

PK listings will be presented using the Safety Analysis Set, and subjects not included in the PK and/or PKPAS will be flagged, as appropriate.

A subject without glycopyrrolate administration will not be included in the listing of PK concentrations and PK parameters.

A subject without any estimable PK parameters will not be included in the listing of PK parameters.

Individual PK concentration-time profiles will be presented graphically for each glycopyrrolate dose using the PKAS on both arithmetic and semi-logarithmic scales.

All concentration summaries and concentration mean figures will be presented using the PKAS, and all PK parameter summaries, PK parameter figures, statistical analyses will be presented using the PKPAS. All PK analysis will be performed separately by PPD PK team.

10.1. Data Handling

10.1.1. Pharmacokinetic Profile Exclusions

Issues which may affect exposure to study drug result in individual PK profiles will be evaluated by the study pharmacokineticist on a case-by-case basis, and may lead to exclusion from treatment summaries, the PKPAS, and/or the PKAS as applicable. All exclusions will be documented throughout the affected data listings.

These issues will include deviations or events that are expected to alter the PK results and not all issues may be due to protocol deviations. Examples that may lead to exclusion of

the subject's PK results from both PKPAS and PKAS (ie from both analysis sets) are provided below. This list is not all inclusive:

- One or both doses on Day 6 are missed.
- The most recent prior dose was administered less than 6 hours prior or more than 18 hours prior to collection of the dose administered on Day 7 (ie, the dose on Day 7 is not within a window of 6 to 18 hours relative to the last dose).
- Deviations related to handling, shipment, or storage of all samples for the subject which result in unreliable bioanalytical results.

Other issues may lead to exclusion of one or more records from the PKPAS and/or PKAS. In this case the affected PK concentrations and/or parameters will be excluded from the summary and/or inferential analyses but the subject is retained in the analysis set(s). Examples that will lead to exclusions are provided below. This list is not all inclusive:

- Incomplete or incorrectly administered dose on Day 7 (including extended coughing during inhalation). (Note, the predose concentration is not affected by this issue).
- Subject discontinuation and/or refusal to finish sample collections through 12 hours. (Note, results may still allow determination of Cmax and tmax)
- Missing evaluable concentrations at critical portions of the concentration-time profile preventing reliable determination of 1 or more PK parameters (eg, immediately after end of inhalation).
- Concentration outside the sample collection window (excluded from summary statistics).

10.1.2. Data Rounding

Data rounding specifications for PK data are documented in the PK TLF shells.

10.1.3. Below the Limit of Quantification

Plasma concentrations that are Below the Limit of Quantification (BLQ) will be treated as zero for calculation of concentration descriptive statistics and estimation of all PK parameters. For the PK analysis, BLQ values will be treated as zero with the exception that a BLQ value between 2 quantifiable concentrations will be set as missing.

10.1.4. Missing Data

All missing concentration data will be presented as missing in concentration data listings and excluded from the estimation of concentration summary statistics. Missing predose concentrations will be treated as missing.

10.1.5. Pre-dose Samples Collected Post-dose

Pre-dose samples collected in error after dosing will be excluded from the calculation of concentration summary statistics and replaced with the 12-hour postdose concentration in the estimation of PK parameters, assuming that steady-state was reached.

10.1.6. Summary Statistics

Summary statistics to be presented for each output are as follows:

- Plasma concentrations and PK parameters: number of subjects (N), number of non-missing observations (n), number of concentrations <LLOQ (n<LLOQ), arithmetic mean, standard deviation (SD), geometric mean, CV%, geometric CV%, median, minimum, and maximum. t_{max} will be summarized using number of observations, median, minimum, and maximum only.

Where only one observation is observed (ie, n=1), only the number of observations, arithmetic mean, median, minimum, and maximum will be presented.

10.2. Plasma Concentrations

Serial blood samples will be collected at the following time points for PK assessment:

- Day 7 of Treatment Periods 1 and 2: Pre-dose (within 30 minutes prior to Day 7 dosing), 10 ± 4, 20 ± 4, and 40 ± 4 minutes post-dose and at 1 ± 0.25, 1.5 ± 0.25, 2 ± 0.25, 4 ± 0.25, 8 ± 0.25, and 12 ± 0.25 hours post-dose.

PK collections that have an actual sampling time (calculated from the start of the inhalation) that deviate (calculated from the end of inhalation) from the predefined collection time windows will be flagged in the data listings and excluded from the calculation of concentration summary statistics.

Plasma concentration will be used to reference the glycopyrronium free base concentration.

Individual plasma concentrations will be plotted at each timepoint over 12 hours for each glycopyrrolate dose by actual time on both linear and semilogarithmic scales using data from both periods combined.

Arithmetic mean plasma concentrations with error bars representing the corresponding standard deviation (i.e., arithmetic mean +/- 1 standard deviation) will be plotted for each glycopyrrolate dose by nominal time on both linear and semi-logarithmic scales with all treatments (overall and by period) overlaid on the same plot. The treatment periods will be identified by different symbols. The arithmetic mean will reflect the mean of all data combined for a given dose level, unless presentation of the by-period means is warranted by the data. Standard deviation may be omitted for the graphic presentation of the by treatment and period presentation.

Plasma PK concentrations will be presented in data listings using the Safety Analysis Set and summarized separately and combined for treatment periods 1 and 2 using the PKAS. Placebo will be excluded from the PK concentration listings.

10.3. Plasma Pharmacokinetic Parameters

Plasma concentration-time data will be analyzed by non-compartmental analysis using Phoenix® WinNonlin® Version 8.3 or higher (Certara USA, Inc., Princeton, NJ) or SAS® (SAS Institute Inc., Cary, North Carolina) Version 9.4 or higher. The following PK parameters will be calculated for glycopyrronium free base, where data permit:

$AUC_{0\text{-}12h}$	Area under the plasma concentration curve (AUC) over the 12-hour dosing interval following the morning dose on Day 7, calculated using the linear trapezoidal rule and using actual sample collection time at time =tau (12 hours). For subjects without a calculable $AUC_{0\text{-}12h}$ values due to early collection of the 12-hour sample outside of the protocol-specified window, $AUC_{0\text{-}last}$ may be used. For subjects with a late 12-hour sample, interpolation will be used to report $AUC_{0\text{-}12h}$. For subjects with a missing predose concentration, the 12-hour sample may be used to calculate $AUC_{0\text{-}12h}$, assuming steady state has been reached.
DN-$AUC_{0\text{-}12h}$	$AUC_{0\text{-}12h}$ normalized for dose.
C_{max}	Highest plasma concentration measured over the dosing interval.
DN-C_{max}	C_{max} normalized for dose.
C_{trough}	Plasma concentration measured prior to dose administration in the morning of Day 7.
$C_{trougheve}$	Plasma concentration measured at 12 hours post dose (relative to start of inhalation) in the evening of Day 7.
C_{avg}	Plasma average concentration measured over the dosing interval, calculated as $AUC_{0\text{-}12h}$ divided by the dosing interval.
t_{max}	Time point corresponding to C_{max}.
CL/F	Apparent clearance from plasma following glycopyrrolate inhalation, calculated as the dose divided by the $AUC_{0\text{-}12h}$. For this calculation, the administered dose of glycopyrrolate will be corrected for the molecular weight difference between the salt (MW: 398.33 g/mol) and free base of glycopyrronium (MW: 318.4 g/mol) as administered dose multiplied by (318.4/398.33).

Actual sampling times (without rounding) relative to the start of the inhalation will be used for the estimation of all plasma PK parameters, and all concentrations associated with scheduled sampling times will be included in the analysis (including concentrations collected outside predefined collection windows), except when actual elapsed times postdose for two or more samples are the same. If a subject has more than one nominal PK sample with the same actual date and time of collection, only a single sample should be

used for PK parameter calculation. The sample used for analysis should be the sample with the actual elapsed time postdose closest to the scheduled time. In the case of samples collected exactly at the midpoint between the scheduled sample collections (eg, 2 samples collected 1.25 hours, i.e. at 1 + 0.25 hours and 1.5 - 0.25 hours), the sample with the label allocated to the earlier nominal time (in this example the 1 ± 0.25 hour sample) should be used in the PK parameter calculations. In the case when 1 of 2 samples which were collected at exactly the same time postdose is non-evaluable (e.g., no bioanalytical result or other bioanalytical issue), results from the later samples may be used in the analysis.

Unscheduled PK samples will not be included in the estimation of PK parameters.

Individual PK parameters and geometric means of PK parameters (C_{max} and AUC_{0-12h} C_{trough}) , both actual and dose-normalized (excluding C_{trough}), will be plotted as scatter plots at each glycopyrollate dose using data from both periods combined. The treatment periods will be identified by different symbols. The geometric mean will reflect the mean of all data combined for a given dose level, unless presentation of the Period means is warranted by the data.

Plasma PK parameters, actual and dose normalized, will be presented in data listings and summarized separately and combined for treatment periods 1 and 2 using the PKPAS.

10.4. Pharmacokinetic Statistical Analyses

10.4.1. Dose Proportionality (Power Model)

A non-linear power model will be used to assess dose-proportionality for glycopyrrolate for treatment periods 1 and 2 combined. The proportional relationship between the expected value of each parameter (C_{max} and AUC_{0-12h}) and dose is written as a power function:

log (parameter) = a + b * log (dose)

where ‘a’ is the intercept and ‘b’ is the slope.

A summary table of the parameter estimates (estimates and corresponding standard errors, 90% confidence intervals) obtained from the non-linear power models will be presented for each PK parameter.

If warranted, this analysis may be repeated utilizing Treatment Period 1 data only.

11. Interim Analysis

No interim analysis is planned in this study.

12. Changes in the Planned Analysis

The occurrence of natural disasters during the conduct of this study led to additional data collection from affected sites on the impact on the study. Information collected will be provided in an additional listing.

13. References

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14. Appendices

Table 14-1 Schedule of Study Procedures

Procedure	Screening	Treatment Periods 1 to 4						EOS	Procedures for EW/T	
	Visit 1	Visits 2, 4, 6, and 8 Day 1		Phone Call	Visits 3, 5, 7, and 9 Day 7 (+ 1 day)		Washout	Phone Call Follow-Up	EW/T Visit	Phone Call Follow-Up
	7 to 10 days prior to Visit 2	Pre-dose	Post-dose	Day 6	Pre-dose	Post-dose	7 (+ 2) Days only after Visits 3, 5, and 7	7 (± 1) Days After V9	As Soon as Possible after EW/T	7 (± 1) Days after EW/T Visit
Informed consent	X									
Inclusion/exclusion criteria	X	X[a]								
Rescue medication dispensing[b]	X	X								
Demographics[c]	X									
Medical, surgical, medication, smoking history, drug/alcohol use history	X									
Serum pregnancy hCG test in all women of child-bearing potential	X									
Urine pregnancy test (for WOCBP)		X								
CXR[d]	X									
Nebulizer equipment materials review/training		X								
12-lead ECG[e]	X	X			X				X	
Complete physical exam; height and weight, BMI calculated[f]	X									
Vital signs[g]	X	X	X		X	X			X	

Procedure	Screening	Treatment Periods 1 to 4						EOS	Procedures for EW/T	
	Visit 1	Visits 2, 4, 6, and 8 Day 1		Phone Call	Visits 3, 5, 7, and 9 Day 7 (+ 1 day)		Washout	Phone Call Follow-Up	EW/T Visit	Phone Call Follow-Up
	7 to 10 days prior to Visit 2	Pre-dose	Post-dose	Day 6	Pre-dose	Post-dose	7 (+ 2) Days only after Visits 3, 5, and 7	7 (± 1) Days After V9	As Soon as Possible after EW/T	7 (± 1) Days after EW/T Visit
Laboratory tests[h]	X				X					
Viral serology[i]	X									
Spirometry (measurements of lung function (FEV1 and FVC) and responsiveness testing[j,k]	X	X	X		X	X				
Register in the IRT	X									
Randomized in IRT		X								
In clinic study medication dosing			X[l]			X[l]				
Concomitant medications/therapies	X	X			X			X	X	X
Pharmacokinetic sample collection (Treatment Periods 1 and 2 ONLY)[m]					X	X				
Study medication dispensing and compliance		X			X					
AE and SAE recording[n]	X	X	X		X	X				
Phone call to subject				X[o]						

Note:

a.Check subject's use of concomitant medications, subject's use for prohibited medications, subject's washout compliance, and that there are no clinically relevant changes in health status that, in the opinion of the investigator, would prohibit the subject from completing the Treatment Period.

b. Study rescue medication should be dispensed once the subject has signed the ICF for subjects that require a withholding period prior to Screening (Visit 1).

c. Demographics to include (date of birth, age, gender, race, ethnicity).

d. A posterior-anterior CXR at Screening or within 12 months prior to Screening showing no clinically significant abnormalities unrelated to COPD is required. If a CXR within the past 12 months is not

available but a CT scan within the same time period is available, the CT scan may be reviewed in place of a CXR.

e. ECGs should be obtained before all other simultaneously scheduled procedures are completed.

f. Complete physical exam at Screening: include assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular, abdomen (spleen and liver), lymph nodes and extremities.

g. Vital signs: (pulse rate, blood pressure) will be at Screening, pre-dose, 1 hour and 4 hours post-dose on Days 1 and Day 7, and at Early Withdrawal/Termination Visit.

h. Hematology: WBC with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), RBC, Hg, HCT, and platelet count.

i. The laboratory test to be performed are specified in Table 15-4

j. On Days 1 and 7 of each Treatment Period, spirometry will be conducted (as specified in Table 14-2).

k. Responsiveness testing only conducted at the Screening Visit.

l. In clinic dosing performed after pre-dose spirometry and pre-dose PK sampling in the morning.

m. PK sample collection times on Day 7 of Treatment Periods 1 and 2 are specified in Table 14-3. PK samples should be taken after all concomitantly scheduled assessments (e.g., ECG, FEV1).

n. AEs will be collected Day 1 through the EOS. SAE's related to study participation will be recorded from the time the subject consents until study discharge.

o. Phone call reminder to subjects to remind them to take their evening dose approximately 12 hours prior to the anticipated arrival time to the clinic on Day 7, to note the time of the Day 6 evening dose was taken and to report that time to site staff at the Day 7 visit, to withhold the Day 7 morning dose until at the clinic, to withhold albuterol within 4 hours of their Day 7 visit, to withhold, if applicable, BID LABA ± BID ICS use within 24 hours of their Day 7 visit, and to bring their unused study medication to the clinic visit the next day.

Table 14-2 Schedule of Spirometry and In-Clinic Dosing with Blinded Study Medication

Every effort should be made to initiate spirometry according to these timings:	Day 1 For Each Treatment Period (Visits 2, 4, 6, and 8)	Day 7 For Each Treatment Period (Visits 3, 5, 7, and 9)
Pre-Dose Spirometry	Two separate timepoints within 40 min prior to dosing.	One timepoint approximately 12 hours following the prior evening dose and prior to Day 7 dosing.
Morning Blinded Study Medication Dosing in the Clinic	Time: Between 6 AM and 10 AM.	Time: Between 6 AM and 10 AM.
Post-Dose Serial Spirometry	30 min, 1-, 2-, and 4-hours post-dose.	30 min, 1-, 2-, 4-, 6-, 8-, and 12-hours post-dose. The 12-hour post-dose spirometry should not start prior to 11.5 hours post-dose.

Rescue medications must have been withheld for ≥ 4 hours prior to spirometry and, if applicable, BID LABA ± BID ICS medications must have been withheld for ≥ 12 hours prior to spirometry.

Table 14-3 Schedule of PK and In-Clinic Dosing with Blinded Study Medication

Every effort should be made to initiate spirometry according to these timings:	Day 1 For Each Treatment Period (Visits 2, 4, 6, and 8)
Pre-Dose PK: 1 sample	One timepoint within 30 minutes prior to Day 7 dosing.
Morning Blinded Study Medication Dosing in the Clinic	Time: Between 6 AM and 10 AM.
Post-Dose Serial PK: 9 samples	10 ± 4, 20 ± 4, and 40 ± 4 minutes post-dose and at 1, 1.5, 2, 4, 8, and 12 hours (all later timepoints at ± 15 minutes) post-dose.

Note: PK samples should be taken after all concomitantly scheduled assessments (e.g., ECG, FEV_1).
Abbreviations: ECG = electrocardiogram; FEV_1 = forced expiratory volume in 1 second; PK = pharmacokinetic.

Table 14-4 Protocol Required Laboratory Assessments

Chemistry	**Hematology**	**Viral Serology**
Albumin	Hemoglobin	Hepatitis B Serology (Markers include HBsAg, anti-HBs, anti-HBc, and others)
Alkaline phosphatase	Hematocrit	Hepatitis C virus antibody
Alanine amino transferase (ALT or SGPT)	Platelet count	
Aspartate amino transferase (AST)	WBC count	
Bilirubin, direct	**Leukocyte differential count**	**Other**
Bilirubin, indirect	Neutrophils, absolute	Pregnancy test for WOCBP[1]
Bilirubin, total	Neutrophils, segs (%)	
Calcium	Neutrophils, bands (%)	
Chloride	Basophils (%)	
CO2 content/Bicarbonate	Eosinophils (%)	
Creatinine	Eosinophils, absolute	
Creatine phosphokinase (CK), total	Lymphocytes (%)	
Gamma glutamyl transferase (GGT)	Monocytes (%)	
Glucose	RBC count	
Phosphorus		
Potassium		
Protein, total serum		
Sodium		
Urea nitrogen (BUN)		
Uric Acid		
1 Pregnancy test for women of childbearing potential. A serum pregnancy test will be conducted at Visit 1. A urine pregnancy test will be conducted at the Day 1 visit for each of the Treatment Periods. Abbreviations: anti-HBc = total hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; WOCBP = women of child-bearing potential.		