SUN-101

LONHALA® MAGNAIR® (GLYCOPYRROLATE) INHALATION SOLUTION

Clinical Study Protocol SUN101-402

A Randomized, Double-blind, Placebo-controlled, 2-Way Crossover Study of the Effect of a Single Dose of Glycopyrrolate Inhalation Solution (GIS) on Lung Hyperinflation in Subjects with Chronic Obstructive Pulmonary Disease (COPD)

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EMERGENCY CONTACTS

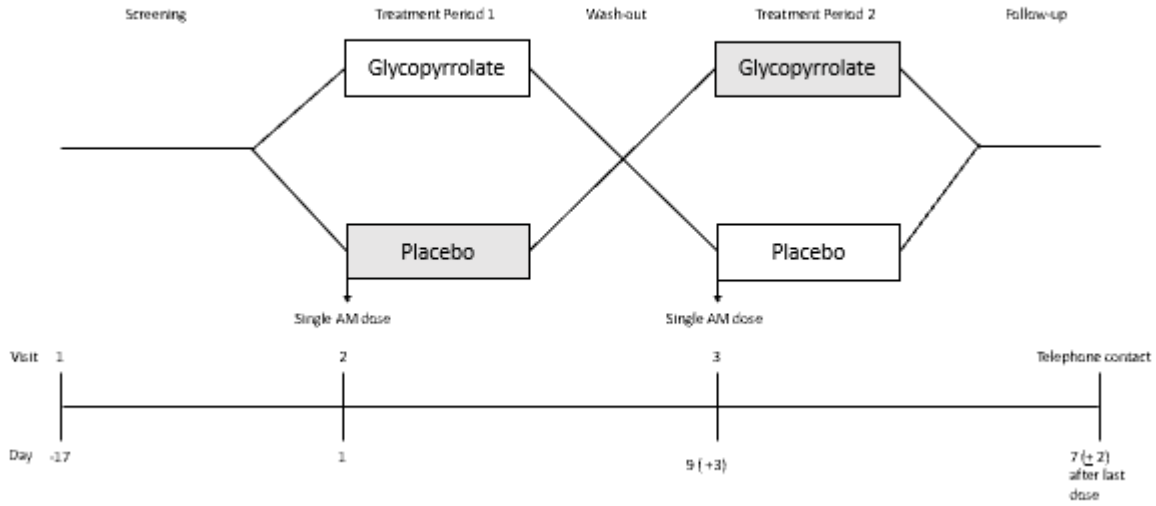
Table 1: Emergency Contact Information

Role in Study	Name	Contact Information
Responsible Physician/ Medical Monitor		Telephone: Email:
SAE/Pregnancy Reporting		Hotline Number: Fax: Email:

1. SYNOPSIS

Name of Sponsor: Sunovion Respiratory Development Inc.
Name of Investigational Product: Lonhala® Magnair®; glycopyrrolate inhalation solution (GIS)
Name of Active Ingredient: Glycopyrrolate
Title of Study: A Randomized, Double-blind, Placebo-controlled, 2-Way, Crossover Study of the Effect of a Single Dose of Glycopyrrolate Inhalation Solution (GIS) on Lung Hyperinflation in Subjects with Chronic Obstructive Pulmonary Disease (COPD)
Proposed Indication: COPD
Study Centers: Single center in the United States
Phase of Development: 4
Study Objectives **Primary Efficacy Objective:** • To compare the efficacy of GIS versus placebo inhalation solution (PIS) on lung hyperinflation following a single dose, as measured by residual volume (RV) at 6 hours postdose. **Other Efficacy Objective:** • To evaluate the effect of a single dose of GIS versus PIS on objective measures of lung function. **Exploratory Objective:** • To evaluate the feasibility of using the accelerateIQ System (ie, the VitalPatch® Biosensor and accelerateIQ Platform).
Study Design: This is a single center, randomized, double-blind, placebo-controlled, single-dose, 2-way crossover study in approximately 20 adult subjects ≥ 40 years of age with COPD. The study is designed to evaluate the effect of a single dose of GIS on lung hyperinflation. The two study treatments, both administered using the Magnair device are: • GIS 25 mcg • PIS The study will consist of a Screening period, a randomized 2-way cross-over treatment period during which subjects will receive two single-doses each separated by a 7-day washout period, and a follow-up 7 (± 2) days after the last study drug dose. A study schematic is provided below.

Study Schematic



GIS = Glycopyrrolate Inhalation Solution
PIS = Placebo Inhalation Solution

Number of Subjects (planned): The study will randomize 10 subjects per treatment sequence, for a total of 20 subjects. At the Sponsor's discretion, additional subjects may be enrolled in an effort to achieve at least 20 completers, with no more than 24 subjects randomized.

Diagnosis and Main Criteria for Subject Inclusion:

Male and female subjects ≥ 40 years of age with a confirmed diagnosis of COPD and smoking history of ≥ 10 pack-years who provide written informed consent are eligible for study participation. Subject has a RV ≥ 130% predicted value at Screening (prior to reversibility testing), and a postbronchodilator (following inhalation of ipratropium bromide) forced expiratory volume in 1 second (FEV1) ≥ 30% and < 80% of predicted normal and FEV1/forced vital capacity (FVC) ratio of < 0.70 at Screening. Subject must also have a score of ≥ 2 on the Modified Medical Research Council Dyspnea Scale (mMRC).

Complete study entry criteria are provided in Section 8.

Investigational Product, Dosage and Mode of Administration:

A single dose of Lonhala 25 mcg will be administered using Magnair.

Additional details are provided in Section 9.1.1.

Duration of Treatment:

Subjects will receive a single dose of GIS and PIS in a crossover manner. The maximum duration of subject participation will be approximately 37 days (up to 17 days Screening, a randomized cross-over treatment period with two single-doses each separated by a 7-day washout, and 7 days post-last dose follow-up).

Reference Therapy, Dosage and Mode of Administration:

A single dose of matching PIS will be administered using Magnair.

Additional details are provided in Section 9.1.1.

Concomitant Medications:

The following concomitant medication restrictions will be employed.

Medication Disallowed for Study Duration	Required Withholding Interval
Albuterol	≥ 6 hours before each study visit, or at any time during study visits
Ipratropium	Study duration, except for reversibility testing at Screening (withhold ≥ 6 hours before reversibility testing)
Ipratropium/albuterol combination	≥ 2 days prior to screening assessments and study duration
Inhaled Corticosteroid/LABA combination	≥ 2 days prior to screening assessments and study duration
Long-acting beta-agonist	≥ 2 days prior to screening assessments and study duration
Long-acting muscarinic antagonist	> 7 days prior to screening assessments and study duration
Leukotriene Inhibitors	> 7 days prior to screening assessments and study duration
Theophylline	> 7 days prior to screening assessments and study duration
PDE-4 inhibitors (eg, roflumilast)	> 14 days prior to screening assessments and study duration

Abbreviations: ICF = Informed Consent Form; ICS = inhaled corticosteroid(s); LABA = long-acting beta agonist; PDE-4 = phosphodiesterase type 4; PFT = pulmonary function test(s)

[a] Subjects taking LABA/ICS or taking ICS monotherapy need to be on a stable dose for at least 4 weeks prior to Screening in order to be eligible for a switch to ICS monotherapy or continuation of ICS monotherapy. This switch can be made at the time the ICF is signed and Screening PFTs can be assessed 48 hours later to allow for the LABA washout.

Criteria for Evaluation:

Primary Efficacy Endpoint

- Change from baseline in RV at 6 hours postdose

Other Efficacy Endpoints

- Standardized change from baseline in RV area under the curve from time 0 to 4 hours postdose (AUC0-4h) and RV area under the curve from time 0 to 6 hours postdose (AUC0-6h)
- Change from baseline in inspiratory capacity (IC) at 6 hours postdose
- Standardized change from baseline in IC AUC0-4h and IC AUC0-6h
- Change from baseline in functional residual capacity (FRC) at 6 hours postdose
- Standardized change from baseline in FRC AUC0-4h and FRC AUC0-6h
- Change from baseline in total lung capacity (TLC) at 6 hours postdose
- Standardized change from baseline in TLC AUC0-4h and TLC AUC0-6h
- Change from baseline in specific airway resistance (sRaw) at 6 hours postdose

- Standardized change from baseline in sRaw AUC0-4h and sRaw AUC0-6h
- Change from baseline in airway resistance (Raw) at 6 hours postdose
- Standardized change from baseline in Raw AUC0-4h and Raw AUC0-6h
- Change from baseline in RV, IC, FRC, TLC, sRaw, and Raw at 1, 2, 3, and 4 hours postdose
- Change from baseline in forced expiratory volume in FEV1 at 6 hours postdose

Safety Endpoints

- Incidence of adverse events, serious adverse events, and adverse events leading to discontinuation

Exploratory Endpoint

- Vital sign data collected at clinic visits and data collected using the accelerateIQ System

Statistical Methods:

General Methodology

The primary efficacy analysis will be based on the modified intention-to-treat (mITT) population, which includes all subjects who are randomized, received at least one dose of study treatment and have a baseline and at least one post-baseline RV measurement within the same period. Should a subject require a rescue medication use during the approximately 6 hours of efficacy endpoint collection, then any efficacy values that occur after the use of the rescue medication will be set to missing in the analysis. The safety population includes all subjects who are randomized and receive at least 1 dose of study medication.

Primary Efficacy Analysis

The primary efficacy estimand is defined as the difference between a single dose of GIS and PIS in the mean change of RV from baseline at 6 hours postdose in COPD patients as characterized by the study inclusion/exclusion criteria, in the hypothetical setting where the subjects were able to stay on study and receive their study drug during their treatment periods.

The change from baseline in RV at 6 hours postdose will be calculated for each treatment period as RV at 6 hours postdose on the day of treatment minus the period baseline of each treatment period. Period baseline is defined as the predose RV value collected 45 minutes prior to the dosing during each treatment period.

For the primary analysis of the primary efficacy endpoint, data will be analyzed using a 2-way crossover analysis of covariance (ANCOVA). The ANCOVA model will include terms for treatment, period and sequence as fixed effects, period baseline as a covariate, and subjects nested within sequence as a random effect. The main estimator of the primary estimand is the Least Squares (LS) mean difference in the change from baseline in RV at 6 hours postdose from the primary ANCOVA model. LS mean (and 95% Confidence Interval [CI]) for each treatment group and LS mean (and 2-sided 95% CI), and the associated p-value for the difference between the single nebulized dose of GIS and PIS will be displayed.

In general, for the primary analysis of the primary efficacy endpoint, missing observations will be treated as missing at random (MAR) and no data imputation will be performed. However, sensitivity analyses may be conducted if there is significant amount of missing data, including missing not at random (MNAR) assumptions.

Supplementary analyses of the primary efficacy endpoint may be conducted as deemed appropriate and details will be provided in the statistical analysis plan (SAP).

Other Efficacy Endpoint Analyses

All other efficacy endpoints will be analyzed using the mITT population.

All other efficacy endpoints will be analyzed using the ANCOVA model similar to the primary efficacy endpoint with appropriate period baseline as a covariate. Additional covariates may be included in select models.

Standardized change from baseline in RV AUC0-4h for each treatment period will be calculated using the trapezoid method from the changes in RV from the period baseline value within each treatment period and dividing by the actual length of the time interval within that treatment period. Changes in RV from period baseline for each time point (1, 2, 3, and 4 hours postdose) will be calculated as the RV values within each treatment minus the period baseline RV for each treatment period. Change in RV from period baseline at time=0 is equal to 0.

Standardized change from baseline in RV AUC0-6h, IC AUC0-4h, IC AUC0-6h, FRC AUC0-4h, FRC AUC0-6h, TLC AUC0-4h, TLC AUC0-6h, sRaw AUC0-4h, sRaw AUC0-6h, Raw AUC0-4h, and Raw AUC0-6h will be calculated similarly.

Changes from baseline in IC, FRC, TLC, sRaw, Raw and FEV1 at 6 hours postdose will be calculated similar to the primary analysis endpoint. All any other postdose lung volume endpoints (RV, IC, FRC, TLC, sRaw and Raw) at 1, 2, 3 and 4 hours postdose will be derived and analyzed similar to the primary endpoint.

Safety Analyses

Adverse events (AEs), serious adverse events (SAEs), and AEs leading to discontinuation during the randomized treatment period will be summarized by counts and percentages of each treatment group. Any AEs occurring during the screening period will only be listed.

Exploratory Endpoint Analyses

Vital sign data collected at clinic visits will be summarized using descriptive statistics. A separate SAP will be created for accelerateIQ System data.

Multiplicity adjustment

No multiple comparison procedures will be employed in this study.

Sample Size: The evaluable sample size for this study was determined by a two-sample t-test (cross-over ANOVA) using nQuery version 4.0 (nQuery + nTerim version 4.0, Statistical Solutions, Cork, Ireland). A sample size of 10 evaluable subjects per treatment sequence, assuming a common standard deviation of 0.4 L, a mean difference of -0.3 L in change from baseline in RV (single dose of GIS compared to PIS), with a one-sided alpha of 0.025, will give a power 88%. Discontinued subjects will not be replaced. At the Sponsor's discretion, additional subjects may be enrolled in an effort to achieve at least 20 completers; however, no more than 24 subjects will be randomized.

Table 2: Schedule of Assessments

Study Period	**Screening[a]**	**Treatment**			**Follow-up/Early Termination[b]**
		Treatment Period 1	**Washout**	**Treatment Period 2 (EOS)**	
Study Visit	**1**	**2**		**3**	**TC/In-clinic**
Study Day	**-17 to -2**	**1**	**2-8**	**9 (+3)**	**7 (± 2) after Last Dose**
Procedure					
Obtain Informed Consent	X				
Review Inclusion and Exclusion Criteria	X				
Review Continuation Criteria[c]		X		X	
Demographics	X				
Medical History	X				
Smoking Status	X				
COPD Exacerbation History (With and Without Hospitalization)	X				
Height and Weight	X				
Modified Medical Research Council Dyspnea Scale (mMRC)[d]	X				
St. Georges Respiratory Questionnaire (SGRQ)	X				
Physical Examination	X				
Vital Signs	X	X[e]		X[e]	
12-lead Electrocardiogram (ECG)	X				
Clinical Laboratory Tests	X				
Pregnancy Test[f]	X			X	X[g]
Begin Washout of Current/Prohibited Medications	X				
Dispense rescue medication (if needed)	X				
Dispense inhaled corticosteroid (if needed)[h]	X				
Plethysmography	X[i]	X[j]		X[j]	
Spirometry	X[i]	X[k]		X[k]	
Observe subject administer placebo via Magnair Nebulizer System[l]	X				
Apply VitalPatch Biosensor[m]	X	X		X	
Randomize Subject		X			
Administer Study Drug in clinic		X		X[n]	
Prior/Concomitant Medication Review	X	X		X	X
Record Pretreatment Events	X	X			
Record Adverse Events	X	X		X	X
Schedule Next Visit	X	X		X	

Abbreviations: COPD = chronic obstructive pulmonary disease; EOS = End of Study; ET = Early Termination; ICS = inhaled corticosteroid; LABA = long-acting bronchodilator; NA = Not applicable; TC = telephone contact

[a] Screening procedures will occur over multiple days. Screening assessments will be performed after informed consent and after applicable wash-out has been completed.

[b] Subjects who discontinue prior to completion of Day 9 will undergo Early Termination procedures and assessments at the time of discontinuation. Female subjects of childbearing potential who were dosed will return to the clinic for a serum pregnancy test and final safety assessments 7 (± 2) days after their last study drug dose. All other dosed subjects will either be contacted by telephone or have an in-clinic visit if deemed clinically warranted by the Investigator 7 (± 2) days after their last study drug dose for a final safety assessment (adverse events and concomitant medication use).

[c] Continuation criteria includes ensuring that the subject has not had an exacerbation of COPD, the subject has completed the 7-day washout period and continues to withhold disallowed medications, and in the opinion of the Investigator, the subject has not had any change that would put the safety of the subject at risk through participation.

[d] The mMRC should be performed prior to any other assessments.

[e] Vital signs will be collected 45 (± 15) minutes prior to dosing and 60 (± 15) minutes postdose. Vital signs will be collected prior to plethysmography and spirometry when collection times coincide.

[f] Serum pregnancy test will be performed for female subjects of child-bearing potential at Visit 1 and at Follow-up/Early Termination. Urine pregnancy test will be performed for female subjects of child-bearing potential at Visit 3.

[g] Female subjects of childbearing potential will return to the clinic for a serum pregnancy test.

[h] COPD subjects who washout of LABA/ICS must switch to ICS monotherapy that is equivalent to that contained in the LABA/ICS.

[i] Screening plethysmography and spirometry will be performed prior to and 30-60 minutes (and no later than 2 hours) following 68 mcg ipratropium MDI (4 puffs of 17 mcg per actuation). Plethysmography will be performed first, followed immediately by spirometry.

[j] Serial plethysmography will be performed 45 minutes predose and again at 1, 2, 3, 4, and 6 hours postdose. At each time point, plethysmography assessments will have a window of ± 15 minutes. Plethysmography will be performed prior to spirometry when timepoints coincide.

[k] Spirometry will be performed 45 minutes predose and again 6 hours postdose after plethysmography. At each time point, spirometry assessments will have a window of ± 15 minutes.

[l] Subjects will administer placebo via the Magnair Nebulizer System for training purposes to ensure that they are able to use the device. Subjects unable to use the Magnair Nebulizer System will be excluded from study participation.

[m] The VitalPatch Biosensor will be applied to subjects who provide additional informed consent for this assessment. If the subject meets the screening criteria, the site will apply the VitalPatch Biosensor, which will be worn for up to 5 consecutive days. The subject will apply a new patch to be worn for up to 5 consecutive days. The VitalPatch Biosensor will be worn until the safety follow-up visit.

[n] Study drug administration during Treatment Period 2 will be administered between approximately 6:00 – 10:00 AM and within 1 hour of Treatment Period 1 dosing.

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The abbreviations and the definition of key study terms used in the clinical study protocol are shown in Table 3 and Table 4.

Table 3: List of Abbreviations

Abbreviation	Full Form
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
$AUC_{0\text{-}x\ hr}$	Area under the curve from time zero to x hours postdose
CAP	College of American Pathologists
CFR	Code of Federal Regulations
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CRF	Case report form
CRO	Contract research organization
CTM	Clinical trial material
ECG	Electrocardiogram
EDC	Electronic data capture
EOS	End of study
ET	Early Termination
FDA	U.S. Food and Drug Administration
FEV_1	Forced expiratory volume in one second
FRC	Functional residual capacity
FVC	Forced vital capacity
GCP	Good Clinical Practice
GIS	Glycopyrrolate inhalation solution
GOLD	The Global Initiative for Chronic Obstructive Lung Disease
IC	Inspiratory capacity
ICF	Informed consent form
ICH	International Council for Harmonization
ICS	Inhaled corticosteroid
IPD	Important protocol deviation

Table 3: List of Abbreviations (Continued)

Abbreviation	Full Form
IRB	Institutional Review Board
LABA	Long-acting beta$_2$-agonists
LABD	Long-acting bronchodilator
LAMA	Long-acting muscarinic agent
LDPE	Low-density polyethylene
MAR	Missing at random
mcg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intention-to-Treat
mMRC	Modified Medical Research Council Dyspnea Scale
MNAR	Missing not at random
PFT	Pulmonary function tests
POC	Point of care
PIS	Placebo inhalation solution
PT	Preferred term
PVG	Pharmacovigilance
Q1	Quartile 1
Q3	Quartile 3
RV	Residual volume
Raw	Airway resistance
SAP	Statistical Analysis Plan
SD	Standard deviation
SAE	Serious adverse event
SGRQ	St. George's Respiratory Questionnaire
SOC	System organ class
sRAW	Specific airway resistance
TLC	Total lung capacity
WBC	White blood cells
WHO-DD	World Health Organization Drug Dictionary

Table 4: Definition of Key Study Terms

Terms	Definition of terms
CRF	A printed, optical, or electronic document designed to record all of the protocol required information to report to the Sponsor for each study subject.
Screened Subject	Any subject who signed the study specific informed consent and completed at least one study related procedure.
Screen Failures	Any subject who signed the study specific informed consent but either failed to meet study requirements during screening or met study requirements at screening but was not enrolled/randomized.
Study Drug (or Study medication)	Term to cover investigational drug and placebo.
Treatment Period	The period of the study in which the study drug is administered.
Randomized Subject	Any subject who was randomized into a treatment sequence of the study and was assigned a randomization number.
Enrolled Subject	Any subject who was successfully screened and enrolled into the pre-randomization period of the study.
Randomization Failures	Any subject who was enrolled but not randomized.
Completed Subject	Any subject who participated throughout the duration of Day 9.
Early Termination Subject	Any subject who was successfully screened and randomized to a treatment sequence, but did not complete both treatments during the randomized treatment period.
End of Treatment	The day that the subject receives the protocol-defined last dose of study drug.
End of Study	The day that the subject completes the study per the study design.

4. INTRODUCTION

4.1. Background

Chronic obstructive pulmonary disease (COPD) is the major component of chronic lower respiratory diseases, which is the fourth leading cause of death in the United States (Kochanek 2016). In addition to mortality COPD also places a large economic burden in the US with direct and indirect cost estimated to be about $52 billion (Guarascio 2013). COPD is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities (GOLD 2019). The main risk factor for COPD is tobacco smoking. Lung hyperinflation (LH) which is defined by an abnormal increase of the volume of gas in the lungs and airways at the end of tidal expiration (Rossi 2015) is another important aspect of COPD that has major clinical consequences (Langer 2014, Thomas 2013). LH plays a central role in the pathophysiology of dyspnea and exercise limitation in COPD and has been shown to be an independent predictor of exacerbations (Chen 2016, Rossi 2015). It has also been linked to impairment of cardiac function by potentially causing by causing increased pressures in the cardiopulmonary system, right-ventricular dysfunction, impaired left-ventricular filling and reduced cardiac output (Hohfeld 2018, Rabe 2018).

Long-acting antimuscarinic antagonists (LAMAs) and long-acting beta$_2$-agonists (LABAs) are central to the long-term maintenance treatment of symptoms in COPD (GOLD 2019). Several studies have demonstrated the benefits of long-acting bronchodilators delivered via dry powder inhalers on lung deflation (Hohfeld 2018, Fujimoto 2017, Watz 2017, Santus 2015, Beeh 2011). Lonhala Magnair is the first approved nebulized LAMA (glycopyrrolate) for the treatment of COPD in the US (Lonhala Magnair product labeling) which allows the investigation of a nebulized LAMA on LH in patients with COPD.

4.2. Study Conduct Rationale

Glycopyrrolate inhalation solution (GIS; Lonhala Magnair) is a nebulized long-acting antimuscarinic antagonist (LAMA) indicated for the long-term maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema. COPD is characterized by expiratory flow limitation, resulting in air trapping and lung hyperinflation. Hyperinflation is the increased volume of air remaining in the lung at the end of spontaneous expirations. Lung hyperinflation is a major contributor to dyspnea in patients with COPD (Laveneziana 2012). Studies in COPD have shown that long-acting bronchodilators (LABD) administered with hand-held devices reduce hyperinflation. It has been hypothesized that distal penetration of LABD administered by nebulization will have a positive impact on hyperinflation irrespective of disease severity (Loh 2015). The Magnair device is a closed system nebulizer using the eFlow technology which generates a soft aerosol mist of the drug solution with a droplet size distribution and acceptable respirable fraction suitable for peripheral lung deposition.

This study will provide information on the effects of a single dose of GIS on lung hyperinflation over 6 hours in COPD subjects with hyperinflation.

4.3. Risk-Benefit Assessment

Lonhala Magnair is indicated for the long-term maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. The recommended dose of LONHALA is the inhalation of the contents of one LONHALA vial (25 mcg) twice-daily using MAGNAIR.

4.4. Hypothesis

In adults with COPD subjects as characterized by the study inclusion/exclusion criteria, after 2 cross-over periods of treatment, the primary null hypothesis for this study is that the mean change of RV from baseline at 6 hours postdose for a single dose of GIS is equal to the mean change of RV from baseline at 6 hours postdose for a single dose of placebo inhalation solution (PIS). The alternative hypothesis is that these means are different.

5. STUDY OBJECTIVES

5.1. Primary Objective

- To compare the efficacy of GIS versus PIS on lung hyperinflation following a single dose, as measured by residual volume (RV) at 6 hours postdose.

5.2. Other Efficacy Objective

- To evaluate the effect of a single dose of GIS versus PIS on objective measures of lung function.

5.3. Exploratory Objective

- To evaluate the feasibility of using the accelerateIQ System (ie, the VitalPatch® Biosensor and accelerateIQ Platform).

6. STUDY ENDPOINTS

6.1. Primary Efficacy Endpoint

- Change from baseline in RV at 6 hours postdose

6.2. Other Efficacy Endpoints

- Standardized change from baseline in RV area under the curve from time 0 to 4 hours postdose (AUC0-4h) and RV area under the curve from time 0 to 6 hours postdose (AUC0-6h)
- Change from baseline in inspiratory capacity (IC) at 6 hours postdose
- Standardized change from baseline in IC AUC0-4h and IC AUC0-6h
- Change from baseline in functional residual capacity (FRC) at 6 hours postdose
- Standardized change from baseline in FRC AUC0-4h and FRC AUC0-6h
- Change from baseline in total lung capacity (TLC) at 6 hours postdose
- Standardized change from baseline in TLC AUC0-4 h and TLC AUC0-6h
- Change from baseline in specific airway resistance (sRaw) at 6 hours postdose
- Standardized change from baseline in specific Airway Resistance (sRAW) AUC0-4h and sRaw AUC0-6h
- Change from baseline in airway resistance (Raw) at 6 hours postdose
- Standardized change from baseline in Raw AUC0-4h and Raw AUC0-6h
- Change from baseline in RV, IC, FRC, TLC, sRaw, and Raw at 1, 2, 3, and 4 hours postdose
- Change from baseline in forced expiratory volume in 1 second (FEV1) at 6 hours postdose

6.3. Safety Endpoints

- Incidence of adverse events, serious adverse events, and adverse events leading to discontinuation

6.4. Exploratory Endpoint

- Vital sign data collected at clinic visits and data collected using the accelerateIQ System

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

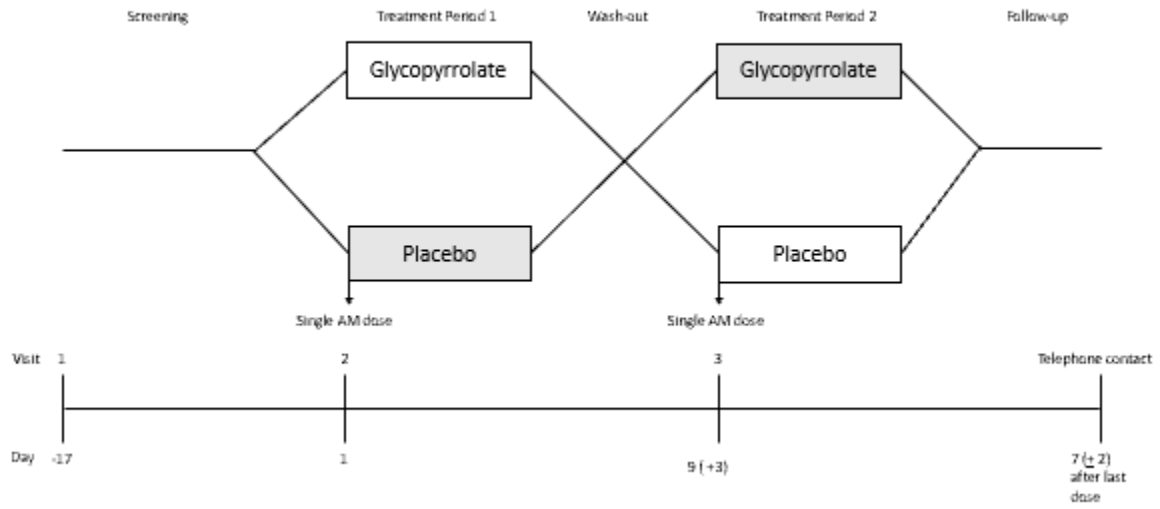
This is a single center, randomized, double-blind, placebo-controlled, single-dose 2-way crossover study in approximately 20 adult subjects ≥ 40 years of age with COPD. The study is designed to evaluate the effect of a single dose of GIS on lung hyperinflation. The two study treatments, both administered using the Magnair device are:

- GIS 25 mcg
- PIS

The study will consist of a Screening period, a randomized 2-way cross-over treatment period during which subjects will receive two single-doses each separated by a 7-day washout period, and a follow-up 7 (± 2) days after the last study drug dose.

A study schematic is provided in Figure 1, and detailed descriptions and timing of assessments is provided in Section 11.

Figure 1: Study Schematic



GIS = Glycopyrrolate Inhalation Solution

PIS = Placebo Inhalation Solution

Visit 1 - Screening (Days -17 to -2)

Written informed consent will be obtained from subjects before any study procedures are performed. Screening visit procedures are outlined in Table 2. Screening (Visit 1) may occur over more than one clinic visit and may last up to 17 days in order to determine study eligibility and to allow for appropriate washout of prohibited medications.

If needed, subjects will be dispensed albuterol as rescue medication at the Screening visit (Visit 1). Subjects who are required to switch from taking LABA/inhaled corticosteroid (ICS) to ICS monotherapy will be provided with an ICS.

Visit 2 – Treatment Period 1 (Day 1)

Subjects will return to the clinical site in the morning on Day 1. Subjects who continue to meet the study eligibility criteria will be randomized to 1 of 2 crossover treatment sequences with a 1:1 allocation ratio. A single dose of study drug will be administered by the clinical staff between approximately 6:00 – 10:00 AM on Day 1 according to the randomization schedule. In order to maintain the blind during study drug administration, an unblinded clinical site staff member will perform the randomization and prepare and administer the study drug according to the randomization schedule. The unblinded study personnel will not perform any other study procedures.

Lung volume measures (plethysmography) will be performed 45 minutes prior to administration of study drug dose on Day 1, and at 1, 2, 3, 4, and 6 hours postdose. Spirometry measures will be performed 45 minutes prior to administration of study drug and again 6 hours postdose. At both timepoints, spirometry will be performed after plethysmography. At each time point, plethysmography and spirometry assessments will have a window of ± 15 minutes. Additional study procedures identified in Table 2 will be completed at this visit.

There will be a wash-out period of 7 (+ 2) days after dosing on Day 1.

Visit 3 – Treatment Period 2/End of Study (EOS): (Day 9 [+3])

Subjects will return to the clinical site in the morning on Day 9 (+ 3) for Treatment Period 2. Subjects who continue to meet the study eligibility criteria will have a single dose of study drug administered by the clinical staff between 6:00 – 10:00 AM (and within 1 hour of Treatment Period 1 dosing time) according to the treatment sequence assigned.

Lung volume measures (plethysmography) will be performed at 45 minutes prior to administration of study drug dose on Day 9, and at 1, 2, 3, 4, and 6 hours postdose. Spirometry measures will be performed 45 minutes prior to dosing and again 6 hours postdose. At both timepoints, spirometry will be performed after plethysmography. At each time point, plethysmography and spirometry assessments will have a window of ± 15 minutes. Additional study procedures identified in Table 2 will be completed at this visit.

Subjects who discontinue prior to completion of Day 9 will undergo Early Termination procedures and assessments at the time of discontinuation.

Follow-up

Female subjects of childbearing potential who were dosed will return to the clinic for a serum pregnancy test and final safety assessments 7 (± 2) days after their last study drug dose. All other dosed subjects will either be contacted by telephone or have an in-clinic visit if deemed clinically warranted by the Investigator 7 (± 2) days after their last study drug dose for a final safety assessment (adverse events and concomitant medication use).

7.2. Treatment Assignment and Blinding

After a subject provides written informed consent, a unique subject number will be assigned at screening, consisting of a 3-digit protocol number, 3-digit site number, and a unique 3-digit subject identifier (eg, the second screened subject from site 001 will be 402001002). Subjects will be numbered consecutively beginning with 001. No subject numbers are to be reused once assigned. This number will track a subject throughout their participation in the study.

Subjects who passed study entry criteria and did not get randomized can be rescreened once to determine eligibility. Subjects who are rescreened must be assigned a new screening number.

7.2.1. Treatment Assignment

The randomization schedule, a sequential list consisting of the randomization numbers and their corresponding treatment sequence assignment, will be generated by a non-study biostatistician according to the process defined by the Sponsor/contract research organization (CRO)'s standard operating procedure (SOP).

Once a subject is deemed eligible to be randomized at Day 1 / Visit 2 and prior to dosing, all eligible subjects will be given a randomization number by the unblinded clinical staff member that assigns them to one of the two treatment sequences. Subjects will be randomized to one of the two following treatment sequences in a 1:1 ratio:

- Treatment sequence A→B (10 subjects): Single dose of GIS 25 mcg (Treatment A) to matching PIS (Treatment B).
- Treatment sequence B→A (10 subjects): Matching PIS (Treatment B) to single dose of GIS 25 mcg (Treatment A).

Between each treatment sequence, subjects will undergo a washout period before returning to the clinic for the corresponding next treatment.

Randomization numbers will be assigned sequentially in the order the subject becomes eligible to participate in the study. Once a randomization number is assigned, it cannot be reused.

7.2.2. Blinding

This is a double-blind study.

During the conduct of the study, in order to maintain the blind during the time of study drug administration, up until the analysis is conducted, an unblinded clinical staff member will perform the randomization and prepare and administer the study drug according to the randomization schedule. The unblinded study personnel will not perform any other blinded study procedures. All study drugs will be dispensed according to the randomization schedule to be supplied by Sponsor's representative, using a written study drug dispensing procedure that will assure that subjects remain blinded to the treatment being administered.

An unblinded clinical staff member will prepare and quality check each dose for each subject as instructed in the pharmacy manual according to the randomization schedule and other applicable local regulations as set forth in the protocol.

Subjects, Investigator staff, persons performing the assessments, clinical operations personnel, data analysts, and personnel at the laboratory will remain blinded to the identity of the treatment

from the time of randomization until database lock and unblinding, using the following method: randomization data are kept strictly confidential (eg, sealed envelopes kept in a locked filing cabinet or placed in a safe at the study center and the randomization schedule created by the randomization administrator are kept in a secure location with restricted access) until the time of unblinding, and will not be accessible by anyone else involved in the treatment study with the exception of the Sponsor's clinical trials materials manager.

Details of blinding will be provided in the pharmacy manual.

7.2.3. Emergency Unblinding Procedures

For emergency unblinding purposes, the Investigator will be provided with a sealed envelope for each subject. The cover sheet of the envelope will contain the protocol number and individual subject randomization number. Inside, this envelope will contain information about the investigational product given to the subject according to the treatment schedule. The envelope may only be opened in the case of emergency when knowledge of the treatment is needed to treat the subject. Date and reason for unblinding are to be documented on the envelope and the case report form (CRF). In the case of unblinding, the Investigator has to withdraw the subject from further study participation. These individual subject envelopes should be stored in a secure location and returned to the Sponsor/CRO, at the end of study.

7.3. Rationale

7.3.1. Rationale for the Study Design

The study was designed to evaluate the effect of a single dose of Lonhala Magnair on lung hyperinflation, as measured by RV, as compared with placebo. The crossover design allows for subjects to serve as their own control.

7.3.2. Rationale for the Dosages

The labeled dose for Lonhala Magnair will be utilized in this study. Results of this study will provide information on the effect of a nebulized LAMA on lung hyperinflation following a single dose.

7.3.3. Rationale for the Study Population

In order to enrich the subjects with hyperinflation, a cutoff value of RV ≥ 130% predicted will be selected for this study. Patients with an RV ≥ 130% predicted are considered to be hyperinflated.

7.3.4. Rationale for the Endpoints

Residual volume was selected because it has been shown to demonstrate the most consistent physiological improvement following acute bronchodilator therapy across The Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages.

7.4. Prevention of Missing Data

In an effort to minimize the number of subjects who are terminated from the study prior to study completion, the following study design and conduct elements are implemented: eg, (i) use of a single study center with an established history of enrolling and following eligible subjects with

chronic respiratory diseases, (ii) use of a study center with experience in conducting plethysmography and spirometry assessments, (iii) train the study center on the importance of continued follow-up and on the informed consent process, ensuring subjects understand the commitment they are making, including the intent to complete the trial, and, (iv) monitor data collection via on-site and/or centralized monitoring for adherence during the study, and (vi) rescue medication will be permitted during the study as indicated in Table 6.

Please see Section 15.3 for statistical considerations related to missing data.

8. SELECTION OF SUBJECTS

8.1. Subject Inclusion Criteria

Subjects who fulfill the following criteria will be included in the study:

1. Subject is male or female and ≥ 40 years of age at Screening with a confirmed diagnosis of COPD.
2. Subject must have the ability to comprehend the informed consent form and be willing to provide informed consent.
3. Subject must possess an educational level and degree of understanding of English that enables them to communicate suitably with the Investigator and the study coordinator.
4. Subject has a postbronchodilator (following inhalation of ipratropium bromide) FEV1 ≥ 30% and < 80% of predicted normal at Screening.
5. Subject has a postbronchodilator (following inhalation of ipratropium bromide) FEV1/FVC ratio of < 0.70 at Screening.
6. Subject has a RV ≥ 130% predicted value at Screening (prior to reversibility testing).
7. Subject is a current or former smoker with at least 10 pack-years of cigarette smoking history at Screening.
8. Subject has a score of ≥ 2 on the Modified Medical Research Council Dyspnea Scale (mMRC) at Screening.
9. Subject, if female of child bearing potential, must have a negative serum pregnancy test at Screening. Females of childbearing potential must be instructed to and agree to avoid pregnancy during the study and must use an acceptable method of birth control: a) an oral contraceptive, an intrauterine device (IUD), implantable contraceptive, transdermal or injectable contraceptive for at least 30 days prior to entering the study with continued use throughout the study and for thirty days following participation; b) barrier method of contraception, eg, condom and /or diaphragm with spermicide while participating in the study; and/or c) abstinence. A follicle stimulating hormone (FSH) test will be used to confirm menopause in postmenopausal females.
10. Subject is willing and able to attend all study visits and adhere to all study assessments and procedures.

8.2. Subject Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from study participation:

1. Subject is female who is pregnant or lactating or are planning on becoming pregnant during the study.
2. Subject has a history of asthma.
3. Subject has a blood eosinophil count > 5% of total white blood cell count.
4. Subject has life-threatening/unstable respiratory status, including upper or lower respiratory tract infection, within the previous 30 days prior to Screening.

5. Recent history of COPD exacerbation requiring hospitalization or need for increased treatments for COPD within 12 weeks prior to Screening.
6. Use of daily oxygen therapy > 12 hours per day.
7. Subject is unable to perform plethysmography.
8. Subject is unable to use the Magnair Nebulizer System.
9. Subject has history of narrow angle glaucoma.
10. Subject has history of or clinically significant ongoing bladder outflow obstruction or history of catheterization for relief of bladder outflow obstruction within the previous 6 months prior to screening.
11. Subject has history of long QT syndrome.
12. Subject has a QTcF > 450 msec (males) or > 470 msec (females) at Screening, unless discussed with and approved by the Medical Monitor.
13. Subject has a cardiac implanted device (internal defibrillator, pacemaker).
14. Current severe heart failure (New York Heart Association Class IV) [New York Heart Association, 1994].
15. Subject has history of malignancies within the past 5 years, with the exception of basal cell carcinoma.
16. Subject has known comorbidities including unstable cardiac, pulmonary, or psychiatric disease, or any other medical conditions that would, in the opinion of the Investigator, preclude the subject from safely completing the required tests or the study, or is likely to result in disease progression that would require withdrawal of the subject.
17. Subject has participated in another investigational drug study (within 30 days prior to Screening).
18. Subjects who are study site staff members or relatives of study site staff members.
19. Subjects with a history of allergic reaction to glycopyrrolate, tiotropium, albuterol, or any components of the study medications.
20. Subjects with a known allergy to hydrocolloid gel adhesive are excluded from wearing the VitalPatch Biosensor.

8.3. Continuation Criteria

- Subject has not had an exacerbation of COPD.
- Subject completes the 7-day washout period and continues to withhold restricted medications.
- In the opinion of the Investigator, the subject has not had any change that would put the safety of the subject at risk through participation.

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Description of Study Drug

9.1.1. Glycopyrrolate and Placebo

Glycopyrrolate and placebo will be provided as solution for inhalation via nebulization (see Table 5).

Glycopyrrolate will be provided as Glycopyrrolate inhalation solution (commercially available Lonhala Magnair Inhalation Solution).

Table 5: Investigational Product

Attribute	Investigational Product	
Product name	Glycopyrrolate	Placebo
Dosage form	Inhalation solution	Inhalation solution
Unit dose	25 mcg	NA
Route of administration	eFlow Closed System Nebulizer	eFlow Closed System Nebulizer
Physical description	Each single use vial contains l mL of clear, colorless, sterile, preservative-free aqueous solution	Each single use vial contains l mL of clear, colorless, sterile, preservative-free aqueous solution

9.1.2. Albuterol

Albuterol HFA will be used as rescue medication on an as-needed basis during the study and will be provided by the site.

9.1.3. Ipratropium

Ipratropium bromide metered dose inhaler (MDI) will be used for reversibility testing at Screening and will be provided by the site.

9.1.4. Inhaled Corticosteroid

An inhaled corticosteroid will be provided by the site to subjects switching from a long-acting $beta_2$ agonist (LABA)/inhaled corticosteroid (ICS) to ICS monotherapy.

Subjects taking LABA/ICS or taking ICS monotherapy need to be on a stable dose for at least 4 weeks prior to Screening in order to be eligible for a switch to ICS monotherapy or continuation of ICS monotherapy. This switch can be made at the time the informed consent form (ICF) is signed and Screening pulmonary function tests (PFTs) can be assessed 48 hours later to allow for the LABA washout.

9.2. Study Drug Packaging and Labeling

A sponsor designee will label, package, and/or ship the appropriate clinical trial material (CTM; including, but not limited to Investigational Medicinal Product (IMP)/Non-Investigational Medicinal Product (NIMP), nebulizers, ancillary supplies, etc.) to the sites.

9.2.1. Package Description

The Glycopyrrolate (Lonhala) will be provided in its commercial packaging (refer to packaging insert). Each carton will include 30 pouches containing 2 unit dose vials each. There will be a clinical label present for accountability purposes. Secondary labeling will be performed by a sponsor designee and will comply with 21 Code of Federal Regulations (CFR) Part 312.6.

Placebo (manufactured at Holopack GmbH, Germany) is supplied in a unit dose low-density polyethylene (LDPE) drug vial. There are 2 vials per foil laminate pouch. There will be a weekly carton containing 9 pouches and a monthly carton containing 30 pouches.

Magnair nebulizer will consist of the approved commercial packaging. Each carton will be clinically labeled.

9.2.2. Labeling Description

All packaging for the study medications may be labeled with:

- Protocol number
- Sponsor’s name and address
- Compound/Code or name of investigational drug (if needed)
- Content (eg number of tablets, strength)
- Caution Statement (as needed)
- Instructions for use and storage
- Blank space for study center number and date opened (if needed)
- Lot number
- Randomization number (if needed)
- Expiration date (if needed)
- Visit number (if needed)
- Unique medication number (if needed)
- Space for subject identifiers (if needed)
- Investigator information (if needed)
- Child proof (if needed)

9.3. Study Drug Storage

Glycopyrrolate and its matching placebo should be stored in the protective foil pouch at 20°-25°C (68°-77°F). After opening the foil pouch, unused unit-dose vials should be returned to, and stored in, the foil pouch. The Investigator or designee is required to return all unused study drug to the Sponsor or designee as instructed. An opened unit-dose vial should be used right away. Empty vials should be returned to their original pouch after dosing. Do not use any unit-dose vial if the solution is not colorless.

9.4. Dispensing of Study Drug

Investigational product should be maintained under the strict control of qualified site staff at all times. Appropriate guidelines should be followed in proper dispensation to the study participant. Proper handling and storage should be followed. This is outlined in the Pharmacy Manual or Appendices supplied to the site. Sponsor-defined dispensing guidelines should be followed for dispensing IP to the subject, in addition to all accountability records where required.

Proper accountability records must be maintained and up to date capturing all drug dispensing activities.

9.5. Study Drug Accountability

The Investigator or designee is responsible for storing the drug in a secure location and for maintaining adequate records of drug disposition that includes the dates, quantity, and use by subjects. If the study is stopped for any reason or completed, all unused supplies of drug will be returned to the Sponsor, unless other instructions are provided in writing by Sponsor/CRO.

To avoid the situation where any expired study drug is dispensed and used, the Sponsor should retrieve all study drug before expiration date. If the study drug is not returned/retrieved from the site before the expiration date, the Investigator or designee should store the expired study drug separately.

9.6. Study Drug Handling and Disposal

A drug inventory record will be supplied from Sponsor/CRO. The Investigator or designee on an ongoing basis must maintain a drug inventory record of supplied, received, dispensed, and returned medication. The Investigator or designee is required to return all unused study drug to the Sponsor or designee as instructed. The Investigator or designee is required to maintain copies of medication shipping receipts, drug accountability records, and records of return or final disposal of the study drug in accordance with local regulatory requirements.

10. TREATMENT OF SUBJECTS

10.1. Study Medication

The glycopyrrolate dose will consist of 25 mcg of oral inhalation solution per vial. Glycopyrrolate doses will be administered via the Magnair Nebulizer System. A single dose will be administered by clinical staff between approximately 6:00 – 10:00 AM on Day 1 or Day 9 according to the randomization schedule.

The placebo dose will consist of 0 mcg of oral inhalation solution per vial. Placebo doses will be administered via the Magnair Nebulizer System. A single dose will be administered by clinical staff between approximately 6:00 – 10:00 AM on Day 1 or Day 9 according to the randomization schedule.

The site will observe the subject administer a dose of placebo via Magnair Nebulizer System during the screening visit to ensure the subject is able to use the device.

10.2. Treatment Compliance

All single-dose treatments will be administered under supervision in the clinic. The Investigator will record the date of dose administration.

10.3. Concomitant Medications and Therapies

The following information on all medication administered between Visit 1 (including medications taken within 30 days prior to Visit 1) and Follow-up or at discontinuation will be recorded on the CRF: Medication name, dose, frequency, route, start date, stop date, and indication.

Information regarding format and version of coding dictionary is provided in the Data Management Plan (DMP). All medications will be coded using World Health Organization Drug Dictionary (WHO-DD).

The following restrictions will be employed.

Table 6: Current COPD Medication Withhold Intervals

Medications Disallowed for Study Duration	Required Withholding Interval
Albuterol	≥ 6 hours before each study visit, or at any time during study visits
Ipratropium	Study duration, except for reversibility testing at Screening (withhold ≥ 6 hours before reversibility testing
Ipratropium/albuterol combination	≥ 2 days prior to screening assessments and study duration
Inhaled Corticosteroid/LABA combination[a]	≥ 2 days prior to screening assessments and study duration
Long-acting beta-agonist	≥ 2 days prior to screening assessments and study duration

Table 6: Current COPD Medication Withhold Intervals (Continued)

Medications Disallowed for Study Duration	Required Withholding Interval
Long-acting muscarinic antagonist	> 7 days prior to screening assessments and study duration
Leukotriene Inhibitors	> 7 days prior to screening assessments and study duration
Theophylline	> 7 days prior to screening assessments and study duration
PDE-4 inhibitors (eg, roflumilast)	> 14 days prior to screening assessments and study duration

Abbreviations: ICF = Informed Consent Form; ICS = inhaled corticosteroid(s); LABA = long-acting beta agonist; PDE-4 = phosphodiesterase type 4; PFT = pulmonary function test(s)

[a] Subjects taking LABA/ICS or taking ICS monotherapy need to be on a stable dose for at least 4 weeks prior to Screening in order to be eligible for a switch to ICS monotherapy or continuation of ICS monotherapy. This switch can be made at the time the ICF is signed and Screening PFTs can be assessed 48 hours later to allow for the LABA washout.

Albuterol HFA will be provided and permitted as rescue medication for as needed use any time during the study. Albuterol must be withheld prior to each study visit for at least 6 hours, and for the duration of each study visit, unless medically necessary. If rescue albuterol is used within 6 hours prior to plethysmography and spirometry testing at any study visit, then the visit must be rescheduled or delayed to allow the appropriate washout. If rescue albuterol is required post-dose at any study visit, plethysmography and spirometry assessments will be continued as scheduled.

10.4. Contraception Requirements

For female subjects

1. Female subject < 65 years-old and of child-bearing potential must be using and willing to continue using a medically acceptable form of birth control for at least 4 weeks prior to study drug administration and for at least 30 days after the last study drug administration. Medically acceptable forms of contraception include oral or patch hormonal contraceptives, intrauterine device, progestin implant or injection, bilateral tubal ligation, or double-barrier (i.e., male condom in addition to a diaphragm or a contraceptive sponge). Women using hormonal contraception must use an additional form of contraception.
2. A female subject is eligible to enter and participate in the study if she is of:
    a. Non-childbearing potential (ie, physiologically incapable of becoming pregnant, including any female who is pre-menarchal or post-menopausal);
        - Postmenopausal females defined as being amenorrheic for greater than two years with an appropriate clinical profile.
        - Women who have not been confirmed as postmenopausal should be advised to use contraception as outlined below.
        - Women who have had a hysterectomy, bilateral oophorectomy or bilateral salpingectomy (as determined by subject's medical history).

b. Child-bearing potential (all females ≤ 65 years of age), has a negative pregnancy test at screening and agrees to satisfy one of the following requirements:

- Complete abstinence from intercourse (as part of an abstinent lifestyle) a minimum of 4 weeks prior to administration of the first dose of study drug, throughout the Treatment Period, and for a minimum of 30 days following last study drug administration,
- Established use of acceptable methods of contraception a minimum of 4 weeks prior to administration of the first dose of study drug, throughout the Treatment Period, and for a minimum of 30 days following last study drug administration.
- Acceptable methods of birth control are listed below:
  - Sterilization (vasectomy) of male partner prior to commencement of female subject's last normal menstrual period prior to administration of the first dose of study drug, and the male partner is the sole partner for that female subject; or
  - Implants of levonorgestrel; injectable progesterone; or hormonal contraceptive (combined or progestogen only) (must have been taking reliably through at least one full menstrual cycle period). Subjects using implants, injectable, or hormonal contraceptives must use additional methods of contraception for the duration of the study ; or
  - Documented placement of an intrauterine device (IUD) with published data showing that the highest expected failure rate is less than 1% per year (not all IUDs meet this criterion); or
- Any other method of contraception with data documented in the product labeling as approved by regulatory agencies, or in the absence of approved labeling, in peer reviewed studies, showing that the highest expected failure rate for that method is less than 1% per year.

Because of the unacceptable failure rate of barrier (chemical and/or physical) methods, the barrier method of contraception must only be used in combination with other acceptable methods. Post-coital methods of contraception are not permitted.

*A female condom and male condom should not be used together due to friction between the 2 barrier methods reducing efficacy.

For Male Subjects

Male subject with female partner(s) of childbearing potential must ensure that their partner(s) uses the methods of contraception as outlined for female subjects above.

10.5. Guidance for Overdose

An overdose of glycopyrrolate may lead to anticholinergic signs and symptoms such as nausea, vomiting, dizziness, lightheadedness, blurred vision, increased intraocular pressure (causing pain, vision disturbances, or reddening of the eye), obstipation or difficulties in voiding (refer to the approved product labeling for Lonhala Magnair).

11. STUDY ASSESSMENTS

A study schematic is presented in Figure 1. A summary of assessments to be conducted at each visit is presented in Table 2.

Assessments will be conducted within the time frames specified. All times are relative to the time of dosing for individual subjects unless otherwise specified.

11.1. Demographics and Baseline Characteristics

Subject demographics (date of birth, sex, ethnicity, race), height and weight will be recorded in the CRF.

COPD exacerbation history (with and without hospitalization) will be recorded in the CRF.

Smoking history will be recorded in the CRF. Number of pack years is calculated as (number of cigarettes per day / 20) x number of years smoked.

Other medical history (relevant/significant medical history and recurrence of any condition) will also be recorded in the CRF.

11.2. Modified Medical Research Council Dyspnea Scale (mMRC)

The mMRC will be used as a screening tool at Visit 1 to determine patient eligibility. The modified Medical Research Council (mMRC) Dyspnea Scale (Mahler 1984), is a five-item instrument (part of the Borg scale) to assess a patient's degree of breathlessness in relation to physical activity. Subjects will be required to read a brief description of an activity and then select a statement that best describes their experience with dyspnea at Visit 1. The questionnaire should be completed before any other assessments are conducted to avoid influencing the responses.

Subjects must have a score ≥ 2 to be eligible for study participation.

11.3. St. George's Respiratory Questionnaire (SGRQ)

Each subject will complete the St. George's Respiratory Questionnaire (SGRQ) at the clinic site during the screening visit (Visit 1). The SGRQ is a standardized disease-specific, 50-item questionnaire designed to measure impact on overall health, daily life, and perceived will-being in patients with obstructive airway disease. The SGRQ must be completed by the subject in the clinic (Jones 1991).

11.4. Efficacy Assessments

11.4.1. Plethysmography

Lung plethysmography (also called body plethysmography) will be used to measure absolute lung volumes. Changes in pulmonary gas volume are estimated by measuring pressure changes in the plethysmograph. Plethysmography measurements will be conducted in accordance with the current ATS/ERS 2005 guidelines (Wanger 2005).

Measurements obtained during the test include:

- Total Lung Capacity (TLC) – The total volume of gas in the lungs after maximal inspiration, or the sum of all volume compartments.
- Functional Residual Capacity (FRC) – The volume of gas present in the lung at end-expiration during tidal breathing.
- Residual Volume (RV) – The volume of gas that remains in lungs after maximal exhalation.
- Inspiratory Capacity (IC) – The maximum volume of gas that can be inspired from FRC.
- Airway Resistance (Raw)
- Specific Airway Resistance (sRaw)

Study-qualifying plethysmography during Screening (Visit 1) may only be performed after the subject has completed the appropriate protocol-specified washout regimen of prohibited medications (See Section 10.3). In order to confirm study eligibility, the subject's RV must be ≥130% predicted value (prior to reversibility testing).

Plethysmography will be performed at Screening prior to and 30-60 minutes (and no later than 2 hours) following 68 mcg ipratropium MDI (4 puffs of 17 mcg per actuation). Plethysmography will be performed prior to spirometry.

Serial plethysmography (Day 1 and Day 9) will be performed 45 minutes predose and again at 1, 2, 3, 4, and 6 hours postdose. At each timepoint, plethysmography assessments will have a window of ± 15 minutes. Plethysmography will be performed prior to spirometry when timepoints coincide.

11.4.2. Spirometry

Spirometry assessments will be performed using a standardized, PC-based pneumotach spirometry system. Spirometry will involve the determination of FEV_1, FVC, and FEV_1/FVC ratio. Predicted FEV_1 will be obtained using the normal prediction equations obtained from The Third National Health and Nutrition Examination Survey (NHANES III). Spirometry measurements will be conducted in accordance with the current ATS/ERS 2005 guidelines (Miller 2005).

Study-qualifying spirometry assessments during Screening (Visit 1) may only be performed after the subject has completed the appropriate protocol-specified washout regimen of prohibited medications (See Section 10.3). In order to confirm study eligibility, the subject's post-bronchodilator FEV_1 (following inhalation of 68 mcg ipratropium MDI) must be ≥ 30% and < 80% predicted normal value. Additionally, the FEV_1/FVC ratio must be < 0.70.

Spirometry will be performed at Screening prior to and 30-60 minutes (and no later than 2 hours) following 68 mcg ipratropium MDI (4 puffs of 17 mcg per actuation). Spirometry will also be performed during the randomized treatment period on Day 1 and Day 9 at 45 minutes predose and again 6 hours postdose after plethysmography. At each time point, spirometry assessments will have a window of ± 15 minutes. Spirometry will be performed following plethysmography.

At least 3 "acceptable" spirometry maneuvers (up to 8 blows total per time point) will be obtained during each assessment. The highest and second highest FEV_1 values and the highest

and second highest FVC values should be within 150 mL to be acceptable. The single highest FEV_1 and the single highest FVC values from acceptable and repeatable maneuvers are reported even if they do not come from the same maneuver. The FEV_1/FVC ratio is determined from the reported highest FEV_1 and highest FVC values.

Spirometry reports will be printed out after each assessment and reviewed by the clinical site staff to ensure subject eligibility and safety; a hard copy should be filed in the subject's source documentation.

11.5. Safety Assessments

The Investigator or appropriate designee will review results of safety assessments on a regular basis.

11.5.1. Pretreatment Events and Adverse Events

Pretreatment events will be collected for each subject from signing informed consent at Visit 1 to the time of the first dose of study medication (ie, the placebo dose administered via the Magnair Nebulizer System at Screening for training purposes).

Adverse events will be collected for each subject from the time of the placebo dose (for training purposes) administered at Visit 1 to Follow-up. Subjects should be queried in a non-leading manner, without specific prompting (eg, "Has there been any change in your health status since your last visit?"). See Section 12, Safety Reporting.

Information regarding format and version of coding dictionary is provided in the DMP.

AEs and serious adverse events (SAEs) will be monitored throughout the study at all visits.

11.5.2. 12-Lead Electrocardiograms (ECG)

All ECGs will be obtained in the supine position, after the subject has been resting supine for at least 5 minutes. ECG assessments will be performed and read locally. ECGs will be 12-lead with a 10-second rhythm strip. The screening ECGs should be obtained prior to obtaining blood samples. Refer to Section 20, Appendix I for additional information.

11.5.3. Clinical Laboratory Tests

The clinical laboratory tests required by protocol are listed in Section 21, Appendix II.

Blood and urine samples will be collected for clinical laboratory tests. All clinical laboratory tests will be performed locally. For detailed instructions regarding clinical laboratory procedures, sampling, and shipping guidelines refer to the local clinical laboratory guidelines. Samples will be processed at a local laboratory. All clinical laboratories will be College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendments (CLIA) (or equivalent) certified.

Any POC (point of care) kits that are performed on site by study personnel rather than in a lab- must be CLIA waived and the study center must possess a CLIA certificate of Waiver.

11.5.4. Physical Examination

A complete physical examination will be performed at Screening.

11.6. Exploratory Assessments

11.6.1. AccelerateIQ System

The accelerateIQ System is a wireless remote patient monitoring system intended for use by healthcare professionals for continuous collection of physiological data in home and healthcare settings. The accelerateIQ System consists of the VitalPatch Biosensor (a 510k-cleared disposable patch with integrated biosensors and a wireless transceiver) and the accelerateIQ Platform (a smartphone with a cellular plan and a mobile application for data transmission, cloud-based information-technology [IT] infrastructure, physiology analytics modules, and clinician user interface).

The patch is worn on the torso for up to 5 days and measures and records physiological data including heart rate, ECG, heart rate variability, R-R interval, respiratory rate, skin temperature, activity (including step count), and posture. Data are transmitted wirelessly from the VitalPatch Biosensor to the accelerateIQ IT platform for storage and analysis and presentation within the clinician user interface.

11.6.2. Vital Signs

Supine systolic and diastolic blood pressures, respiratory rate, pulse rate, and oral temperature will be measured following 5 minutes of seated rest. Vital signs will be collected at Screening and during the randomized treatment period on Day 1 and Day 9 at 45 (± 15) minutes prior to dosing and 60 (± 15) minutes postdose. Vital signs will be collected prior to plethysmography and spirometry when collection times coincide.

11.7. Study Visits and Assessments

11.7.1. Screening: Visit 1 (Day -17 to -2)

Subjects who provide written informed consent to participate in this study will be evaluated at the Screening Visit to determine eligibility. Screening may occur over more than one visit.

Abnormal Screening clinical laboratory tests may only be repeated after discussion with the Medical Monitor.

To determine subject eligibility, Screening ECG may only be repeated due to technical issues.

The following study-related procedures will be performed in the suggested order:

- Review inclusion and exclusion criteria.
- Record demographics.
- Record medical history.
- Record smoking status.
- Record COPD exacerbation history with and without hospitalization.

- Record height and weight.
- Administer Modified Medical Research Council Dyspnea Scale (score must be ≥ 2).
- Administer St. Georges Respiratory Questionnaire (SGRQ)
- Perform physical examination.
- Obtain vital signs.
- Perform 12-lead ECG
- Collect blood and urine samples for:
  - Clinical safety laboratory tests
  - Serum βHCG pregnancy test (female subjects of childbearing potential)
  - Urinalysis
- Begin washout of current/prohibited medications.
- Dispense albuterol (rescue medication) if needed.
- Dispense inhaled corticosteroid if needed. (Note: COPD subjects who washout of LABA/ICS must switch to ICS monotherapy that is equivalent to that contained in the LABA/ICS.)
- Perform prebronchodilator plethysmography (RV must be ≥ 130% of predicted).
- Perform prebronchodilator spirometry.
- Perform postbronchodilator (ipratropium bromide) plethysmography.
- Perform postbronchodilator spirometry immediately after plethysmography (FEV1 must be ≥ 30% and < 80% of predicted and FEV1/FVC ratio must be < 0.70).
- Observe subject administer placebo via the Magnair Nebulizer System to ensure that they are able to use the device. Subjects unable to use the Magnair Nebulizer System will be excluded from study participation.
- Apply VitalPatch Biosensor. (Note: The VitalPatch Biosensor will be applied to subjects who provide additional informed consent for this assessment.)
- Record prior and concomitant medications.
- Record pretreatment events (up to time of administration of placebo via Magnair Nebulizer System for training purposes).
- Record adverse events (after administration of placebo via Magnair Nebulizer System for training purposes).
- Schedule next visit.

11.7.2. Treatment Period

11.7.2.1. Treatment 1: Visit 2 (Day 1)

Subjects will return to the clinic on Day 1. The Day 1 visit is to begin in the morning to allow for study drug dosing between approximately 06:00 and 10:00 AM.

The following study-related procedures will be performed:

- Review continuation criteria to ensure:
  - The subject has not had an exacerbation of COPD.
  - The subject has not had any changes that would put subject safety at risk.
- Record adverse events.
- Record concomitant medications.
- Apply VitalPatch Biosensor.
- Obtain vital signs 45 (± 15) minutes prior to dosing.
- Perform plethysmography 45 (± 15) minutes prior to dosing.
- Perform spirometry 45 minutes (± 15 minutes) prior to dosing.
- Randomize subject (Day 1).
- Administer single dose of study drug in the clinic between approximately 6:00 and 10:00 AM.
- Perform plethysmography at 1, 2, 3, and 4 hours after dosing. At each timepoint, assessments will have a window of ± 15 minutes.
- Perform plethysmography at 6 hours (± 15 minutes) after dosing.
- Perform spirometry at 6 hours (± 15 minutes) dosing.
- Record vital signs 60 (± 15) minutes after dosing.
- Record adverse events.
- Remind subjects to continue to withhold restricted medications during the 7-day washout period.
- Schedule next visit.

11.7.3. Treatment 2/End of Study: Visit 3 (Day 9 + 3)

Subjects will return to the clinic on Day 9. The Day 9 visit is to begin in the morning to allow for study drug dosing between approximately 06:00 and 10:00 AM.

The following study-related procedures will be performed:

- Review continuation criteria to ensure:
  - The subject has not had an exacerbation of COPD.

  - The subject completes the 7-day washout period and continues to withhold restricted medications.
  - The subject has not had any changes that would put subject safety at risk.
- Record adverse events.
- Record concomitant medications.
- Perform urine pregnancy test.
- Apply VitalPatch Biosensor.
- Obtain vital signs 45 (± 15) minutes prior to dosing.
- Perform plethysmography 45 (± 15) minutes prior to dosing.
- Perform spirometry 45 minutes (± 15 minutes) prior to dosing.
- Administer single dose of study drug in the clinic between approximately 6:00 and 10:00 AM and within 1 hour of Treatment Period 1 dosing.
- Perform plethysmography at 1, 2, 3, and 4 hours after dosing. At each timepoint, assessments will have a window of ± 15 minutes.
- Record vital signs 6 hours (± 15 minutes) after dosing.
- Perform plethysmography at 6 hours (± 15 minutes) after dosing.
- Perform spirometry at 6 hours (± 15 minutes) dosing.
- Record vital signs 60 (± 15) minutes after dosing.
- Record adverse events.
- Schedule follow-up assessment.

11.7.4. Follow-up/Early Termination

All subjects will have a follow-up 7 (± 2) days after their last dose of study drug.

Female subjects of childbearing potential who were dosed are required to return to the clinic for a serum pregnancy test and final safety assessment (adverse events and concomitant medication use).

All other dosed subjects will either be contacted by telephone or have an in-clinic visit if deemed clinically warranted by the Investigator for final safety assessment (adverse events and concomitant medication use).

Subjects who discontinue prior to completion of Day 9 will undergo Early Termination procedures and assessments at the time of discontinuation.

12. SAFETY REPORTING

12.1. Definitions

12.1.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Untoward medical occurrences that occur between the time of signing the ICF and first drug administration (ie, the placebo dose administered via the Magnair Nebulizer System at Screening for training purposes) are pre-treatment events. Those that occur after first administration of study drug (ie, the placebo dose administered via the Magnair Nebulizer System at Screening for training purposes) are considered AEs.

An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease occurring after the administration of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. AEs may include the onset of new illness and the exacerbation of pre-existing conditions. AEs will be collected from after first administration of study drug to the last study visit/EOS visit.

New signs and symptoms of underlying disease, or signs and symptoms of emerging disease must be recorded as AEs.

The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and not the individual signs/symptoms.

12.1.2. Serious Adverse Events

A serious adverse event (SAE) is an AE that meets one or more of the following criteria:

- Results in death.
- Is life-threatening.
- Requires hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event that may jeopardize the subject or may require a medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization.

The term "severe" is often used to describe the severity of a specific event (as in mild, moderate, or severe myocardial infarction) (see Section 12.3); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning as defined by the criteria above.

During the study, if a subject has a hospitalization or procedure (eg, elective surgery) that was scheduled before the study entry, ie, before informed consent for an event/condition that occurred before the study, the hospitalization is considered a therapeutic intervention and not the result of a SAE. However, if the event/condition worsens during the study, it should be reported as an AE (or SAE, if the event/condition results in a serious outcome such as prolongation of hospitalization).

Life-threatening means that the subject was, in the view of the Investigator, at immediate risk of death from the event as it occurred. This definition does not include an event that had it occurred in a more severe form might have caused death.

SAE criteria information will be captured on the CRF.

12.2. Objective Findings

Clinically significant abnormal objective findings (eg, clinical laboratory value, ECG value, and physical examination observation) will also be recorded as AEs.

When a clear diagnosis is available that explains the objective findings, this diagnosis will be recorded as the AE, and not the abnormal objective finding (eg, viral hepatitis will be recorded as the AE, not transaminase elevation). If a definite diagnosis is not available, then record the sign (eg, clinically significant elevation of transaminase levels) or symptom (eg, abdominal pain) as the AE.

Clinical laboratory test results will be reviewed by the Investigator. The Investigator must determine the clinical significance of all out of range values. Clinical laboratory test with possibly drug-related or clinically relevant abnormal values of uncertain causality may be repeated. Any abnormal values that persist should be followed at the discretion of the Investigator.

Clinical Laboratory Tests Outside the Normal Range: Any value outside the normal range will be flagged for the attention of the Investigator or appropriate designee at the study center. The Investigator or appropriate designee will indicate whether or not the value is of clinical significance. If the result of any test (or repeat test, if done) from the samples taken during Screening is indicated as clinically significant and is not covered by the inclusion criteria in Section 8.1 , the subject will **not** be allowed into the study. Additional testing during the study may be done if medically indicated. If a clinically significant abnormality is found in the samples taken after dosing, during the study, and/or at the Follow-Up Visit, this should be recorded as an AE and the subject will be followed until the test(s) has (have) normalised or stabilised.

All on-site ECG tracings will be reviewed by the Investigator. The Investigator must determine the clinical significance of all abnormal ECGs. ECG with possibly drug-related or clinically relevant abnormal findings of uncertain causality may be repeated. Any abnormal ECGs that persist should be followed at the discretion of the Investigator. ECG tracings will be initialed and dated on all pages by the Investigator.

12.3. Collection and Recording of Adverse Events

All pre-treatment events and AEs must be recorded in the subject's study records/source documents in accordance with the Investigator's normal clinical practice. All pre-treatment events and AEs/all AEs must be recorded on the CRF.

All AEs will be followed until resolution, stabilization of the condition, the event is otherwise explained, or the subject is lost to follow-up.

Each AE is to be evaluated for duration, severity, frequency, seriousness, action taken with the study treatment, outcome, and causal relationship to the study treatment. Definitions for severity, frequency, action taken with the study treatment, outcome, and causal relationship to the study treatment are presented below.

The severity of AE:

- **Mild** - Ordinarily transient symptoms that do not influence performance of subject's daily activities. Other treatment is not ordinarily indicated.
- **Moderate** - Marked symptoms sufficient to make the subject uncomfortable. Moderate influence on performance of subject's daily activities. Other treatment may be necessary.
- **Severe** - Symptoms cause considerable discomfort. Substantial influence on subject's daily activities. May be unable to continue the study, and other treatment may be necessary.

The frequency of AE:

- **Once** – an isolated episode.
- **Intermittent** – occurs on two or more separate occasions.
- **Continuous** – does not abate from date of onset to date of resolution.

The action taken with the study treatment:

- **Drug Interrupted** – Study drug stopped temporarily.
- **Drug Withdrawn** – Study drug stopped permanently.
- **Not Applicable.**
- **Unknown**

The outcome of the AE:

- **Recovered/Resolved**
- **Recovering/Resolving**
- **Not Recovered/Not Resolved**
- **Recovered/Resolved with Sequelae**
- **Fatal**
- **Unknown**

The causal relationship of the AE to the study treatment:

- **Not related**
  - **Not related -** Improbable temporal relationship and is plausibly related to other drugs or underlying disease.
- **Related**
  - **Possible** - occurred in a reasonable time after study drug administration, but could be related to concurrent drugs or underlying disease.
  - **Probable** - occurred in a reasonable time after study drug administration, is unlikely to be attributable to concurrent drugs or underlying disease, and there is a plausible mechanism to implicate the study drug.
  - **Definite** - occurred in a reasonable time after study drug administration and cannot be explained by concurrent drugs or underlying disease. The adverse event should respond to dechallenge/rechallenge, however, this is not mandatory before assigning a definite causality.

The Medical Monitor is the initial contact person for protocol related questions or discussion of AEs. The contact information for the Medical Monitor as well as other emergency contact information can be found in Table 1 of this protocol.

12.4. Immediately Reportable Events

The following medical events must be immediately reported to the Sponsor:

- SAE
- Pregnancy

Emergency contact information can be found in Table 1.

12.4.1. Serious Adverse Event

If the Investigator or study center staff becomes aware of a SAE that occurs in a study subject after signing the informed consent through 30 days following the last dose of the study medication, this must be reported immediately to the Sponsor whether considered related or unrelated to the study drug. SAEs must be recorded on the CRF and the data recorded should agree with that on the SAE form.

Following the end of subject participation in the study, the Investigator or an authorized delegate should report SAEs “spontaneously” to PPD-PVG if considered at least possibly related to the study drug.

SAEs will be followed until resolution, loss to follow-up, stabilization of condition, or the event is otherwise explained.

In addition to the initial telephone notification, an initial SAE form as applicable must be completed and signed and sent via fax or email (see Table 1) to PPD-PVG within 1 business day of the Investigator or study center staff becoming aware of the event. The SAE form must be

signed by the Investigator or appropriate designee. The Sponsor provides the SAE form used to report SAEs.

The Sponsor or designee will promptly notify all study centers and Investigators of a SAE that is determined to be expedited to the Regulatory Authorities in accordance with applicable law(s) and regulation(s). These SAEs must be promptly reported to the Institutional Review Board (IRB) by the Investigator or the appropriate person at the study center if required per IRB guidelines.

12.4.2. Pregnancy

Pregnancies that occur from the time that informed consent is signed through 30 days following the last dose of the study medication will be collected and reported on the Pregnancy Event Form.

If a subject becomes pregnant during the course of the study, she will be instructed to commence discontinuation of the study medication. Further, the subject (or female partner of male subject) will be instructed to return within 48 hours of the first notification of pregnancy to the study center and undergo a serum/urine pregnancy test, as confirmation of pregnancy. If positive, the female pregnant subject will no longer receive any additional study medication. All pregnancies, whether or not the subject received any additional study medication, will be followed until resolution (ie, termination [voluntary or spontaneous] or birth).

To report a pregnancy, the Pregnancy Event Form must be completed and sent via fax to the PPD-PVG within 1 business day of the Investigator or study center staff becoming aware of the pregnancy.

If the subject received blinded study medication, unblinding of the study medication will be offered to the subject when knowledge of such treatment may have an impact on further treatment decisions. Otherwise, information regarding to what treatment the subject was assigned may be provided when the study has ended.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication or other AEs were detected.

13. TERMINATION OF SUBJECT FROM STUDY/DISCONTINUATION OF STUDY DRUG

Subjects may be terminated from the study/discontinued from the study drug at any time for any of the following reasons:

- Adverse event
- Lost to follow-up (specify)
- Withdrawal by subject (specify)
- Protocol deviation (specify)
- Death
- Screen failure
- Site terminated by Sponsor
- Study terminated by Sponsor
- Other (specify)

If at any time during the course of the study, in the opinion of the Investigator, the subject may no longer safely participate due to a change in medical status (eg, experiences an AE, becomes pregnant), the subject must be discontinued from the study drug.

The reason and information on the epoch for study drug discontinuation will be recorded on the appropriate CRF. In case of death, the date of death should be captured on the CRF.

Discontinued subjects will not be replaced. At the Sponsor's discretion, additional subjects may be enrolled in an effort to achieve at least 20 completers, with no more than 24 subjects randomized.

Subjects who discontinue prior to completion of Day 9 will undergo Early Termination procedures and assessments at the time of discontinuation.

14. STUDY TERMINATION

The Sponsor reserves the right to discontinue the study for safety or administrative reasons at any time while safeguarding that early termination does not compromise subjects' safety or well-being. In particular, a study center that does not recruit at an acceptable rate may be closed. Should the study be terminated and/or the study center closed for whatever reason, all documentation and study medications pertaining to the study must be returned to the Sponsor or its representative.

If, in the opinion of the Investigator, clinical observations suggest it may be unsafe to continue, the Investigator may terminate part or the entire study after consultation with the Sponsor.

In the event of study or site termination, subjects will have follow-up 7 (± 2) days after their last dose of study drug for a final safety assessment:

- Female subjects of childbearing potential who were dosed are required to return to the clinic for a serum pregnancy test and final safety assessment (adverse events and concomitant medication use).
- All other dosed subjects will either be contacted by telephone or have an in-clinic visit if deemed clinically warranted by the Investigator for final safety assessment (adverse events and concomitant medication use).

All subjects will be provided with access to standard care.

15. STATISTICS

A comprehensive statistical analysis plan (SAP) will be finalized for this study prior to locking the database. The structure and content of the SAP will provide sufficient detail to meet the requirements identified by the FDA and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials to support the use of this study for registration applications. A separate SAP will be created for the exploratory accelerateIQ System data. Any deviations from the main SAP after the database lock, should be documented in the changes in the planned analyses form and in the Clinical Study Report (CSR).

15.1. Sample Size

The evaluable sample size for this study was determined by a two-sample t-test (cross-over ANOVA) using nQuery version 4.0 (nQuery + nTerim version 4.0, Statistical Solutions, Cork, Ireland). A sample size of 10 evaluable subjects per treatment sequence (20 subjects in total), assuming a common standard deviation (SD) of 0.4 L, a mean difference of -0.3 L in change from baseline in RV (single dose of GIS compared to PIS), with a one-sided alpha of 0.025, will give a power of 88%. Discontinued subjects will not be replaced. At the Sponsor's discretion, additional subjects may be enrolled in an effort to achieve at least 20 completers.

15.2. Analysis Populations

Modified Intention-to-Treat Population: The modified intention-to-treat (mITT) population will consist of subjects who are randomized, receive at least one dose of study treatment, and have a baseline and at least one post-baseline RV measurement within the same period. Should a subject require rescue medication use during the approximately 6 hours of efficacy endpoint collection, then any efficacy values that occur after the use of the rescue medication will be set to missing. Subjects will be analyzed according to randomized treatment group.

Safety Population: The safety population will consist of all subjects who are randomized and received at least one dose of study medication. Subjects will be analyzed according to treatment received.

15.3. Data Analysis

In general, descriptive summaries will be provided where appropriate for each of the endpoints. Continuous outcomes will be summarized for the number of subjects, mean, 95% Confidence Interval (CI) for the mean, SD, median, quartile 1 (Q1), quartile 3 (Q3), minimum, and maximum. For categorical outcomes, the number and percentage of subjects will be presented.

All statistical inference analyses will be performed with 2-sided tests at a significance level of 0.05, unless otherwise specified. No adjustments for multiplicity will be applied.

For analyses of change from baseline, period baseline will generally be defined as the last measurement collected prior to dosing on Day 1 or Day 9 as scheduled.

All data from the CRFs, as well as any derived variables, will be presented in subject data listings. Unscheduled measurements will be included in the listings and will not be included in summary tables, unless specified otherwise.

SAS® software Version 9.4 or higher will be used for all analyses.

15.3.1. Subject Disposition

The number and percentage of subjects screened, screen failed, enrolled, randomized, dosed, completing each period, and completing the study will be summarized. The number and percentage of subjects who terminate early will also be summarized, along with reasons of termination.

15.3.2. Drug Exposure and Compliance

A data listing, by subject, containing the study medication dosing and any dosing errors, if any, will be provided. Since dosing of subjects occurs in the clinic, treatment compliance will not be summarized.

15.3.3. Important Protocol Deviations

Important protocol deviations (IPDs) will be identified and documented based on a review of potentially IPDs. The potentially IPDs will be identified through programmatic checks of study data, as well as through review of selected data listings. The potentially IPDs to be reviewed include, but are not limited to, subjects who:

- Did not meet inclusion/exclusion criteria.
- Received any disallowed concomitant medication, including rescue medication use during the efficacy endpoint collection.

Individual IPDs will be presented in a data listing.

15.3.4. Demographic and Baseline Characteristics

Summaries for demographic characteristics will be presented for overall using the mITT and Safety populations. Demographic characteristics include age (in years), age categories (< 65 years, and ≥ 65 years), gender, race, ethnicity, weight, height, body mass index. Baseline characteristics (eg, screening plethysmography and spirometry results, smoking status, COPD exacerbation history, mMRC dyspnea scale grades and SGRQ component and total scores) will also be summarized.

The medical history of each subject will be coded by Medical Dictionary for Regulatory Activities (MedDRA) (see the DMP for version number) system organ class (SOC) and preferred term (PT). The number and percentage of subjects with medical history findings in each SOC and PT will be summarized by overall for the Safety and mITT populations.

15.3.5. Efficacy Analyses

All efficacy endpoints will be summarized for the mITT population using descriptive statistics. Should a subject require rescue medication during the approximately 6 hours of efficacy endpoint collection, then any efficacy values that occur after the use of the rescue medication will be set to missing. Continuous variables will be summarized using the number of subjects, mean, standard deviation, median, Q1 and Q3, minimum, and maximum. Categorical variables will be summarized using counts and percentages. Significance tests will be 2-sided and conducted at an alpha level of 0.05, unless otherwise specified.

15.3.5.1. Primary Efficacy Endpoint Analysis

The primary efficacy estimand is defined as the difference between a single dose of GIS and PIS in the mean change of RV from baseline at 6 hours postdose in COPD patients as characterized by the study inclusion/exclusion criteria, in the hypothetical setting where the subjects were able to stay on study and receive their study drug during their treatment periods.

The change from baseline in RV at 6 hours postdose will be calculated for each treatment period as RV at 6 hours postdose on the day of treatment minus the period baseline of each treatment period. Period baseline is defined as the predose RV value collected 45 minutes prior to the dosing during each treatment period.

For the primary analysis of the primary efficacy endpoint, data will be analyzed using a 2-way crossover analysis of covariance (ANCOVA) using the mITT population. The ANCOVA model will include terms for treatment, period and sequence as fixed effects, period baseline as a covariate, and subjects nested within sequence as a random effect. The Kenward and Roger correction for the degrees of freedom will be used. No structure (i.e., unstructured) will be assumed for the intra-subject correlation. If convergence is not met, other variance covariance structures may be utilized. The main estimator of the primary estimand is the Least Squares (LS) mean difference in the change from baseline in RV at 6 hours postdose from the primary ANCOVA model. LS mean (and 95% CI) for each treatment group and LS mean (and 2-sided 95% CI), and the associated p-value for the difference between the single dose of GIS and PIS will be displayed.

Graphical displays of the LS Mean (95% CI) and the LS Mean Difference (95% CI) versus PIS for RV will be presented for each postdose time point (1, 2, 3, 4 and 6 hours postdose) using the mITT population.

Subject profile plots for the RV efficacy endpoint at baseline and each post-baseline time point will be presented by subject, period and treatment sequence using the mITT population. Group means by period will also be plotted for each treatment sequence using the mITT population.

15.3.5.1.1. Sensitivity Analyses

In general, for the primary analysis of the primary efficacy endpoint, missing observations will be treated as missing at random (MAR) and no data imputation will be performed. However, sensitivity analyses may be conducted if there is significant amount of missing data, including missing not at random (MNAR) assumptions.

15.3.5.1.2. Supplementary Analyses

Supplementary analyses of the primary efficacy endpoint may be conducted as deemed appropriate and details will be provided in the SAP.

15.3.5.2. Other Efficacy Endpoint Analysis

All other efficacy endpoints will be analyzed using the mITT population.

All other efficacy endpoints will be analyzed using the ANCOVA model similar to the primary efficacy endpoint with appropriate baseline as a covariate. Additional covariates may be included in select models.

Standardized change from baseline in RV AUC0-4h for each treatment will be calculated using the trapezoid method from the changes in RV from the period baseline value within each treatment and dividing by the actual length of the time interval within that treatment. Changes in RV from period baseline for each time point (1, 2, 3, and 4 hours postdose) will be calculated as the RV values within each treatment minus the period baseline RV for each treatment. Change in RV from period baseline at time=0 is equal to 0.

Standardized change from baseline in RV AUC0-6h, IC AUC0-4h, IC AUC0-6h, FRC AUC0-4h, FRC AUC0-6h, TLC AUC0-4h, TLC AUC0-6h, sRAW AUC0-4h, sRaw AUC0-6h, RAW AUC0-4h, and Raw AUC0-6h will be calculated similarly.

Changes from baseline in IC, FRC, TLC, sRaw, Raw and FEV1 at 6 hrs postdose will be calculated similar to the primary analysis endpoint. All any other postdose lung volume endpoints (RV, IC, FRC, TLC, sRaw and Raw) at 1, 2, 3 and 4 hours postdose will be derived and analyzed similar to the primary endpoint.

Mean change from baseline in RV at each postdose time point will be plotted by treatment using the mITT population.

Subject profile plots for the RV AUC0-6h efficacy endpoint will be presented by subject, period and treatment sequence using the mITT population. Group means by period will also be plotted for each treatment sequence using the mITT population.

15.3.5.3. Adjustment for Multiplicity

No multiple comparison procedures will be employed in this study.

15.3.6. Exploratory Endpoint Analyses

A separate SAP will be created for the accelerateIQ System data.

Height and weight are collected only at Screening. They will be summarized in the demographic tables and will be listed.

Summary statistics for actual values and the change from baseline for vital signs collected at the clinical visits will be presented by treatment for each parameter. Period baseline is defined as the last non-missing predose value on each treatment day. All such vital sign data will be listed.

15.3.7. Safety Analyses

15.3.7.1. Adverse Events

All AEs will be coded using MedDRA (see the DMP for version number). AEs are untoward medical occurrences:

- That occurred on or after the first dose of study medication,
- With a missing start date and a stop date on or after the first dose of study medication, or
- With both a missing start and stop date.

AEs during the randomized treatment period starting at Day 1 will be defined as AEs:

- That occurred on or after the first dose of study medication given during the randomized treatment period,
- With a missing start date and a stop date on or after the first dose of study medication given during the randomized treatment period, or

with both a missing start and stop date.

The following AEs during the randomized treatment period will be summarized and presented by treatment group and by MedDRA SOC and PT for the Safety population:

- All AEs (including number of events and subject incidence).
- AEs by severity (mild, moderate, severe).
- AEs by relationship to the study treatment (related, or not related).

Additional AE analyses may be conducted as appropriate.

The following conventions will be followed in summarizing the AEs during the randomized treatment period:

- For subject incidence summaries, each subject will be counted only once within each SOC and within each preferred term.
- An AE that occurs on or after the date/time of the treatment, up through and excluding the date/time of the next treatment, will be assigned to the treatment group associated with the former treatment. An AE that occurs on or after the date/time of the last treatment will be assigned to the treatment group associated with the last treatment.
- If the AE start date is missing, then the AE will be assigned to all treatments received on or prior to the known AE end date. If both the AE start date and end date are missing, then the AE will be assigned to all treatments the subject received.
- If a subject reports more than one AE within a preferred term and/or a body system, the AE with the highest known severity within each body system and within each preferred term will be included in the summaries by severity. Any AE with a missing severity will be treated as "severe" and counted in the severe category.
- For summaries by relationship to the study medication, AEs will be grouped as "related" or "not related." AEs assessed as "possible," "probable," or "definite," will be grouped as "related." If a subject reports more than one AE within the same treatment, SOC and PT, and any are related, it will be summarized as related.

Summaries of non-serious AEs with a 5% cutoff, SAEs, and AEs leading to study discontinuation may be provided.

A listing of all AEs, as well as a listing of deaths, SAEs, AEs leading to discontinuation, and a listing of pre-treatment untoward medical events will be presented.

15.3.7.2. Clinical Laboratory Assessments

Clinical lab assessments are collected at Screening for eligibility. Any clinical lab parameter data (hematology, chemistry, and urinalysis) will be provided in a listing only.

15.3.7.3. 12-Lead ECGs

12-lead ECGs are recorded only at Screening for eligibility. Any ECG data will be provided in a listing.

15.3.7.4. Physical Examination

Findings from the physical examination will be presented as follows: pre-existing clinically significant conditions recorded as medical history will be summarized, and new clinically significant conditions recorded as an AE.

15.3.7.5. Prior and Concomitant Medications

All medications will be coded using WHO-DD. All medications will be coded to indication-specific Anatomical Therapeutic Chemical (ATC) classification and PT according to the WHO-DD (see the DMP for version number).

Other than the study drug, any medications that start prior to the randomized treatment period, but continue into the randomized treatment period, and those that start during the randomized treatment period, will be considered as concomitant. Medications stopped prior to the date/time of the first study medication during the randomized treatment period will be considered as prior medications.

The number and percentage of subjects using each prior and concomitant medication will be summarized for each treatment by ATC class and PT. Subjects with multiple uses of a medication will be counted only once for a given drug class or PT.

A detailed listing of prior and concomitant medications taken by subjects will be provided.

15.3.8. Interim Analysis

No interim analysis is planned.

15.3.9. Treatment of Missing Data

Methods to account for missing data will include the following:

- For the calculation of an AUC, any intermittent missing measurements will be ignored, and the trapezoidal rule will simply span the missing time point(s). For AUC0-6h, the 6-hour time point will be used as the end of the interval. If the 6-hour time point is missing, then the AUC0-6h calculation will be based on the time interval up to the last non-missing time point prior to hour 6. Similar rules will be applied for other AUC calculations.

16. PROCEDURE FOR CLINICAL STUDY QUALITY CONTROL /DATA COLLECTION, MANAGEMENT, AND QUALITY ASSURANCE

16.1. Data Collection/Electronic Data Capture (EDC)

The results from Screening and data collected during the study (except the accelerateIQ System data) will be recorded in the subject's electronic CRF. The study centers will use an EDC system that is compliant with relevant FDA regulatory requirements per 21 CFR Part 11 (Medidata Rave). Password protected access to the EDC system will be via a secure website. Data queries and data corrections will be handled through the same system. All transactions within the EDC system are fully documented within an electronic audit trail. Each set of completed CRFs must be reviewed and electronically signed and dated by the Investigator.

16.2. Study Monitoring

This study will be monitored using a risk-based approach from initiation to completion by the Sponsor or its representative. Monitoring will include centralized data monitoring, personal visits, and telephone or email communication to assure that the investigation is conducted according to protocol and in order to comply with International Council for Harmonization (ICH) Good Clinical Practice (GCP). Central and/or on-site review of CRF data will include a risk-based review of critical process compliance, critical data quality, data completeness and clarity, and, where required, consistency with source documents available for each subject.

16.3. Audits

The study may be subject to audit by the Sponsor/designee. If such an audit occurs, the Investigator must agree to allow access to required subject records. This is dependent on the subject granting consent by signing the ICF. By signing this protocol, the Investigator grants permission to personnel from the Sponsor or its representatives for on-site monitoring and auditing of all appropriate study documentation, as well as on-site review of the procedures employed in CRF generation, where clinically appropriate.

In accordance with ICH GCP the Sponsor may select this study for audit. During the audit the Sponsor representative will carry out an inspection of center facilities (eg, pharmacy, drug storage areas, laboratory) and review study related records in order to evaluate the study compliance with the Sponsor/center SOPs, protocol, ICH GCP and local regulations. The PI or appropriate designee must also agree to inspection of all study documents by the regulatory authorities and the IRB. Should the PI or appropriate designee be notified of a regulatory inspection involving this study they should notify the Sponsor immediately.

16.4. Study Documentation

Study records are comprised of source documents, CRFs, and all other administrative documents, eg, IRB correspondence, clinical study materials and supplies shipment manifests, monitoring logs, Sponsor and CRO correspondence, etc. A study specific binder will be provided with instructions for the maintenance of study records.

Source document is defined as any hand written or computer-generated document that contains medical information or test results that have been collected for or are in support of the protocol specifications, eg, clinical laboratory reports, clinic notes, drug disbursement log, subject sign in sheets, subject completed questionnaires if applicable, telephone logs, ECGs, etc. All draft, preliminary and pre-final iterations of a final report are also considered to be source documents, eg, faxed laboratory reports and hard copy laboratory reports, faxed initial results and hard copy, final report.

16.5. Clinical Laboratory Certification and Normal Values

A local/site laboratory will be used for analysis for the clinical labs for this study. The local laboratory/site personnel will provide Sponsor/CRO with laboratory certification(s), a dated copy of normal range values for the local/site clinical laboratory selected to analyze clinical specimens.

17. ETHICAL AND REGULATORY OBLIGATIONS

17.1. Study Conduct

The Investigator agrees that the study will be conducted according to the protocol, ICH GCP, ICH guidelines and the ethical principles that have their origin in the Declaration of Helsinki. The Investigator will conduct all aspects of the study in accordance with applicable local law(s) and regulation(s).

The Investigator will assure proper implementation and conduct of the study including those study-related duties delegated to other appropriately qualified individuals. The Investigator will assure that study staff cooperate with monitoring and audits.

The Investigator must sign and return to Sponsor/CRO the “Investigator Approval" page.

The Investigator must provide a copy of current curriculum vitae (including a copy of a current medical license, where applicable), and financial disclosure information.

The Investigator must sign and return a completed Form FDA 1572 "Statement of Investigator" to Sponsor/CRO.

17.2. Institutional Review Board

Documented approval for conducting the study from appropriate Institutional Review Board (IRB) will be obtained for all participating study centers prior to initiation of the study, according to ICH GCP, applicable local law(s) and regulation(s). When necessary, an extension, amendment or renewal of the IRB approval must be obtained and also forwarded to the Sponsor. The IRB must supply the Sponsor a list of the IRB membership, and a statement to confirm that the IRB is organized and operates according to ICH GCP, applicable law(s) and regulation(s).

A copy of written IRB approval or favorable opinion of the protocol, informed consent form and subject recruitment material (if applicable) must be provided to Sponsor/CRO prior to start of the study. The approval or favorable opinion letter must be signed by the IRB chairman or designee identify the IRB name and address, identify the clinical protocol by title and/or protocol number, and include the date that approval or favorable opinion was granted. The letter must also contain a statement that the IRB complies with the requirements in 21 CFR Part 56 for a study conducted under a US IND or ICH GCP, as applicable.

The Investigator/CRO is responsible for obtaining from the IRB continued review of the clinical research or submitting periodic progress reports, in accordance with applicable regulations, at intervals not to exceed one year and (if applicable) as otherwise additionally specified by the IRB. The Sponsor must be supplied with written documentation of continued review of the clinical research.

The Investigator must promptly inform their IRB of all SAEs reported by subjects enrolled in the study or other safety information reported from Sponsor/CRO in accordance with applicable law(s) and regulation(s).

17.3. Informed Consent

The Sponsor/CRO will prepare the informed consent form and provide the form to the site for approval prior to submission to the IRB. The informed consent form will be approved by the Sponsor/CRO prior to submission to the IRB. The Sponsor/CRO may provide a template informed consent form to be qualified by each research facility to conform to local requirements. All informed consent forms must contain the minimum elements as mandated by ICH GCP, applicable local law(s) and regulations and will be subject to Sponsor/CRO approval as well as IRB approval. The Sponsor/CRO may submit informed consent forms to a central IRB/IEC for review and approval or favorable opinion contingent upon prior Investigator permission and review.

Before recruitment and enrollment, each prospective subject will be given a full explanation of the study, allowed to read the approved informed consent form and be provided ample time and the opportunity to ask any questions that may arise. Once all questions have been answered and the Investigator is assured that the prospective subject understands the implications of participating in the study, the prospective subject will be asked to give consent to participate in the study by signing the informed consent form. As part of the consent process, each prospective subject must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB review, and regulatory inspection. It should be clearly explained to each prospective subject that participation in each and every clinical visit and assessment is expected. The subject may be discontinued from study medication, but that does not necessarily negate the expectation that the subject will continue to participate in the study through the final visit/assessment. The Investigator will provide a copy of the signed informed consent form to each subject and will record the date of the informed consent on the CRF.

If an amendment to the protocol changes the subject participation schedule in scope or activity, or if important new information becomes available that may be relevant to the subject's consent, the informed consent form must be revised, submitted to the IRB for review and approval or favorable opinion. The revised informed consent form must be used to obtain consent from a subject currently enrolled in the study if he or she is affected by the amendment. The revised informed consent form must be used to obtain consent from any new subjects who are enrolled into the study after the date of the approval or favorable opinion of the protocol amendment.

17.4. Subject Privacy

The Sponsor (or Sponsor representative) or any designees affirm to uphold the subject's confidentiality. The subject will be identified by unique code only; full names will be masked prior to transmission to the Sponsor. The confidentiality of the subject's personal data shall be protected in accordance with appropriate laws and regulations.

17.5. Protocol Amendments and Emergency Deviations

All revisions and/or amendments to this protocol must be approved in writing by the Sponsor and the appropriate IRB. The Investigator will not make any changes to the conduct of the study or the protocol without first obtaining written approval from the Sponsor and the IRB, except where necessary to eliminate an apparent immediate hazard to a study subject.

Emergency deviations or modifications may be initiated without Sponsor or IRB approval or favorable opinion, only in cases where the deviation or modification is necessary to eliminate or avoid an immediate apparent hazard to subjects. Emergency deviations or modifications must be reported to the Sponsor/CRO and the IRB immediately, or in accordance with applicable regulatory requirements.

17.6. Records Retention

The Investigator/the study center must arrange for retention of study records at the study center for at least 15 years from time of participation in the study or longer in accordance with applicable regulations and Sponsor SOPs. The Investigator/site should take measures to prevent accidental or premature destruction of these documents. Documents cannot be destroyed without written Sponsor authorization. The Sponsor will inform the Investigator/the study center when the destruction of documents is permitted.

17.7. Inspection of Records

In the event of an inspection, the Investigator agrees to allow representatives of the Sponsor and its representative and, the regulatory authorities' access to all study records. The Investigator will promptly notify the Sponsor/CRO of all requests to inspect a Sunovion-sponsored study by government agencies and will promptly forward a copy of all such inspection reports.

17.8. Financial Disclosure

By signing this protocol, the Investigator agrees to provide to the Sponsor prior to start of study accurate financial information to allow the Sponsor to submit complete and accurate certification and disclosure statements as required by the US FDA regulations (21 CFR Part 54). The Investigator further agrees to provide this information on a Financial Disclosure/Certification Form that is provided by the Sponsor. The Investigator will update this information if there are any relevant changes during the conduct of the study and for one year after completion of the study.

The Investigator also consents to the transmission of this information to the Sponsor for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

17.9. Publication Policy

Any formal presentation or publication of data collected as a direct or indirect result of the study will be considered a joint publication by the Investigators and the appropriate personnel of the Sponsor. For multicenter studies, it is mandatory that the first publication is based on all data obtained from all analyses as stipulated in the protocol. Investigators participating in multicenter studies must agree not to present data gathered individually or by a subgroup of centers before the full, initial publication, unless this has been agreed to by all other Investigators and by the Sponsor.

17.10. Compensation

If subjects have any adverse event or injury directly resulting from the study medications or procedures, the Sponsor will appropriately compensate in accordance with applicable regulatory requirements.

18. REFERENCES

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19. INVESTIGATOR APPROVAL

I have read the protocol, SUN101-402, Version 1.00, A Randomized, Double-blind, Placebo-controlled, 2-Way, Crossover Study of the Effect of a Single Dose of Glycopyrrolate Inhalation Solution (GIS) on Lung Hyperinflation in Subjects with Chronic Obstructive Pulmonary Disease (COPD)", and agree that it contains all necessary details for conducting the study and to conduct the study in strict accordance with the specifications outlined herein.

I agree that no additional procedure(s) will be added during the conduct of the study except through protocol amendment by Sunovion Respiratory Development Inc. and after documentation of IRB approval.

Investigator Signature: _____

Print Investigator Name: _____

Date: _____

20. APPENDIX I. CARDIAC SAFETY MONTIORING (ECG)

1. Requirements for Testing

ECG equipment and supplies will be provided by the clinical site and should be used for all in-clinic protocol ECG assessments.

- All 12-lead ECGs will be recorded in the same manner.
- The study center personnel must be adequately trained in performing ECGs on the specific ECG equipment used in this protocol.
- To the extent possible, the same ECG machine and personnel should be used to acquire a subject's ECGs throughout the period of their participation in the study.
- ECGs will be recorded with at least one 10-second single-lead tracing recorded from Lead II.

2. Subject Restrictions and Instructions

- Prior to ECG acquisition, the subject will have rested at least 5 minutes in the supine position and will remain so until the ECG is obtained.

3. Reporting

- It is the responsibility of the Investigator to perform a safety review of the ECG data for changes from previous assessments and/or emergent cardiac dysfunction, and to determine subjects' eligibility or continuance in the study. Abnormalities require comment as NCS (Not Clinically Significant) or CS (Clinically Significant). Typically, CS designated events will be reported as adverse events.
- ECGs will be reviewed, signed and dated by the Investigator listed on the Form FDA 1572 (MD or DO) after each ECG collection. The same Investigator should review all ECG reports for a given subject whenever possible.
- The ECG tracing will be kept with subject's source documentation and / or CRF unless it is specified otherwise. The original ECG will be retained at the study center and the Sponsor may collect a copy.

21. APPENDIX II. CLINICAL LABORATORY TESTS

Clinical Safety Panel

HEMATOLOGY: (Differential reported as % and absolute value)
Hemoglobin, Hematocrit, Platelet Count, red blood cell (RBC) Count, RBC indices (MCV, MCH, MCHC), white blood cell (WBC) - Total Count, WBC Differential, (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils), Hemoglobin A1c (HbA1c)

BLOOD CHEMISTRIES: Alanine aminotransferase (ALT), Alkaline Phosphatase (ALP), Aspartate aminotransferase (AST), Bicarbonate (HCO_3), Bilirubin (Total, Direct, Indirect), Blood Urea Nitrogen (BUN), Calcium (Ca), Chloride (Cl), Creatinine (Cr), Glucose (GLU), Magnesium (Mg), Phosphorus (P), Potassium (K), Protein (Total), Sodium (Na), Uric Acid (UA), Albumin (ALB)

URINALYSIS: Blood, Glucose, Ketones, Leukocyte esterase, Microscopic examination, Nitrites, pH, Protein, specific gravity

OTHER TESTS: Serum Pregnancy (β-HcG) (female subjects < 65 years old), Urine Pregnancy Test (female subjects < 65 years old)

Laboratory reports will be initialed and dated on all pages by the Investigator listed on the Form FDA 1572 (MD or DO). Laboratory test results will be reviewed by the Investigator as they become available. The Investigator must determine the clinical significance of all out-of-range lab values (except drug screens). Possibly drug-related or clinically relevant abnormal values of uncertain causality must be repeated. Any abnormal values that persist should be followed at the discretion of the Investigator.