# Verona Pharma

# Statistical Analysis Plan: A Study Assessing the Effect of Ensifentrine on COPD Assessment Test (CAT™) Scores over 12 Weeks in Subjects with Moderate to Severe COPD (Ensifentrine CAT Study)

Prepared by

[redacted]

**Document Revision History:**

| Version | Date | Content/Modifications |
|---|---|---|
| 01 | 07/30/2024 | Initial draft |
| 02 | 12/11/2024 | Added additional details for instructions on failed model convergence and added SAS platform and version number. |
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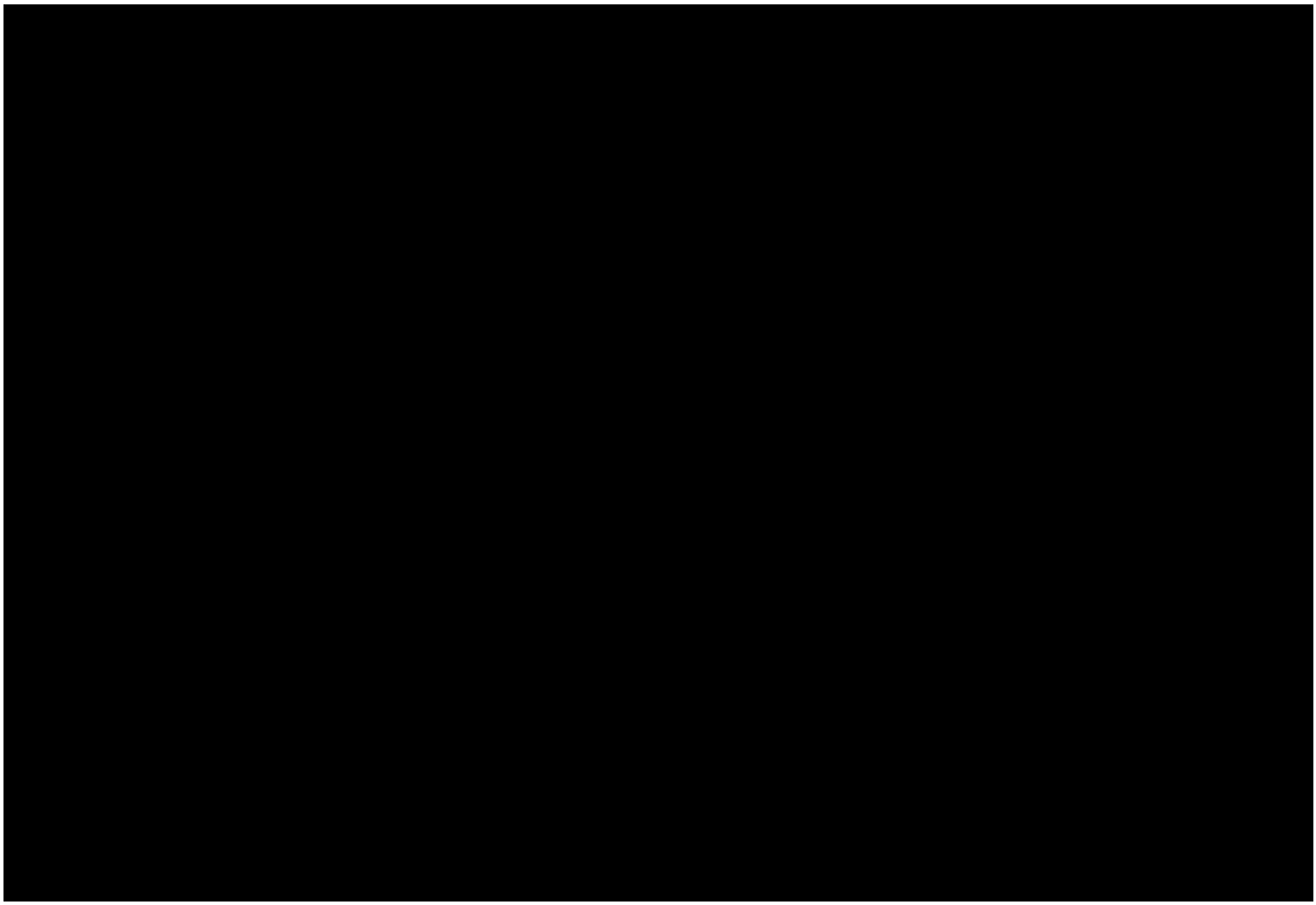
**Statistical Analysis Plan**

**Approval**

**Signature Page**



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# 1 Abbreviations

| | |
|---|---|
| AE | Adverse Event |
| ATC | Anatomical Therapeutic Chemical |
| BID | Twice daily |
| BMI | Body Mass Index |
| CAT | COPD Assessment Test |
| CI | Confidence Interval |
| COPD | Chronic Obstructive Pulmonary Disease |
| EOT | End of Treatment |
| FAS | Full Analysis Set |
| $FEV_1$ | Forced Expiratory Volume in 1 Second |
| GOLD | Global Initiative for Chronic Obstructive Lung Disease |
| ICS | Inhaled Corticosteroid(s) |
| LABA | Long-Acting β2 Agonist |
| LAMA | Long-Acting Muscarinic Antagonist |
| LSM | Least Square Mean |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mMRC | Modified Medical Research Council Dyspnea Scale |
| PDE | Phosphodiesterase |
| PT | Preferred Term |
| SAE(s) | Serious Adverse Event(s) |
| SAP | Statistical Analysis Plan |
| SAS® | Statistical Analysis Software® |
| SAS | Safety Analysis Set |
| SD | Standard Deviation |
| SOC | System Organ Class |
| TEAE | Treatment-Emergent Adverse Event(s) |
| WHO | World Health Organization |
| WOCBP | Women of Childbearing Potential |

# 2 Introduction

## 2.1 Background

Chronic obstructive pulmonary disease (COPD) is characterized by progressive airflow obstruction which is largely irreversible. COPD is predicted to be the third leading cause of death and fourth most common cause of disability worldwide by 2030 (Stuckler, 2008). The primary goals of pharmacological treatment of COPD are to reduce symptoms, exacerbation frequency and exacerbation severity as well as to improve overall quality of life in patients with COPD. Current standard-of-care treatments include inhaled short- and long-acting bronchodilators (i.e., muscarinic antagonists [LAMA] and β2 agonists [LABA]) and inhaled corticosteroids (ICS) are utilized to manage symptoms of COPD (GOLD, 2024).

Tools to assess if treatment goals are attained include several patient-reported outcome questionnaires to assist in communications between the patient and physician. However, the uptake of these questionnaires into routine clinical practice is integral to the assessment of individualized treatment regimens (Stanford, et al., 2019). The COPD Assessment Test [CAT™; CAT] (Jones, et al., 2009) is a validated, short, and simple patient completed questionnaire. The CAT is often used in a clinical setting to assess further the COPD symptoms and impact of a patient's well-being.

Verona Pharma plc. is developing inhaled nebulized ensifentrine for the maintenance treatment of chronic obstructive pulmonary disease (COPD). Ensifentrine is a novel, small molecule, potent, and selective dual inhibitor of Phosphodiesterase 3 (PDE3) and PDE4. The dual mechanism of action of ensifentrine has both bronchodilatory and anti-inflammatory effects and has the potential to offer an important maintenance treatment option for the treatment of obstructive and inflammatory diseases of the respiratory tract, such as COPD, cystic fibrosis, and asthma (Donahue et al., 2023). Ensifentrine has been evaluated in 22 completed clinical studies involving approximately 3,000 subjects, of which 16 studies involving over 2,800 subjects comprise the COPD development program including pharmacokinetic, pharmacodynamic, Phase IIb, and Phase III studies. In two Phase III studies (RPL554-CO-301 [n=760] and RPL554-CO-302 [n=789]) ensifentrine (3 mg) treatment consistently demonstrated the bronchodilator profile of ensifentrine in subjects with moderate to severe COPD over 12 weeks while significant effects were shown across all key $FEV_1$ endpoints and a significant improvement in exacerbation frequency and severity was shown in both studies (Anzueto, et al., 2023). This Phase IIIb study will assess the effect of ensifentrine on CAT scores in subjects with moderate to severe COPD when added to standard of care in routine clinical practice.

### 2.2 Changes to Planned Analyses

Not applicable as this is the initial version of the SAP.

## 3 Study Objectives

The objectives for this study are as follows:

Primary Efficacy Objective: The primary efficacy objective for this study is to assess the proportion of responders to treatment with ensifentrine, defined as subjects with an improvement in individual CAT scores of $\geq 2$, when added to standard of care in symptomatic subjects with moderate to severe COPD in routine clinical practice.

Secondary Efficacy Objective: To investigate the effects of ensifentrine on COPD symptoms, as measured by the CAT in symptomatic subjects with moderate to severe COPD when added to standard of care in routine clinical practice.

Safety Objective: To summarize the safety profile of subjects treated with ensifentrine.

# 4 Investigational Plan and Study Design

This is a Phase IIIb, single-center, open-label study investigating the effect of treatment with twice daily nebulized ensifentrine (3 mg) over 12 weeks on CAT scores in subjects with moderate to severe COPD when added to standard of care in routine clinical practice.

At Visit 1, potential subjects will be provided with the informed consent for participation in the study. Following signature on the informed consent, the following information will be collected, and procedures performed to confirm subject eligibility for participation in the study in the following sequence:

- CAT Training followed by subject completion of the CAT on paper
- Modified Medical Research Council Dyspnea Scale (mMRC)
- Collect and record demographic data
- Eligibility review (inclusion and exclusion criteria)
- Review and record medical, surgical, COPD and smoking history
- Review of prior and concomitant medication

At Visit 2, subject eligibility will be confirmed (screening tests will be verified, and it will be assured that the subject meets all inclusion criteria, and no exclusion criteria). Subjects who are screen failures may be rescreened with approval from the Medical Monitor. Rescreened subjects should be assigned a new subject number different from the initial screening event. Spirometry will be performed, a physical examination completed, and vital signs will be assessed. Eligible subjects will receive a nebulizer and compressor and will be administered their first dose of ensifentrine (3 mg) in-clinic during training on nebulizer use. Adverse events will be assessed. Subjects will receive a 6-week supply of ensifentrine (3 mg) to be administered twice-daily (BID) with a standard jet nebulizer. Ensifentrine will be administered BID for a total of 12 weeks.

At Visit 3 (Week 6), subjects will return and complete the CAT first, their concomitant medication will be reviewed, their vital signs and safety will be assessed. Subjects will receive a 6-week supply of ensifentrine (3 mg) administered BID.

At Visit 4 (Week 12), subjects will complete the CAT first, their concomitant medication will be reviewed, their vital signs and safety will be assessed. After 12 weeks, treatment with nebulized ensifentrine (3 mg) will end.

A follow-up phone call will be made to the subject approximately one week after the end of treatment.

Subjects may remain on prescribed short- and long-acting COPD medications throughout participation provided they are not included in the prohibited medication list. COPD exacerbations should be treated at physician's discretion as per usual practice.

A subject is considered to have completed the study if he/she has successfully completed all scheduled visits and completed follow-up contact. With no rescheduled visits, the study should last approximately 14 weeks.

# 5 Sample Size Justification

A sample size of approximately 20 subjects provides the ability to demonstrate a responder proportion estimate statistically differs from zero. Assuming a 30 percent response rate in the study population, 20 subjects would provide an expected count of 6 events. The two-sided 95% confidence interval for the number of events generated via normal approximation is (1.199, 10.801). Thus,20 subjects provide the ability to demonstrate the derived proportion differs from zero determined by the lower two-sided 95% confidence limit derived from the estimated count using a normal approximation assuming a standard error equal to the square root of 6.

Twenty subjects also provide the ability to demonstrate the estimates of mean change from baseline does not extend to the clinically meaningful deterioration limit of (+2 units). Assuming estimated mean improvement of 1 unit with a corresponding standard deviation equal to 4.5, 20 subjects provide the ability to demonstrate the upper 95% confidence interval for a mean change from baseline estimate does not exceed 2 units.

# 6 Visit Schedule and Visit Windows

## Table 1: Schedule of Assessments and Procedures

| | Study Start | Treatment Period | | | Study End | Early Withdrawal / Termination[¥] | |
|---|---|---|---|---|---|---|---|
| | Screening | Day 1 (≤7 days) | Week 6 (42 ± 3 days) | Week 12 (42 ± 3 days) | 7 ± 3 days after Visit 4 | As Soon as Possible after EW/T | 7 ± 3 days after EW/T Visit |
| | Visit 1 | Visit 2 | Visit 3 | Visit 4 (EOT) | Follow-up | EW/T Visit | Follow-Up |
| Informed consent [A] | X | | | | | | |
| Inclusion/exclusion criteria (eligibility review) | X | Review, Update | | | | | |
| Demographics (date of birth, age, gender, race, ethnicity) | X | | | | | | |
| CAT™ training | X | | | | | | |
| CAT™ [B] | X* | | X* | X* | | | |
| mMRC (administered by study team) | X | | | | | | |
| Medical, surgical, smoking history | X | Review, Update | | | | | |
| Prior and concomitant medication | X | | | | | | |
| Vital signs (blood pressure and pulse rate) | | X | X | X | | X | |
| Height and Weight; BMI calculated | | X | | | | | |
| Brief physical exam [C] | | X | | | | | |
| Urine pregnancy test [D] | | X | X | X | | | |
| Pre- and post-bronchodilator Spirometry [E] | | X | | | | | |
| Nebulizer equipment materials dispensing, review, and training; collection at end [F] | | X | | X | | | |
| Study medication dispensing [G] | | X | X | | | | |
| In clinic study medication dosing | | X | | | | | |
| Concomitant medication review | | X | X | X | X | X | X |
| Study medication compliance | | | X | X | | X | |
| AE and SAE recording | | X | X | X | X | X | X |
| Phone call to subject | | | | | X | | X |

**Note**: Information and details on most of the Study Assessments and Procedures can be found in the protocol in Section **Error! Reference source not found.**. * The CAT™ is completed by the subject on paper first before any procedures and assessments. ¥ The early withdrawal / termination visit should be conducted as soon as possible. If possible, subjects should remain on study medication through the early termination visit (protocol Section **Error! Reference source not found.**).

A. Informed consent must be obtained by the process described in **Error! Reference source not found.** of the protocol. Consent must be obtained prior to any study procedures being performed.
B. Following informed consent, the CAT™ is performed first before any procedures and assessments.
C. Assessments of the Cardiovascular, Respiratory, Gastrointestinal, and Neurological systems.
D. Pregnancy Testing: Pregnancy testing will be conducted on women of childbearing potential only (refer to **Error! Reference source not found.** of the protocol).
E. Spirometry: Pre-bronchodilator testing will be conducted prior to dosing with albuterol. Post-bronchodilator testing should be conducted between 15- and 30-minutes following administration of 4 puffs of albuterol.
F. Collect study supplied compressor if allowed per local site practices.
G. Information on study medication, dosing and compliance, nebulizers and compressor can be found in protocol Section **Error! Reference source not found.**.

**Abbreviations**: AE=Adverse Event; BMI= Body Mass Index; CAT™ = COPD Assessment Test™, COPD=Chronic Obstructive Pulmonary Disease; EOT=End of Treatment; mMRC=Modified Medical Research Council Dyspnea Scale; SAE=Serious Adverse Event; V=Visit; WOCBP=Women of Child-bearing Potential.

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# 7 Study Populations

Allocation of subjects to the analysis populations (and whether any subjects or specific data from a subject will be excluded) will be determined prior to database lock. Study populations will be defined as follows:

**Enrolled Analysis Set**: The Enrolled Analysis Set (EAS) will consist of all subjects who provided informed consent for this study. Subjects will be classified according to administration of study medication at study Day 1, and will be summarized with and without the administration of study medication.

**Full Analysis Set**: The Full Analysis Set (FAS) will consist of all subjects that were administered the study medication at Visit 2 and have a CAT completed at baseline and from at least one post-treatment visit. The full analysis set will be used for all efficacy analyses.

**Safety Analysis Set**: The Safety Analysis Set (SAS) will consist of all subjects who were administered the study medication at Visit 2. The safety analysis set will be used for all safety analyses and baseline summaries.

# 8 Statistical Methods

## 8.1 General Reporting Conventions

Study data will be made available in listings or electronic format as requested. Study results will be reported in tabular form using descriptive and inferential statistics. Standard numeric descriptive statistics include number observed (n), mean, standard deviation (SD), median, minimum, and maximum values. Standard categorical descriptive statistics include the count and percentages of subjects for each level of the variable summarized. Confidence intervals (CIs) will be two-sided 95% intervals. Unless specified otherwise, two-sided p-values of less than or equal to 0.05 or one-sided p-values of less than or equal to 0.025 will be considered statistically significant. All summaries and statistical analyses will be completed using Version 9.4 or later of the SAS Statistical Analysis System (SAS Institute, Inc. Cary, NC) for Windows x64.

## 8.2 Adjustments for Interim Analyses and Multiplicity of Endpoints

No interim analyses are planned for this study. As there is only one primary efficacy endpoint, no adjustments will be made for multiplicity.

## 8.3 Handling of Missing Data

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

## 8.4 Evaluations and Statistical Analyses

### 8.4.1 Subject Disposition

Study disposition will be summarized overall and presented in listing format. Disposition and baseline information will be summarized using the Enrolled population. For subjects undergoing more than 1 screening assessment, the last screening assessment will be included in disposition summaries. Study disposition information will be summarized through:

- Number of subjects screened.
- Number of screen failures and reason for failure.
- Number of subjects in each analysis population (EAS, FAS, and SAS).
- Number of subjects that completed the study.
- Number of subjects that completed each follow-up visit (Day 1, Week 6, Week 12, Follow-up phone call)
- Number of discontinued subjects and reason for discontinuation.
- Duration of follow-up in days summarized as a continuous variable.

Additionally, the number of subjects with major protocol deviations will be summarized by deviation type and category of violation overall. Major protocol deviations will also be included in subject listings.

### 8.4.2 Demographics and Baseline Characteristics

Demographics and baseline data including age, gender, race, ethnicity, height, weight, and BMI will be summarized descriptively overall and presented in listing format for the Safety Analysis Set. Medical history will be coded using MedDRA and summarized descriptively by SOC and PT for the Safety Analysis Set. Medical history will be provided in subject listings for the Safety Analysis Set. COPD history including COPD type, COPD diagnosis history, and COPD exacerbation history will be summarized descriptively and presented in listing format for the Safety Analysis Set. Smoking history will be summarized descriptively and presented in listing format for the Safety Analysis Set. Results from the Modified Medical Research Council (mMRC) dyspnea scale questionnaire will be presented in listing format for the Safety Analysis Set.

### 8.4.3 Prior and Concomitant Medications

Prior and concomitant medications will be coded using World Health Organization (WHO) drug code and summarized separately by Anatomical Therapeutic Chemical (ATC) levels 1, 2 and 4 for the Safety Analysis Set. Prior medications will denote medications used prior to the first dose of study medication. Concomitant medications will denote medications started prior to but continuing after receipt of study medication or medications started after receipt of study medication.

### 8.4.4 Treatment Compliance

Compliance to study medication will be based on dispensed and returned unused ampules for the safety population. Compliance will be presented for 12 weeks using summary statistics by time intervals (Day 1 to Week 6, Weeks 6-Week 12, and full study length), as well as using frequency counts by subgroups: <80%, 80-90%, 90-100%, >100%.

Compliance with study medication will be calculated on the number of ampules count (total dispensed – total returned) divided by the prescribed number of ampules expressed as a percentage, see calculations below. Patients should take the study medication twice daily. Patients are dispensed ampules at Visit X and return at Visit Y, however in the eCRF returned ampules will be recorded under Visit X.

For time interval compliance to study medication will be calculated as follows:

([N of Ampules dispensed at Visit X] − [N of Ampules returned at Visit Y])/ Denominator1 ∗ 100 Where Denominator1 is calculated with the following rules:

- N1 = Number of ampules expected. Calculated based on total N of Ampules dispensed at Week 6 and at Week 12, considering 2 ampules per day, apart from first dose (Week 6) or last dose (Week 12) date for completed patients where we would only consider 1 ampule per day calculated: {{[Date of Visit Y] - [Date of Dispensing at Visit X] + 1} * 2 - 1} for Week 6. *Note: this calculation considers the first dose administered on Day 1 at the site is included in the number dispensed for Week 6.*
- N2= Number of ampules between dispensing and returning visit calculated: {{[Date of Visit Y] - [Date of Dispensing at Visit X] + 1} * 2} - 1 for Week 6 and = Number of ampules between dispensing and returning visit calculated: {{[Date of Visit Y] - [Date of Dispensing at Visit X] + 1} * 2} - 2 for Week 12. *Note: this calculation considers the first dose administered on Day 1 at the site is included in the number dispensed for Week 6.*

- Week 6 and Week 12 summaries will use N2 for Denominator 1.
- In overall summaries if N1 ≥ N2 then Denominator1 = N2.
- In overall summaries if N1<N2 then Denominator1 = N1.

Overall compliance to study medication will be calculated 100 times (100*) the sum of Week 6 and Week 12 compliance divided by the sum of Denominator 1 over Week 6 and Week 12.

### 8.4.5 Primary Efficacy Endpoint

#### *8.4.5.1 Primary Efficacy Hypothesis*

The primary efficacy endpoint for this study is the proportion of CAT responders, defined as an improvement from baseline ≥ 2, at Week 12. This will be evaluated for the null hypothesis that the proportion is not different than 0:

$$H_0: p = 0 \text{ vs. } H_1: p > 0$$

Where p is the proportion of subjects at Week 12 with an improvement from baseline of at least 2 in CAT total score. A two-sided unadjusted 95% confidence interval for the proportion will be used to determine study success with the lower bound of the CI > 0 indicating success.

#### *8.4.5.2 Primary Efficacy Analysis*

The FAS population will be used to assess the primary efficacy endpoint of proportion of CAT total score responders defined as improvement from baseline ≥ 2 at Week 12. The proportion of subjects classified as responders at week 12, standard errors, and corresponding 95% CI will be estimated by negative binomial regression with timepoint and background therapy (LABA+LAMA or LABA+LAMA+ICS) included as fixed effects, and with baseline CAT total score included as a covariate. The scale parameter in the negative binomial model will be held fixed by specifying a noscale option.

#### *8.4.5.3 Sensitivity and Supporting Analyses*

As a supporting analysis the proportion of CAT total score responders defined as improvement from baseline ≥ 2 will be analyzed at Week 6 in the same manner as the primary efficacy analysis.

As a sensitivity analysis the primary efficacy endpoint analysis will also be analyzed with subject included as a repeated measure to provide a robust standard error for the estimated proportion and to accommodate model misspecification. The scale parameter in the negative binomial model will be held fixed by specifying a noscale option.

### 8.4.6 Secondary Efficacy Endpoint

#### *8.4.6.1 Change from Baseline CAT Total Score*

The secondary endpoint of change from baseline in CAT total score will be evaluated at Week 6 and Week 12. Scores for the CAT total score ranges from 0-40. CAT total score will be summarized descriptively at baseline and each timepoint. A mixed model for repeated measures with timepoint and background therapy (LABA+LAMA or LABA+LAMA+ICS) included as fixed effects, and with baseline CAT total score included as a covariate. Subject will be included as a random effect and an unstructured covariance matrix will be used. The Kenward-Rogers approximation will be used for the denominator degrees of freedom. In the event the model fails to converge, a compound symmetry covariance structure will be used. Should the model fail to converge with a compound symmetry covariance structure, an ANCOVA model at each timepoint will be performed with background therapy included as a fixed effect and baseline

CAT total score included as a covariate. Least square mean estimates, standard errors, and corresponding 95% confidence limits will be presented for each post-treatment time of assessment. A plot of the least square means change from baseline in total score over time will be presented.

#### *8.4.6.2 Change from Baseline CAT Individual Item Analyses*

The CAT questionnaire contains 8 individual items with scores ranging from 0-5. Each individual item will be summarized at Week 6 and Week 12 in the same manner as the change from baseline CAT Total Score secondary efficacy endpoint. The baseline for individual items is the item score at the baseline assessment. Least square mean estimates, standard errors, and corresponding 95% confidence limits will be presented at each post-treatment time of assessment

### 8.4.7 Safety Evaluations and Analyses

All safety evaluations will be conducted on the safety population. Safety analyses will include incidence of adverse events and vital sign summaries.

#### *8.4.7.1 Adverse Events and SAEs*

An adverse event (AE) is any untoward medical occurrence in a subject or subject, temporally associated with the use of study medication, whether considered related to the study medication or not. AEs will be collected from time of first dose to follow-up contact. Medical and COPD condition(s) identified during screening will be documented as medical history and not as an AE unless the condition worsens during the study and meets the definition of an AE. Treatment-emergent adverse events (TEAE) are any events that occur after the first dose of study treatment. Serious adverse events (SAE) include any occurrence defined as an AE that results in any of the following:

- Death
- Is life-threatening
- Requires in-patient hospitalization or prolongation of hospitalization
- Results in persistent disability/incapacity
- Is a congenital anomaly/birth defect
- Other

AEs requiring hospitalization include any events at a hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE. For the "Other" criteria for SAEs, medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

In addition to seriousness, AEs will be classified based on intensity (mild, moderate, severe), and relatedness/causality (reasonable possibility or no reasonable possibility). AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC) and preferred term (PT). TEAEs, for the Safety Analysis Set, will be listed and summarized descriptively as the count and percentage of subjects experiencing the event in tabular form. Seriousness, relatedness, and outcome will be identified in the listings. AE summaries will include the following:

- Overall TEAE Summary
- TEAEs by SOC and PT
- Serious TEAEs by SOC and PT
- Treatment-related TEAEs by SOC and PT
- Serious treatment-related TEAEs by SOC and PT
- TEAEs by Severity and SOC and PT
- TEAEs Resulting in Discontinuation of Study Medication by SOC and PT
- TEAEs Resulting in Withdrawal from Study by SOC and PT
- TEAEs Resulting in Death by SOC and PT
- Listing of all TEAEs
- Listing of all Serious TEAEs
- Listing of all TEAEs Resulting in Death
- Listing of all TEAEs Resulting in Discontinuation of Study Medication
- Listing of all TEAEs Resulting in Withdrawal from Study

Adverse events will be counted once per patient per SOC and PT. Incidence of TEAEs will be presented by SOC and PT and broken down further by maximum severity and relationship to study medication. Severity is classed as mild/ moderate/ severe (increasing severity). TEAEs starting after the first dose of study medication with a missing severity will be classified as severe. If a patient reports a TEAE more than once within that SOC/ PT, the AE with the worst-case severity will be used in the corresponding severity summaries. Relationship to Study Medication, as indicated by the Investigator, is classed as “unknown”, “unrelated”, “unlikely to be related”, “possibly related” and “probably related” (increasing probability of relationship). A “related” TEAE is defined as a TEAE with a relationship to study medication as “possibly related” or “probably related” to study medication. TEAEs with a missing relationship to study medication will be regarded as “probably related” to study medication. If a patient reports the same AE more than once within that SOC/ PT, the AE with the worst-case relationship to study medication will be used in the corresponding relationship summaries. TEAEs leading to discontinuation of study medication are AEs recorded as “Study Treatment Permanently Discontinued” on the “Adverse Events” page of the eCRF. Serious adverse events (SAEs) are those events reported as “Serious” in “Adverse Events”. TEAEs leading to Death are those events reported as “Fatal”.

#### *8.4.7.2 Vital Signs*

Vital signs will be collected at Day 1, Week 6, and Week 12 visits and will include blood pressure and pulse rates. Vital signs, for the Safety Analysis Set, will be summarized

descriptively in tabular format as the values at each visit and change from baseline values for each parameter. Vital sign measurements will also be included in listing format. Abnormal and markedly abnormal values will be identified in the vital sign listings. Markedly abnormal values are defined in Table 2.

**Table 2: Markedly Abnormal Post-Baseline Vital Signs**

| Variable | Unit | Abnormally Low | Abnormally High |
|---|---|---|---|
| SBP | mmHg | • A decrease from Baseline of ≥ 40<br>• Value ≤ 90 | • An increase from Baseline of ≥ 40<br>• Value ≥ 180 |
| DBP | mmHg | • A decrease from Baseline of ≥ 20<br>• Value ≤ 50 | • An increase from Baseline of ≥ 20<br>• Value ≥ 105 |
| Pulse Rate | Bpm | • A decrease from Baseline of ≥ 30<br>• Value ≤ 50 | • An increase from Baseline of ≥ 30<br>• Value ≥ 110 |

#### *8.4.7.3 Physical Examination*

A brief physical exam will be conducted on the Day 1 visit and will include assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Physical examination results, for the Safety Analysis Set, will be provided in listing format.

#### *8.4.7.4 Pregnancy Test Results*

Urine pregnancy tests will be conducted at the Day 1, Week 6, and Week 12 visits on women of childbearing potential only. Urine pregnancy test results, for the Safety Analysis Set, will be provided in listing format.

# 9 References

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| Listing Number | Title | Population |
|---|---|---|
| 16.1.1 | Study Enrollment and Disposition | All Subjects |
| 16.1.2 | Screen Failures and Reason for Failure | All Subjects |
| 16.1.3 | Major Protocol Deviations | SAS Subjects |
| 16.1.4 | Demographics and Baseline Characteristics | SAS Subjects |
| 16.1.5 | Medical History | SAS Subjects |
| 16.1.6 | Smoking History | SAS Subjects |
| 16.1.7 | COPD History | SAS Subjects |
| 16.1.8.1 | Prior Medications | SAS Subjects |
| 16.1.8.2 | Concomitant Medications | SAS Subjects |
| 16.1.9 | Treatment Compliance | SAS Subjects |
| 16.1.10 | Modified Medical Research Council (mMRC) Dyspnea Scale Results | SAS Subjects |
| 16.2.1 | CAT Total Score Results by Timepoint | FAS Subjects |
| 16.2.2 | CAT Individual Item Score Results by Timepoint | FAS Subjects |
| 16.3.1.1 | Treatment-Emergent Adverse Events | SAS Subjects |
| 16.3.1.2 | Serious Treatment-Emergent Adverse Events | SAS Subjects |
| 16.3.2 | Vital Sign Results | SAS Subjects |
| 16.3.3 | Physical Exam Results | SAS Subjects |
| 16.3.4 | Urine Pregnancy Test Results | SAS Subjects |

| Figure Number | Title | Population |
|---|---|---|
| 14.2.1 | Plot of CAT Total Score LSM Change from Baseline Over Time | FAS Subjects |

# 11 Table, Figure and Listing Shells

Output shells will be provided in a separate document.