CLINICAL STUDY PROTOCOL

Protocol Title:	A Study Assessing the Effect of Ensifentrine on CAT™ Scores over 12 Weeks in Subjects with Moderate to Severe COPD
Protocol Number:	RPL554-CO-303
Version:	4.0
Investigational Product:	Ensifentrine
Short Title:	Ensifentrine CAT Study
Study Phase:	IIIb
Principal Investigator:	[redacted]
Sponsor Name:	Verona Pharma plc
Legal Registered Address	3 More London Riverside London, SE1 2RE UK
Regulatory Agency Identifying Number(s):	US IND Number: 133146 US NDA Number: 217389
Date of Protocol:	19 August 2024

Sponsor Signatory:

Medical Monitor name and contact information can be found in Appendix 2.

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document History

Protocol Version	Amendment #	Version Date	Substantial - timing
Version 1.0	Original protocol	11 April 2024	Original protocol
Version 2.0	Amendment 1.0	03 June 2024	Yes – prior to enrollment
Version 3.0	Amendment 2.0	27 June 2024	No – during enrollment
Version 4.0	Amendment 3.0	19 August 2024	No – during enrollment

Protocol Version 2.0, Amendment 1.0: 03 June 2024

Overall Rationale for the Amendment:

The protocol is amended to revise study objective and endpoint order, in addition to updating Table 5. Prohibited Medications/Therapy; Table 5. Permitted Medications; Table 6. Study Administrative Structure; Safety information; and Appendix 3 and Appendix 4. Minor administrative items were also addressed (e.g., spelling, punctuation, spaces, linked sections, and tables as well as Table and Section numbering, as appropriate).

Description of Changes in Protocol Version 2.0, Amendment 1.0: 03 June 2024		
Section # and Name	**Description of Change**	**Brief Rationale**
1.1. Synopsis 3.1. Objectives	The primary and secondary objectives were re-ordered as follows (bold=added text, strikethrough=deleted text): • Primary: **To assess the proportion of responders to treatment with ensifentrine based on the improvement in individual CAT scores when added to standard of care in symptomatic subjects with moderate to severe COPD in routine clinical practice.** ~~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.~~ • Secondary: **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.** ~~Assess the proportion of responders to treatment with ensifentrine based on the improvement in individual CAT when added to standard of care in routine clinical practice.~~	Objectives and endpoints were re-ordered.

1.1. Synopsis
3.2. Endpoints
	The primary and secondary endpoints were re-ordered as follows (bold=added text, strikethrough=deleted text):
	
	• Primary: **The proportion of CAT score responders, defined as an improvement from baseline of ≥2, at Week 12.**
	• **Secondary:**
	  • **The proportion of CAT score responders, defined as an improvement from baseline of ≥2, at Week 6.**
	  • **CAT score at Week 6 and Week 12 (change from baseline).**
	  • **CAT score at Week 6 and Week 12 (item-level change from baseline).**	

Description of Changes in Protocol Version 2.0, Amendment 1.0: 03 June 2024		
Section # and Name	**Description of Change**	**Brief Rationale**
1.1. Synopsis 4.1. Overall Design	Sentence was revised as follows (bold=added text, strikethrough=deleted text): 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 ~~are met~~, and no exclusion criteria ~~are met~~).	Clarifies Visit 2.
1.3. Schedule of Activities	The column heading for 'End of Study' was revised as follows (bold=added text, strikethrough=deleted text): ~~Week 13~~ 7 ± 3 days **after Visit 4** Eligibility and history revised to review, update for Visit 2. Review, ~~Confirm~~ **Update** Nebulizer equipment dispensing/collection was marked with 'X" at Visit 3 and Visit 4 to Section 6.1 and Section 6.6. Concomitant medication review was marked with 'X' at Follow-up visit (At Visit 4 and EW/T Visit) because it is listed in the protocol in Sections 6.8 and 8.1.5. Footnote F modified for clarity. [F]. Collect study supplied compressor if allowed per local site practices~~, otherwise study supplied compressors will note be returned and collected~~.	Clarifies to match the schema.
2.3. Benefit/Risk Assessment	This section was revised as follows (bold=added text): **Non-clinical and clinical data to date do not indicate any areas of medical safety concern considered related to ensifentrine treatment. Hypertension may be a potential risk due to incidence of hypertension adverse events (AEs) ≥1% and greater than placebo in both RPL554-CO-301 and RPL554-CO-302 (2.5% vs 1.4% and 1.0% vs 0.3% in ensifentrine and placebo groups, respectively). An increase in psychiatric adverse reactions were reported with use of ensifentrine. The most commonly reported psychiatric adverse reactions in the pooled 24-week safety population from the Phase III studies were insomnia (6 patients [0.6%] ensifentrine 3 mg; 2 patients [0.3%] placebo), and anxiety (2 patients [0.2%] ensifentrine 3 mg; 1 patient [0.2%] placebo). Depression-related reactions were reported including depression (1 subject [0.1%]), major depression (1 subject [0.1%]), and adjustment disorder with depressed mood (2 subjects [0.2%]) in patients receiving ensifentrine and no patients receiving placebo. One patient who received ensifentrine in the pooled 24-week safety population experienced a suicide-related adverse reaction (suicide attempt), and in Phase IIb study RPL554-CO-203, one patient who received ensifentrine 1.5 mg experienced a suicide-related adverse reaction (suicide). A causal relationship between ensifentrine and increased rates of psychiatric events could not be established.** **In a reproductive performance study, male rats had decreased sperm counts in the testis were observed at all doses. The clinical relevance of this observation is undetermined.** **Ensifentrine has demonstrated statistically and clinically significant bronchodilator as well as anti-inflammatory effects in non-clinical models and clinical studies with the potential to treat obstructive and inflammatory diseases of the respiratory tract, such as COPD, non-CF bronchiectasis, CF, and asthma. Ensifentrine has been assessed in clinical studies to date in COPD, CF, hospitalized COVID-19, and asthmatic patients. Considering the consistent improvements in lung function in subjects with COPD, asthma and**	Change reflects updated language to Investigator Brochure.

Description of Changes in Protocol Version 2.0, Amendment 1.0: 03 June 2024		
Section # and Name	**Description of Change**	**Brief Rationale**
	CF, and improvements in symptoms, and health-related quality of life across multiple studies in subjects with COPD, and substantial reduction in the rate and risk of moderate/severe COPD exacerbations along with the overall favorable safety profile in studies to date, the benefit- risk profile of ensifentrine is considered positive. **As always, Investigators should remain alert to the possibility of AEs manifesting in their patients and should handle these in accordance with protocol requirements.** ~~No significant medical risks to subjects have been identified from studies conducted thus far with ensifentrine administered in the solution formulation, suspension formulation, or dry powder formulation. A slight increase in mean heart rate (up to 12 beats per minute [bpm]) without reported medical significance at a 6 mg supratherapeutic doses has been reported in healthy volunteers (RPL554-PK-101). In subjects with COPD, transient increases in peak heart rate of 3 bpm vs placebo have been observed with the 6 mg twice daily dose only over 4 weeks. Rare cases of suicidal ideation and behavior, including one completed suicide, were also observed; however, a causal relationship with ensifentrine could not be established. Otherwise, the non-clinical and clinical data to date do not indicate any areas of particular medical safety concern.~~ ~~Effects on reproductive performance in male rats given the highest dose of 15.5 mg/kg/day included lower number of pairings of dosed males resulting in pregnancy in undosed females, higher pre and post implantation loss resulting in lower mean litter size, and lower sperm motility and higher abnormal sperm. No ensifentrine-related adverse effects were observed at 5.75 mg/kg/day (20.5 times the maximum recommended human dose based on area under the curve [AUC]). There were no effects on embryo-fetal survival and development in either rats or rabbits in the main embryo-fetal development studies. Ensifentrine had no effects on fertility or reproductive performance in female rats. Ensifentrine has statistically and clinically significant bronchodilator as well as antiinflammatory effects. As such, the clinical development of ensifentrine is focused on the treatment of obstructive and inflammatory lung diseases, including COPD. Considering the consistent improvements in lung function, symptoms, and health-related quality of life across multiple studies in subjects with COPD and the overall favorable safety profile in studies to date, the benefit/risk profile of ensifentrine is considered positive.~~	
4.2. Justification for Dose	The 1st and 2nd paragraphs of this section were revised to read as follows (bold=added text, strikethrough=deleted text): A 3 mg twice daily dose was selected as the Phase III dose based on data from two 4-week Phase IIb studies RPL554-CO-203 and RPL554-CO-205 which show clinically meaningful and statistically significant improvements in pulmonary function with the 3 mg dose over the 12-hour dosing interval, in **subjects** ~~patients~~ with or without additional bronchodilator background therapy. **Two phase III studies, RPL554-CO-301 and RPL554-CO-302 confirmed the efficacy and safety of 3 mg ensifentrine BID in subjects with COPD.** A review of safety and tolerability across all COPD studies including over 24 and 48 weeks has shown a safety profile similar to placebo, even when added on top of other bronchodilator therapies**, including LAMA and LABA therapies with or without ICS**.	Updated for justification.

<table>
<tr><th colspan="3">Description of Changes in Protocol Version 2.0, Amendment 1.0: 03 June 2024</th></tr>
<tr><th>Section # and Name</th><th>Description of Change</th><th>Brief Rationale</th></tr>
<tr><td>6.7.1. Permitted Medications</td><td>Table 4. Permitted medications was revised to read as follows (bold=added text):

Medication: LAMA+LABA ± ICS
Condition: Subjects will be required to remain on their maintenance COPD treatment inhaler(s) at a stable dose for the duration of the study. Must withhold prior to Visit 2 spirometry: 48 (once-daily) or 24 (twice-daily) hours.
Only approved COPD doses of ICS are permitted for enrollment and during study participation (e.g., Trelegy containing 100 mcg FF).
Maintenance therapy should resume once Visit 2 has been completed.</td><td>Changes to clarify COPD dose of inhaled corticosteroid.</td></tr>
<tr><td>6.7.2. Prohibited Medications/Therapy</td><td>Table 5. Prohibited Medications/Therapy was revised as follows (bold=added text, strikethrough=deleted text):

<table>
<tr><th>Medication</th><th>Time interval withheld prior to ~~screening~~ Visit 2</th></tr>
<tr><td>Inhaled Corticosteroids (e.g., ICS monotherapy, high dose inhaled corticosteroids)</td><td>IF taking LAMA+LABA, the use of ICS is prohibited at least 8 weeks prior and prohibited during the study.
IF taking LAMA+LABA+ICS, the use of ICS must be at a stable dose for at least 8 weeks prior and continue for the duration of the study.
IF taking LAMA+LABA+ICS, ICS doses not approved for COPD are prohibited for 8 week prior and during study participation (e.g., > 100 mcg/day).
ICS monotherapy is not permitted. ICS should not be initiated, dose changed, or discontinued during the study except for safety reasons</td></tr>
<tr><td>~~High dose inhaled corticosteroids (e.g., >1000 mcg of fluticasone propionate or equivalent)~~</td><td>~~4 weeks prior and prohibited during the study.~~</td></tr>
<tr><td>Theophylline and PDE4 inhibitors (e.g., roflumilast, apremilast, crisaborole)</td><td>8 weeks ~~48 hours~~ prior and prohibited during the study.</td></tr>
</table></td><td>Changes reflect when medications should not be used in relation to Visit 2 as well as clarification for steroid use (oral, systemic, or inhaled).</td></tr>
<tr><td>8.1.2.3</td><td>End of this section was revised to read as follows (bold=added text):
Investigators should pay special attention to clinical signs to ensure subjects have had no previous serious physical or mental illness(es). Refer to Note at the end of Section 8.1.1.5.</td><td>Clarification for Physical Exam</td></tr>
<tr><td>8.1.4. Visit 4</td><td>The following bullet was added to match with Table 1 (bold=added text):
Study equipment (Section 6.1) will be collected.</td><td>To match Table 1.</td></tr>
</table>

Description of Changes in Protocol Version 2.0, Amendment 1.0: 03 June 2024		
Section # and Name	**Description of Change**	**Brief Rationale**
8.4.7. Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs	The 2nd paragraph of this section was revised to read as follows (bold=added text): COPD exacerbations are an expected disease-related outcome, **unless the exacerbations manifest in an unusual or uncharacteristic manner**. COPD exacerbations including daily expected COPD symptoms (e.g., dyspnea, chest tightness, wheezing, cough, sputum, that are not associated with the dosing event) will not be collected as an AE unless they meet the definition of an SAE.	Clarification necessary for COPD exacerbation events.
8.4.8. Device Incidents	The 1st paragraph of this section was revised to read as follows (bold=added text): The Investigator, or responsible person according to local requirements (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device incidents to the IRB/IEC, **device manufacturer, or regulatory authorities, as required**. A device incident is defined as an incident related to the failure of a medical device, deterioration in its effectiveness, or inadequacy in its labeling or directions that led to the death or serious deterioration in health of a ~~patient~~ **subject**, user, or other person, or could do so were it to recur.	Clarification necessary for device events.
9.3.4 Safety Analyses	This section was revised to read as follows (bold=added text): TEAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC) and preferred term (PT) for each treatment. Adverse events will be included in **subject** ~~patient~~ listings. Seriousness, relatedness, and outcome will be identified in **subject** ~~patient~~ listings. Vital signs will be summarized as change from baseline values for each parameter. Vital signs will be included in **subject** ~~patient~~ listings. Abnormal values and marked abnormalities will be identified in subject listings.	Administrative change
Appendix 2. Regulatory, Ethical, and Study Oversight Consideration	Table 6. Study Administrative Structure was revised for pharmacovigilance as follows (bold=added text, strikethrough=deleted text): **United BioSource, LLC** (UBC) ~~920 Harvest Drive, Blue Bell, PA 19422~~ **1000 Continental Drive, Suite 600** **King of Prussia, PA 19406** All SAE **paper reporting CRFs** should be sent to **UBC (Appendix 3).**	Changes reflect new address for UBC .
Appendix 3. Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting	The section entitled "Events not Meeting the AE Definition" is revised as follows (bold=added text): Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure **should be assessed** using the AE/**SAE definitions**. The section entitled "Assessment of Causality" was revised as follows (bold=added text, strikethrough=deleted text): The Investigator may change his/her opinion of causality ~~in light of~~ **considering** follow-up information and send a SAE follow-up report with the updated causality assessment. The section entitled "Follow-up of AEs and SAEs" was revised to add (bold=added text) as **applicable local regulatory requirements will allow**.	SAEs will be reported on a paper form. Changes reflect how SAEs are reported and the SAE email address.

Description of Changes in Protocol Version 2.0, Amendment 1.0: 03 June 2024		
Section # and Name	**Description of Change**	**Brief Rationale**
	The section entitled "SAE Reporting to the Sponsor/Sponsor's designee via an Electronic Data Collection Tool" was removed entirely because there is no electronic data collection tool for SAEs for this study. The section entitled "SAE Reporting to Sponsor/ Sponsor's Designee via Paper CRF if eCRF is not Available" is revised as follows (bold=added text, strikethrough=deleted text): SAE Reporting to Sponsor/ Sponsor's Designee via Paper Form ~~CRF if eCRF is not Available~~ • **The Medical Monitor contact information can be found in Appendix 2 (Table 7).** • The primary mechanism for reporting an SAE to the Sponsor/Sponsor's designee will be the paper SAE reporting form. ~~electronic data collection tool~~. • **The SAE reporting form should be sent by fax to the fax number which appears on the form. As an alternative, the completed SAE reporting form can be scanned and sent as an attachment via email to: VeronaSafety@ubc.com.** • ~~If the eCRF is not available, facsimile transmission of the SAE paper CRF may be used to transmit this information to the Medical Monitor or the SAE coordinator.~~ • In rare circumstances and in the absence of facsimile **or scanning** equipment, notification by telephone is acceptable with a copy of the SAE data collection forms sent by overnight mail or courier service to ~~the medical monitor or the SAE coordinator~~ **UBC**. **The address is listed in Appendix 2 (Table 6).** • Initial notification via telephone does not replace the need for the Investigator to complete and sign the **SAE** ~~CRF~~ pages within the designated reporting time frames. • ~~Contacts for SAE reporting can be found in Appendix 2 on the Medical Monitor Contact Information page.~~	
Appendix 4. Contraceptive Guidance and Collection of Pregnancy Information	Minor administrative change was made to section entitled "Pregnancy Testing" (bold=added text): WOCBP should only be included after a negative pregnancy test ~~at~~ **during** screening is conducted prior to study medication dispensing. The section entitled "Male subjects with partners who become pregnant" is revised as follows (strikethrough=deleted text): 1st paragraph: The Investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in the study. ~~This applies only to male subjects who receive glycopyrrolate.~~ The section entitled "Female subjects who become pregnant" is revised as follows (bold=added text, strikethrough=deleted text): 1st Bullet - • The Investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor/**Sponsor Designee** within 24 hours of learning of a subject's pregnancy. o **The Medical Monitor contact information can be found in Appendix 2 (Table 7).** o **The primary mechanism for reporting Pregnancy to the Sponsor/Sponsor's designee will be the paper Pregnancy reporting form.**	Changes reflect those made in Appendix 3.

Description of Changes in Protocol Version 2.0, Amendment 1.0: 03 June 2024		
Section # and Name	**Description of Change**	**Brief Rationale**
	○ **The Pregnancy reporting form should be sent by fax to the fax number which appears on the form. As an alternative, the completed form can be scanned and sent as an attachment via email to: VeronaSafety@ubc.com.** 2nd Bullet – • **Any female subject who becomes pregnant while participating in the study will discontinue study medication.** The subject will be **approached and asked to consent to being** followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the subject and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will be no longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure. 3rd Bullet - • While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. **For SAE reporting, refer to Appendix 3.** Last Bullet- • ~~Any female subject who becomes pregnant while participating in the study will discontinue study medication and be withdrawn from the study.~~	

Protocol Version 3.0, Amendment 2.0: 27 June 2024

Overall Rationale for the Amendment:

The protocol is amended to reflect the FDA approval of ensifentrine (OHTUVAYRE™) for the maintenance treatment COPD in adult patients and the updated Clinical Investigator Brochure (v25). Minor administrative items were also addressed.

Description of Changes in Protocol Version 3.0, Amendment 2.0: 27 June 2024		
Section # and Name	**Description of Change**	**Brief Rationale**
Section 1.1. Synopsis	**Ensifentrine is a selective dual inhibitor of PDE3 and PDE4 which has demonstrated pronounced bronchodilation in subjects with chronic obstructive pulmonary disease (COPD) as well as anti-inflammatory effects in healthy subjects in clinical studies. Ensifentrine inhalation suspension 3 mg twice daily was recently approved in the United States (US) for the maintenance treatment of COPD in adult patients and is marketed under the tradename OHTUVAYRE™ (NDA 217389)** . ~~Verona Pharma plc. (Verona) is developing inhaled nebulized ensifentrine for the maintenance treatment of chronic obstructive pulmonary disease (COPD). A New Drug Application for ensifentrine (3 mg) inhalation suspension for the maintenance treatment of COPD was submitted to the US Food and Drug Administration (FDA) on 26 June 2023 and is currently under review by the FDA with a Prescription Drug User Fee Act target action date of 26 June 2024.~~	Ensifentrine was approved in the US by the FDA and is marketed as Ohtuvayre™ .

Description of Changes in Protocol Version 3.0, Amendment 2.0: 27 June 2024		
Section # and Name	**Description of Change**	**Brief Rationale**
Section 2.1. Study Rationale	~~Verona Pharma plc. (Verona) is developing inhaled nebulized ensifentrine for the maintenance treatment of chronic obstructive pulmonary disease (COPD). A New Drug Application for ensifentrine (3 mg) inhalation suspension for the maintenance treatment of COPD was submitted to the US Food and Drug Administration (FDA) on 26 June 2023 and is currently under review by the FDA with a Prescription Drug User Fee Act target action date of 26 June 2024.~~ **Ensifentrine inhalation suspension 3 mg twice daily was recently approved in the United States (US for the maintenance treatment of COPD in adult patients and is marketed under the tradename OHTUVAYRE™ (NDA 217389, "OHTUVAYRE").**	Ensifentrine was approved and is marketed as Ohtuvayre™ by the FDA.
Section 2.2.3. Ensifentrine	Ensifentrine is a novel, small molecule, **and is a** potent, selective dual inhibitor of Phosphodiesterase 3 (PDE3) and PDE4. **This novel mechanism of action leads to downstream bronchodilatory and anti-inflammatory effects and represents an important potential additional treatment option for patients with moderate to severe COPD, and other respiratory indications such as non-cystic fibrosis bronchiectasis (NCFBE), asthma and cystic fibrosis whose disease is manifest by airways obstruction and/or inflammation. Ensifentrine inhalation suspension 3 mg twice daily was recently approved in the United States (US) for the maintenance treatment of COPD in adult patients and is marketed under the tradename OHTUVAYRE for use with a standard jet nebulizer. As a new treatment for COPD, this new mechanism of action allows ensifentrine to be used as a monotherapy or added to current inhaled standard of care bronchodilator and anti-inflammatory therapies, producing complementary effects in patients needing additional therapeutic options.** ~~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.8~~	Ensifentrine was approved and is marketed as Ohtuvayre™ by the FDA.
Section 2.3. Benefit/Risk Assessment	Non-clinical and clinical data to date do not indicate any areas of medical safety concern considered related to ensifentrine treatment. Hypertension may be a potential risk due to incidence of hypertension adverse events (AEs) ≥1% and greater than placebo **in both phase III studies**, RPL554-CO-301 and RPL554-CO-302 (2.5% vs 1.4% and 1.0% vs 0.3% in ensifentrine and placebo groups, respectively). An increase in psychiatric adverse reactions were reported with use of ensifentrine. The most commonly reported psychiatric adverse reactions in the pooled 24-week safety population from the phase **III**~~3~~ studies were insomnia (6 subjects [0.6%] ensifentrine 3 mg; 2 subjects [0.3%] placebo), and anxiety (2 subjects [0.2%] ensifentrine 3 mg; 1 subject [0.2%] placebo). Depression-related reactions were reported including depression (1 subject [0.1%]), major depression (1 subject [0.1%]), and adjustment disorder with depressed mood (2 subjects [0.2%]) in subjects receiving ensifentrine and no subjects receiving placebo. One subject who received ensifentrine in the pooled 24-week safety population experienced a suicide-related adverse reaction (suicide attempt), and in Phase **II**b study RPL554-CO-203, one subject who received ensifentrine 1.5 mg experienced a suicide-related adverse reaction (suicide). A causal relationship between ensifentrine and increased rates of psychiatric events could not be established. In a reproductive ~~performance~~ **toxicity** study, ~~male rats had~~ decreased sperm counts in the testis were observed **male rats** at all doses. The clinical relevance of this observation is undetermined.	Administrative change.
Section 4.2. Justification for Dose	A 3 mg twice daily dose was selected as the ~~P~~**p**hase **III** ~~3~~ dose **for the COPD clinical trials** based on data from two 4-week Phase IIb studies	Ensifentrine was approved

Description of Changes in Protocol Version 3.0, Amendment 2.0: 27 June 2024		
Section # and Name	**Description of Change**	**Brief Rationale**
	RPL554-CO-203 and RPL554-CO-205 which show**ed** clinically meaningful and statistically significant improvements in pulmonary function with the 3 mg dose over the 12-hour dosing interval, in subjects with or without additional bronchodilator background therapy. Two ~~P~~**p**hase **III** ~~3~~ studies, RPL554-CO-301 and RPL554-CO-302 confirmed the efficacy and safety of 3 mg ensifentrine BID in subjects with COPD. **Ensifentrine 3 mg twice daily (OHTUVAYRE) is the approved dose and regimen for the maintenance treatment of COPD in adult patients (OHTUVAYRE Prescribing Information).** ~~A review of safety and tolerability across all COPD studies including over 24 and 48 weeks has shown a safety profile similar to placebo, even when added on top of other bronchodilator therapies, including LAMA and LABA therapies with or without ICS.~~ ~~No dose-related trends in AEs (including those related to cardiovascular or gastrointestinal systems) have been observed up to and including 6 mg twice daily ensifentrine in subjects with COPD.~~ ~~Changes in electrocardiogram (ECG) parameters and vital signs (blood pressure and pulse) have not been observed at any dose (except for a small and transient increase in peak heart rate [~3 bpm] with the 6 mg BID dose in COPD subjects after 4 weeks~~. ~~24-hour Holter monitoring in 324 subjects after 4 weeks (RPL554-CO-203) has not shown any data trends suggesting arrhythmogenic potential or difference compared to placebo including 6 mg twice daily ensifentrine.~~	and is marketed as Ohtuvayre by the FDA.
Section 6.0. Study Treatment.	In this protocol the terms 'investigational product,' and 'study medication' are the same and refer to the nebulized ensifentrine (3 mg) **or OHTUVAYRE**	Ensifentrine was approved and is marketed as Ohtuvayre by the FDA.
Appendix 2. Regulatory, Ethical, and Study Oversight Consideration	Table 6: Study Administrative Structure Added via email or fax to UBC information	Administrative change.
Appendix 3. Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting	The section entitled ***Assessment of Causality*** was updated to read as follows: **All efforts should be made to classify the AE according to the above categories.** The section entitled ***SAE Reporting to Sponsor/ Sponsor's Designee via Paper Form*** was updated to read as follows: • The Medical Monitor contact information can be found in Appendix 2 (Table 7). • The primary mechanism for reporting an SAE to the Sponsor/Sponsor's designee will be the paper SAE reporting form. • The SAE reporting form should be sent by fax to the fax number which appears on the form. As an alternative, the completed SAE reporting form can be scanned and sent as an attachment via email to: VeronaSafety@ubc.com. • ~~In rare circumstances and in the absence of facsimile or scanning equipment, notification by telephone is acceptable with a copy of the SAE data collection forms sent by overnight mail or courier service to UBC. The address is listed in Appendix 2 (Table 6).~~ • Initial notification via telephone **or email** does not replace the need for the Investigator to complete and sign the SAE pages within the designated reporting time frames.	Administrative change.

Protocol Version 4.0, Amendment 3.0: 19 August 2024

Overall Rationale for the Amendment:

The protocol is amended to increase the number of enrolled subjects from 7 to 10 taking triple COPD maintenance therapy (LAMA+LABA+ICS).

Changes are reflected in the Synopsis and in Section 5.1, Inclusion Criteria #9:

- Demonstrates stable use of dual (LAMA+LABA) or triple (LAMA+LABA+ICS) maintenance therapy, in any form (except nebulized) for at least 8 weeks prior to screening and agrees to continue use for the duration of the study. *Note: The number taking LAMA+LABA+ICS will be capped at ~~seven (7)~~ ten (10). The use of LAMA or LABA alone or with ICS is not permitted (e.g., LABA+ICS, LAMA).*

1.0 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title

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

Short Title

Ensifentrine CAT study.

Rationale

Ensifentrine is a selective dual inhibitor of PDE3 and PDE4 which has demonstrated pronounced bronchodilation in subjects with chronic obstructive pulmonary disease (COPD) as well as anti-inflammatory effects in healthy subjects in clinical studies. Ensifentrine inhalation suspension 3 mg twice daily was recently approved in the United States (US) for the maintenance treatment of COPD in adult patients and is marketed under the tradename OHTUVAYRE™ (NDA 217389).

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.[1] 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.[2]

The COPD Assessment Test (CAT™; CAT)[3–5] 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. This study will assess the effect of ensifentrine on CAT scores in patients with moderate to severe COPD when added to standard of care in routine clinical practice.

Objectives

<u>Efficacy</u>

- Primary: To assess the proportion of responders to treatment with ensifentrine based on the improvement in individual CAT scores when added to standard of care in symptomatic subjects with moderate to severe COPD in routine clinical practice.
- Secondary: 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

- Safety of ensifentrine.

Endpoints

Efficacy

- Primary: The proportion of CAT score responders, defined as an improvement from baseline of ≥2, at Week 12.
- Secondary:
  - The proportion of CAT score responders, defined as an improvement from baseline of ≥2, at Week 6.
  - CAT score at Week 6 and Week 12 (change from baseline).
  - CAT score at Week 6 and Week 12 (item-level change from baseline).

Safety

- Incidence and proportion of AEs.
- Change from baseline in vital signs (blood pressure and pulse rate).

Overall 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). 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, their concomitant medication 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, their concomitant medication reviewed, their vital signs and safety will be assessed. After 12 weeks, treatment with nebulized ensifentrine (3 mg) will end.

> *The CAT will be completed on paper at Visits 1, 3 and 4 prior to any study procedures to avoid influencing the subject's response. All questions must be answered. Answers to each question will be logged into the eCRF by the study team.*

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.

Investigators and Study Centers

One Investigator and study center is expected to participate in this study.

Subjects

Approximately 20 subjects are planned to be enrolled in and complete this study.

Potential subjects will be included if the following criteria are met: aged 40 – 80 years with a clinical diagnosis of stable, moderate-to-severe COPD (forced expiratory volume in 1 second [FEV_1] ≥30% and ≤75% of predicted normal); spirometry-confirmed airflow obstruction (pre- and post-bronchodilator FEV_1/FVC <0.70), a score of ≥10 on the CAT™; a score of ≥2 on the mMRC; taking inhaled (but not nebulized) LAMA+LABA or LAMA+LABA+ICS (capped at 10 subjects) for at least 8 weeks, and are able to use the standard jet nebulizer correctly.

Potential subjects with asthma or other significant lung disease, recent hospitalizations, or serious infections; are pregnant or breastfeeding; or are unsuitable to participate, as judged by the Investigator, will be excluded.

Refer to the complete eligibility list in Section 5.0.

Treatment Groups and Duration

All subjects meeting eligibility criteria and consenting to participation in the study will receive nebulized ensifentrine (3 mg) BID with a standard jet nebulizer for 12 weeks.

Total duration of subject participation is approximately 14 weeks.

Recruitment is anticipated to take 3 months.

Statistical Methods

In general, unless stated otherwise, continuous variables will be summarized using descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum values) and for categorical (nominal) variables, the number and percentage of subjects will be used.

Continuous endpoints will be summarized as change from baseline using a mixed model for repeated measures with model terms for time and background therapy, and with baseline included as a covariate. Within subject error will be modeled using an unstructured covariance matrix, and Kenward-Roger method will be used to estimate degrees of freedom. Least square mean estimates, standard errors, and corresponding 95% confidence limits will be presented at each post-treatment time of assessment.

Response frequencies will be summarized by negative binomial regression with model terms for time and background therapy, and with baseline included as a covariate. Response proportions, standard errors, and corresponding 95% confidence limits will be generated from estimated frequencies and presented for each post-treatment time of assessment. Within subject correlation in responder status will be modeled using an unstructured covariance matrix.

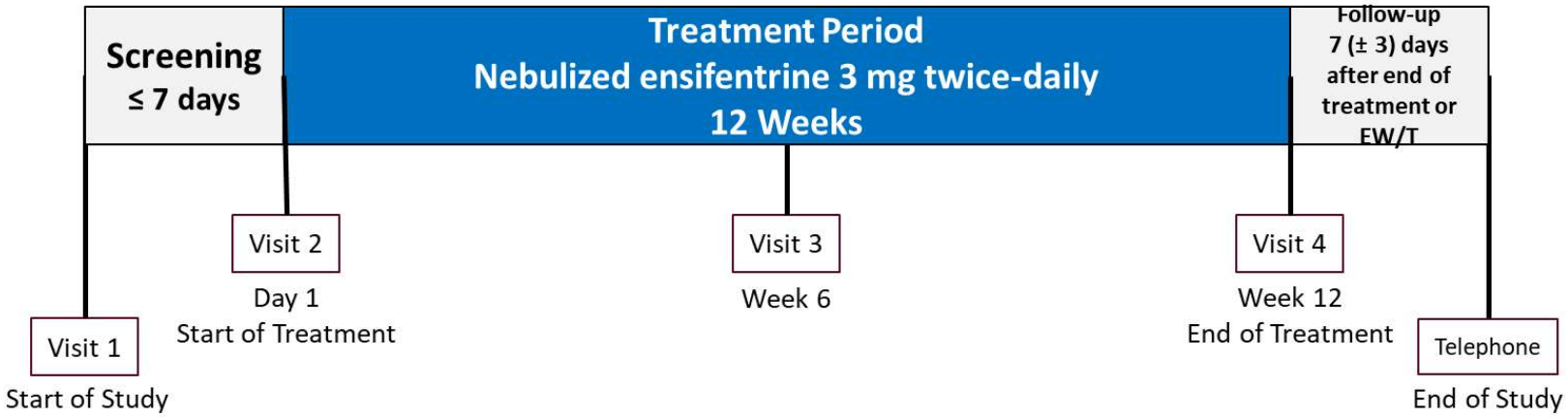
Sample Size

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 provides 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 and a standard error equal to square root of 6.

Twenty subjects also provides 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 provides the ability to demonstrate the upper 95% confidence interval for a mean change from baseline estimate does not exceed 2 units.

1.2 Schema

Figure 1: Study Schematic



Note: Once treatment with study medication ends, there will be a follow-up telephone call, regardless of study completion or early discontinuation of study medication.

Abbreviations: EW/T = early withdrawal or termination from study.

1.3 Schedule of Activities

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	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 Section 8.0. *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 (Section 7.2).

A. Informed consent must be obtained by the process described in Appendix 2. 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 Appendix 4).
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 Section 6.0.

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.

2.0 INTRODUCTION

2.1 Study Rationale

Ensifentrine inhalation suspension 3 mg twice daily was recently approved in the United States (US) for the maintenance treatment of COPD in adult patients and is marketed under the tradename OHTUVAYRE™ (NDA 217389, "OHTUVAYRE").

The COPD Assessment Test [CAT™; CAT][3–5] 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. This 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 Background

2.2.1 Chronic Obstructive Pulmonary Disease

COPD is characterized by progressive airflow obstruction which is largely irreversible. Chronic inflammation of the respiratory tract, acute exacerbations primarily caused by viral and/or bacterial infections, airway remodeling, and excessive mucus production are believed to contribute to the airflow obstruction and lung parenchymal destruction. COPD is predicted to be the third leading cause of death and fourth most common cause of disability worldwide by 2030, and chronic tobacco smoke exposure is believed to be a key etiological factor.[6]

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 and current standard-of-care treatments include inhaled short- and long-acting bronchodilators (i.e., muscarinic antagonists [LAMA] and β_2 agonists [LABA]) and inhaled corticosteroids (ICS) are utilized to manage symptoms of COPD.[1]

2.2.2 COPD Assessment Test™ (CAT™)

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.[2]

The CAT™ (CAT) is a validated, short, simple questionnaire that permits the evaluation and monitoring over time of COPD disease burden in routine clinical practice. The aim of the CAT is to aid health status assessment and communication between the patient and physician.[3,7]

Results can be viewed immediately since only the sum of the answers is needed to see the total score, in which the ranges correspond to the impact of COPD on the well-being and daily life of the patient. The ranges include 0-9 (mild impact), 10–20 (moderate impact), 21–30 (severe impact), and 31–40 (very severe impact). There are 8 subdomains, each having only one question, and these include Cough, Mucus, Chest Tight, Breathless, Limited Activities, Confident, Sleep and Energy. Patients rate their experience on a 6-point scale, ranging from 0 (no impairment) to 5 (maximum impairment).

2.2.3 Ensifentrine

Ensifentrine is a novel, small molecule, and is a potent, selective dual inhibitor of Phosphodiesterase 3 (PDE3) and PDE4. This novel mechanism of action leads to downstream bronchodilatory and anti-inflammatory effects, and represents an important potential additional treatment option for patients with moderate to severe COPD, and other respiratory indications such as non-cystic fibrosis bronchiectasis (NCFBE), asthma and cystic fibrosis whose disease is manifest by airways obstruction and/or inflammation. Ensifentrine inhalation suspension 3 mg twice daily was recently approved in the US for the maintenance treatment of COPD in adult patients and is marketed under the tradename OHTUVAYRE for use with a standard jet nebulizer. As a new treatment for COPD, this new mechanism of action allows ensifentrine to be used as a monotherapy or added to current inhaled standard of care bronchodilator and anti-inflammatory therapies, producing complementary effects in patients needing additional therapeutic options.[8]

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 one Phase IIb dose-ranging study (RPL554-CO-205) where subjects were dosed with ensifentrine (3 mg arm n=82) or placebo (n=84) BID in addition to once-daily tiotropium (5 mg), the CAT score was assessed at baseline, following a 2-week run in on tiotropium, and after 2 and 4 weeks after treatment. Results in the 3 mg arm demonstrated a larger score reduction from baseline than placebo at both time points and the pattern of improvement in the CAT score at Weeks 2 and 4 was similar to the improvement pattern observed with COPD symptoms and quality of life.

In two Phase III studies (RPL554-CO-301 [n=760] and RPL554-CO-302 [n=791]) ensifentrine (3 mg) treatment consistently demonstrated the bronchodilator profile of ensifentrine in subjects with moderate to severe COPD over 12 weeks.[9] Significant effects were shown across all key FEV_1 endpoints in both studies. Furthermore, ensifentrine-treated subjects showed significant improvements in dyspnea measured via Transition Dyspnea Index at Weeks 6, 12 and 24 and subjects also experienced improvements in COPD symptoms and quality of life in both studies. Over 24 weeks of treatment, ensifentrine-treated subjects demonstrated a substantial reduction in the frequency of moderate/severe exacerbations (RPL554 CO-301: 36% reduction, p=0.050;

RPL554 CO-302: 43% reduction, p=0.009) compared to placebo-treated subjects. There was also a reduction in the risk of moderate/severe exacerbations compared to placebo observed in both studies (RPL554 CO-301: 38% reduction, p=0.038; RPL554 CO-302: 42% reduction, p=0.009).[9]

Overall, ensifentrine was well-tolerated with a low incidence of adverse events (AEs), with rates generally similar to placebo (refer to the Investigator's Brochure [IB] for further detail).

2.3 Benefit/Risk Assessment

Non-clinical and clinical data to date do not indicate any areas of medical safety concern considered related to ensifentrine treatment. Hypertension may be a potential risk due to incidence of hypertension adverse events (AEs) ≥1% and greater than placebo in both phase III studies, RPL554-CO-301 and RPL554-CO-302 (2.5% vs 1.4% and 1.0% vs 0.3% in ensifentrine and placebo groups, respectively). An increase in psychiatric adverse reactions were reported with use of ensifentrine. The most commonly reported psychiatric adverse reactions in the pooled 24-week safety population from the phase III studies were insomnia (6 subjects [0.6%] ensifentrine 3 mg; 2 subjects [0.3%] placebo), and anxiety (2 subjects [0.2%] ensifentrine 3 mg; 1 subject [0.2%] placebo). Depression-related reactions were reported including depression (1 subject [0.1%]), major depression (1 subject [0.1%]), and adjustment disorder with depressed mood (2 subjects [0.2%]) in subjects receiving ensifentrine and no subjects receiving placebo. One subject who received ensifentrine in the pooled 24-week safety population experienced a suicide-related adverse reaction (suicide attempt), and in Phase IIb study RPL554-CO-203, one subject who received ensifentrine 1.5 mg experienced a suicide-related adverse reaction (suicide). A causal relationship between ensifentrine and increased rates of psychiatric events could not be established.

In a reproductive toxicity study, decreased sperm counts in the testis were observed in male rats at all doses. The clinical relevance of this observation is undetermined.

Ensifentrine has demonstrated statistically and clinically significant bronchodilator as well as anti-inflammatory effects in non-clinical models and clinical studies with the potential to treat obstructive and inflammatory diseases of the respiratory tract, such as COPD, non-CF bronchiectasis, CF, and asthma. Ensifentrine has been assessed in clinical studies to date in COPD, CF, hospitalized COVID-19 and asthmatic subjects. Considering the consistent improvements in lung function in subjects with COPD, asthma and CF, and improvements in symptoms, and health-related quality of life across multiple studies in subjects with COPD, and substantial reduction in the rate and risk of moderate/severe COPD exacerbations along with the overall favorable safety profile in studies to date, the benefit-risk profile of ensifentrine is considered positive.

As always, Investigators should remain alert to the possibility of AEs manifesting in their subjects and should handle these in accordance with protocol requirements.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of ensifentrine can be found in the Verona Pharma plc. Ensifentrine Clinical IB.

3.0 OBJECTIVES AND ENDPOINTS

3.1 Objectives

Efficacy

- Primary: To assess the proportion of responders to treatment with ensifentrine based on the improvement in individual CAT scores when added to standard of care in symptomatic subjects with moderate to severe COPD in routine clinical practice.
- Secondary: 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

- Safety of ensifentrine.

3.2 Endpoints

Efficacy

- Primary: The proportion of CAT score responders, defined as an improvement from baseline of ≥2 at Week 12.
- Secondary:
    - The proportion of CAT score responders, defined as an improvement from baseline of ≥2, at Week 6.
    - CAT score at Week 6 and Week 12 (change from baseline).
    - CAT score at Week 6 and Week 12 (item-level change from baseline).

Safety

- Incidence and proportion of AEs.
- Change from baseline in vital signs (blood pressure and pulse rate).

4.0 STUDY DESIGN

4.1 Overall 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. The CAT is a validated, short, and simple patient completed questionnaire which has been developed for use in routine clinical practice to measure the health status of patients with COPD.

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 (refer to Table 5 for Prohibited Medications)

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). 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.

> *The CAT will be completed on paper at Visits 1, 3 and 4 prior to any study procedures to avoid influencing the subject's response. All questions must be answered. Answers to each question will be logged into the eCRF by the study team.*

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.

4.2 Justification for Dose

A 3 mg twice daily dose was selected as the phase III dose for the COPD clinical trials based on data from two 4-week Phase IIb studies RPL554-CO-203 and RPL554-CO-205 which showed clinically meaningful and statistically significant improvements in pulmonary function with the 3 mg dose over the 12-hour dosing interval, in subjects with or without additional bronchodilator background therapy. Two Phase III studies, RPL554-CO-301 and RPL554-CO-302 confirmed the efficacy and safety of 3 mg ensifentrine BID in subjects with COPD. Ensifentrine 3 mg twice daily (OHTUVAYRE) is the approved dose and regimen for the maintenance treatment of COPD in adult patients (OHTUVAYRE Prescribing Information).

4.3 End of Study Definition

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.

The end of the study is defined as the date of the last follow-up contact of the last subject in the study.

5.0 STUDY POPULATION

Prospective approvals of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

5.1 Inclusion Criteria

1. Capable of giving informed consent indicating that they understand the purpose of the study and study procedures and agree to comply with the requirements and restrictions listed in the ICF and in this protocol.
2. Aged 40 to 80 years of age inclusive, at the time of screening.
3. Sex:

   - Males are eligible to participate if they agree to use contraception as described in the contraceptive guidance (Appendix 4) from screening and throughout the study and for at least 30 days after the last dose of study medication.
   - Females are eligible to participate if they are not pregnant, not breastfeeding, and ≥ 1 of the following conditions apply:
     a) Not a woman of childbearing potential (WOCBP) as defined in Appendix 4.
     OR
     b) A WOCBP who agrees to follow the contraceptive guidance in Appendix 4 from screening and throughout the study and for at least 30 days after the last dose of study medication.

4. Current or former cigarette smoker with a history of cigarette smoking ≥ 10 pack years. *Note: Pipe and/or cigar use cannot be used to calculate pack-year history. Former smokers are defined as those who have stopped smoking at least 6 months prior to screening. Smoking cessation programs are permitted during the study.*
5. An established clinical history of COPD as defined by the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines[10] with symptoms compatible with COPD.
6. Pre- and post-bronchodilator (4 puffs of albuterol) spirometry at Visit 2 demonstrating the following:

   - Pre- and post-albuterol FEV_1/forced vital capacity (FVC) ratio of < 0.70.
   - Post-albuterol FEV_1 ≥ 30 % and ≤ 75% of predicted normal.[11]

7. A score of ≥ 2 on the modified Medical Research Council Dyspnea Scale at Visit 1.
8. A score of ≥ 10 on the COPD Assessment Test™ at Visit 1.
9. Demonstrates stable use of dual (LAMA+LABA) or triple (LAMA+LABA+ICS) maintenance therapy, in any form (except nebulized) for at least 8 weeks prior to screening and agrees to continue use for the duration of the study. *Note: The*

number taking LAMA+LABA+ICS will be capped at ten (10). The use of LAMA or LABA alone or with ICS is not permitted (e.g., LABA+ICS, LAMA).

10. Capable of withholding short-acting rescue medications for 4 hours, Twice-Daily maintenance therapy for 24 hours or Once-Daily maintenance therapy for 48 hours prior to Visit 2.
11. Capable of using the study nebulizer correctly.
12. Ability to perform acceptable spirometry in accordance with ATS/ERS guidelines.[12]
13. Willing and able to attend all study visits and adhere to all study assessments and procedures.

5.2 Exclusion Criteria

1. Hospitalizations for COPD (or COPD exacerbation), pneumonia, or other serious infection or treatment with oral or parenteral (oral, intravenous, or intramuscular) glucocorticoids within the past 12 weeks.
2. Lower respiratory tract infection within the past 6 weeks or an active infection at screening.
3. History of life-threatening COPD, including Intensive Care Unit admission and/or requiring intubation within 1-year of screening.
4. Major surgery (requiring general anesthesia) within the past 6 weeks, lack of full recovery from surgery at screening, or planned surgery through the end of the study.
5. Concomitant clinically significant pulmonary disease other than COPD (e.g., asthma, tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, interstitial lung diseases, sleep apnea (unless controlled with stable continuous positive airway pressure [CPAP] use), known alpha-1 antitrypsin deficiency, core pulmonale or other non-specific pulmonary disease).
6. Severe comorbidities including unstable cardiac, (e.g., myocardial infarction within 1 year prior to screening, unstable angina within 6 months prior to screening, or unstable or life-threatening arrhythmia requiring intervention within 3 months prior to screening) or any other clinically significant medical conditions including uncontrolled diseases (e.g., endocrine, neurological, hepatic, gastrointestinal, renal, hematological, urological, immunological, psychiatric or ophthalmic diseases) 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.
7. HIV infection or other immunodeficiency.
8. Previous lung resection or lung reduction surgery within 1-year.
9. Long term oxygen use defined as oxygen therapy prescribed for greater than 12 hours per day. *Note: As needed oxygen use (≤ 12 hours per day) is not exclusionary.*

10. Pulmonary rehabilitation unless such treatment has been stable from 4 weeks prior to screening and remains stable during the study. *Note: Pulmonary rehabilitation programs should not be started or completed during participation in the study.*
11. History of or current malignancy of any organ system, treated or untreated within the past 5 years, except for localized basal or squamous cell carcinoma of the skin.
12. Significant psychiatric disease that would likely result in the subject not being able to complete the study, in the opinion of the Investigator.
13. Findings on physical examination that an investigator considers to be clinically significant.
14. Known alanine aminotransferase (ALT) ≥ 2 × upper limit of normal (ULN), alkaline phosphatase and/or bilirubin > 1.5 × ULN (isolated bilirubin > 1.5 × ULN is acceptable if fractionated bilirubin < 35%).
15. Known diagnosis of severe chronic kidney disease.[13]
16. Any other known abnormal clinical, cardiac or laboratory (hematology, biochemistry or viral) findings, deemed by an investigator to be clinically significant. *Note: Clinically significant abnormal chemistry and/or hematology may be repeated during the screening process.*
17. Use of prohibited medications within the time intervals defined in Section 6.7.2.
18. Current or history of drug or alcohol abuse within the past 5 years.
19. Women who are breast feeding.
20. Use of an experimental drug within 30 days or 5 half-lives of screening, whichever is longer, and/or participation in a study treatment-free follow-up phase of a clinical study within 30 days prior to screening.
21. Use of an experimental medical device or participation in a follow-up phase of an experimental medical device clinical study within 30 days prior to screening.
22. Affiliation with the investigator site, including an Investigator, Sub-Investigator, study coordinator, study nurse, other employee of participating investigator or study site or a family member of the aforementioned.
23. A disclosed history or one known to the Investigator of significant noncompliance in previous investigational studies or with prescribed medications.
24. Any other reason that the Investigator considers makes the subject unsuitable to participate.

5.3 Rescreening

Subjects who are screen failures (Section 5.4) may be rescreened with approval from the Medical Monitor. Rescreened subjects should be assigned a new subject number different from the initial screening event.

Rescreening due to failure to meet the following Inclusion Criteria is not allowed for Inclusion Criteria # 5, 6, 7, or 8.

5.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but did not receive study medication. See Section 7.1.1 for instructions on managing subjects who did not meet the eligibility criteria but received study medication in error.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

6.0 STUDY TREATMENT

Subjects will receive ensifentrine administered using the inhaled route via a standard jet nebulizer supplied by the Sponsor.

In this protocol the terms 'investigational product,' and 'study medication' are the same and refer to the nebulized ensifentrine (3 mg) or OHTUVAYRE.

6.1 Dispensing of Medical Devices

Subjects will be dispensed study supplied medical devices as per the schedule outlined in the Schedule of Activities (SoA) (Table 1).

No Sponsor manufactured medical device is used in this study.

Each eligible subject will be dispensed a study supplied nebulizer, with a compressor:

- PARI LC ®Sprint nebulizer
- PARI PRONEB ®Max Aerosol Delivery System or equivalent

At Visit 3, a new PARI LC Sprint® nebulizer will be supplied, if needed. Instructions for medical device use are provided in the package insert.

The study medication should only be administered with the study provided nebulizer. No medications other than the study medication should be administered with the study provided nebulizer.

6.2 Dispensing of Study Medication

Subjects will be dispensed study medication kit(s) as per the schedule outlined in the Schedule of Activities (SoA) (Table 1).

6.3 Administration of Study Medication

Study medication will be administered by inhalation of an aerosol generated by the study supplied reusable nebulizer attached to the compressor.

6.3.1 Dosing in the Clinic

At Visit 2, the first dose of study medication will be administered in-clinic with the study supplied nebulizer and compressor.

- Following informed consent and eligibility confirmation, study medication will be administered by inhalation of an aerosol generated by the reusable study supplied nebulizer attached to a study supplied compressor.
- The site staff member will need to follow the nebulizer Set-Up instructions provided with the nebulizer and the Pharmacy Manual to prepare and administer study medication.

- Administration of nebulized study medication will be observed by the site staff member from start of nebulization until end time of nebulization. The site staff member MUST administer and observe study medication.
- Study medication nebulization time should be approximately 5 to 10 minutes.
- The end time of study medication nebulization is when a slight sputtering sound from the nebulizer is heard.
- The date, the start time, and the end time of study medication nebulization will be recorded by the site staff member in the subject source document and the electronic case report form (eCRF).

6.3.2 Dosing at Home

Subjects will take their study supplied nebulizer and compressor as well as instructions home for use during the study.

Following Visit 2, subjects will self-administer their daily morning and evening doses of study medication at home at approximately the same times each day, approximately 12 hours apart, for 12 weeks.

- Prior to dosing at home, subjects must take their background maintenance COPD medication approximately 2 minutes prior to taking study medication.
- The morning doses of COPD maintenance medication and study medication must be taken at home in the morning prior to Visit 3 and Visit 4.
- Each subject will follow the Nebulizer Set-Up instructions and study medication label to prepare and self-administer the study medication by inhalation using the reusable study supplied nebulizer attached to the study supplied compressor.
- Study medication nebulization time should be approximately 5 to 10 minutes; until a slight sputtering sound from the nebulizer is heard.

Subjects will be instructed as follows:

- Only a study supplied nebulizer and compressor may be used to administer study medication. Only study medication may be used in the study supplied nebulizer and compressor.
- Discard used study medication ampules and open foil pouches of used study medication at home.
- Return ***unused*** study medication ampules to the clinic at Visit 3 and Visit 4 for collection, and assessment of medication compliance by a site staff member (Section 6.6).

6.4 Investigational Product/ Study Medication

Investigational product/study medication is described in Table 2.

Table 2: Investigational Product/Study Medication Details

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

The ensifentrine formulation [redacted], and supplied as a 2.5 mL nominal fill in single unit-dose low density polyethylene (LDPE) translucent ampule overwrapped in a foil pouch.

Ensifentrine is manufactured using aseptic manufacturing techniques in accordance with Good Manufacturing Practice guidelines and will be provided to the site as subject kits to be dispensed at Visit 2 and Visit 3.

6.4.1 Study Medication Formulation Information

The study medication formulation constituent and concentrations are described in Table 3.

[redacted]

6.5 Preparation/Handling/Storage/Accountability

Study medication should be stored below 25°C (77°F) at controlled room temperature and should not be frozen.

An investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study medication received and any discrepancies are reported and resolved before use of the study medication.

All study medication must be stored in a secure, environmentally controlled, limited access, monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized study center staff.

The temperature should be monitored, and logs maintained in areas where study medication is stored. If temperature conditions have been compromised or any study medication has not been stored appropriately, this should be documented, and the study medication quarantined until the Sponsor has been notified and confirmed whether it may be used.

Only subjects meeting the eligibility criteria in the study may receive study medication and only authorized study center staff may supply or administer study medication.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study medication accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study medication are provided in the Pharmacy Manual.

The Investigator, a member of the study center staff, the site pharmacist, or pharmacy team member must maintain an adequate record of the receipt and distribution of all study medication using the Drug Accountability Form. These forms must be available for inspection at any time.

6.6 Study Medication Compliance

The prescribed dosage, timing, and mode of administration may not be changed. Any departures from the intended regimen must be recorded in the eCRFs.

At Visit 3 (Week 6), prior to dispensing study medication, previously dispensed/unused study medication will be retrieved, and compliance assessed by the site staff member. Subjects exhibiting poor compliance, as assessed by the number of ampule/foil pouch counts dispensed and returned, should be counseled on the importance of good compliance to the study dosing regimen and this counseling should be documented in the subject source document.

At Visit 4 (Week 12), previously dispensed/unused study medication will be retrieved, and compliance assessed by the site staff member.

Non-compliance is defined as taking less than 70% of study medication during any evaluation period (visit to visit).

6.7 Concomitant Therapy

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy (Table 7).

6.7.1 Permitted Medications/Therapy

Permitted COPD rescue and maintenance medications are provided in Table 4. Subjects must demonstrate stable use of prescribed long-acting maintenance medications for at least 8 weeks prior to screening.

Subjects may continue use of their prescribed inhaled short-acting muscarinic antagonists (SAMA), short-acting β2 agonist (SABA), LABA+LAMA or LABA+LAMA+ICS in any form (except nebulized) while participating. Changes in any of these treatments should not occur during participation, except in the case of a safety issue. New medications or treatments should not be started during participation unless necessary for safety reasons.

Table 4: Permitted Rescue and Background Medications

Medication	Condition
SABA and/or SAMA (e.g., albuterol, ipratropium)	For use as rescue medication only during the study, on an as needed basis. Must withhold prior to Visit 2 spirometry: 4 hours.
LAMA+LABA ± ICS	Subjects will be required to remain on their maintenance COPD treatment inhaler(s) at a stable dose for the duration of the study. Must withhold prior to Visit 2 spirometry: 48 (once-daily) or 24 (twice-daily) hours. Only approved COPD doses of ICS are permitted for enrollment and during study participation (e.g., Trelegy containing 100 mcg FF). Maintenance therapy should resume once Visit 2 has been completed.
Abbreviations: COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroids; LAMA = long-acting muscarinic antagonist; LABA = long-acting β2 agonist; SAMA = short-acting muscarinic antagonists; SABA = short-acting β2 agonist.	

6.7.2 Prohibited Medications/Therapy

Prohibited medications and therapies are provided in Table 5. Prohibited medications are not to be taken during study conduct.

Table 5: Prohibited Medications/Therapy

Medication	Time interval withheld prior to Visit 2
Oral, systemic or parenteral steroid therapies	3 months prior and prohibited during the study.
Antibiotics for lower respiratory tract infection or chronic use of antibiotics	6 weeks prior and prohibited during the study.
Inhaled Corticosteroids (e.g., ICS monotherapy, high dose inhaled corticosteroids)	IF taking LAMA+LABA, the use of ICS is prohibited at least 8 weeks prior and prohibited during the study. IF taking LAMA+LABA+ICS, the use of ICS must be at a stable dose for at least 8 weeks prior and continue for the duration of the study. IF taking LAMA+LABA+ICS, ICS doses not approved for COPD are prohibited for 8 week prior and during study participation (e.g., > 100 mcg/day). ICS monotherapy is not permitted. ICS should not be initiated, dose changed, or discontinued during the study except for safety reasons.
Oral leukotriene inhibitors (i.e., montelukast, zafirlukast, zileuton)	48 hours prior and prohibited during the study.
Theophylline and PDE4 inhibitors (e.g., roflumilast, apremilast, crisaborole)	8 weeks prior and prohibited during the study.
Terbutaline	24 hours prior and prohibited during the study.
Nebulized SABA, SAMA, LAMA, LABA or ICS	8 weeks prior and prohibited during the study.
Oral $beta_2$-agonists	1 week prior and prohibited during the study.
Abbreviations: COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroids; LAMA = long-acting muscarinic antagonist; LABA = long-acting β2 agonist; SAMA = short-acting muscarinic antagonists; SABA = short-acting β2 agonist.	

6.7.3 Recording Use of Concomitant Medications

Information on all medications and therapies the subject takes other than the study medication, including over-the-counter drugs, must be collected, and recorded.

All COPD medications used within the past 3 months should be recorded on the concomitant medication page of the eCRF along with reason for use, dates of administration (start and end dates), and dosing information (dose and frequency).

- Documentation of background maintenance medications (LAMA+LABA or LABA+LAMA+ ICS) use prior to and during the study should be recorded on the concomitant medication page of the eCRF along with reason for use, dates of administration (start date), and dosing information (dose and frequency). End date should be documented as “Ongoing.”
- Documentation of rescue medication use prior to and during the study should be recorded on the concomitant medication page of the eCRF along with reason for use, dates of administration (start and end dates), and dosing information (dose and frequency). End date should be documented as “Ongoing.”

Any vaccine that is recommended by the subject's healthcare provider is permitted during the study and should be collected and recorded.

All non-COPD medications will be recorded in the eCRF at Visit 1 and changes recorded during the study. Information recorded will include, but may not be limited to items such as:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including route, dose, and frequency.

6.8 End of Study Procedures

Seven ± 3 days after Visit 4 (or Early Withdrawal/Termination) (Table 1), the site should contact the subject by telephone to complete the following assessments:

- Concomitant medications
- AEs and SAEs

6.9 Treatment After the End of Study

There are no plans to provide post-study treatment, including study medication for compassionate use, following study completion.

After the End of Study Follow-up phone call (Table 1), subjects may resume conventional COPD therapy as prescribed by the investigator or other physician.

Medications initiated after the end of study treatment should not be entered into the eCRF except for those given for a SAE.

7.0 DISCONTINUATION OF STUDY MEDICATION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Medication

Subjects may permanently discontinue study medication before the end of the study if they choose to or at the Investigator's discretion. Subjects who permanently discontinue study medication are required to withdraw from the study after completion of the Early Withdrawal/Termination procedures described in Table 1 and Section 7.2 as soon as possible.

Circumstances potentially requiring or actually resulting in discontinuation of study medication are described below.

7.1.1 Does Not Meet Criteria

A subject who does not meet the Eligibility Criteria (Section 5.0) should not receive study medication, will be considered a screen failure (Section 5.4), and may be eligible for rescreening (Section 5.3).

If a subject who does not meet the Eligibility Criteria inadvertently receives study medication, the Medical Monitor must be contacted and will consult with the Sponsor to determine if the subject may continue, must be discontinued from study medication, and/or discontinued from the study. Such subjects, if discontinued, may be replaced, but are not eligible for rescreening (Section 7.1.1).

7.1.2 Positive Pregnancy Test in Females

Women who are pregnant or breastfeeding are not eligible to participate. Pregnancy testing will be conducted in women of childbearing potential during screening and at other times specified in the SoA (Table 1).

Women exhibiting a positive pregnancy test during the study will be discontinued from study medication and followed-up per the Collection of Pregnancy Information guidelines in Section 8.4.5 and Appendix 4.

7.1.3 COPD Exacerbation Withdrawal Criteria

A subject that experiences a COPD exacerbation during participation may be withdrawn from the study if requested by the subject or at the discretion of investigator.

7.1.4 Liver Chemistry Stopping Criteria

Subjects may be withdrawn for abnormal liver function as considered by the investigator if it is in best interest of the subject.
If any of these criteria are met, immediately discontinue study medication, and contact the Medical Monitor:

1. ALT ≥ 3 x ULN and bilirubin ≥ 2 x ULN (35% direct bilirubin) (or ALT ≥ 3 x ULN and INR > 1.5, if INR measured. INR measurement is not required, and the threshold value stated will not apply to subjects receiving anticoagulants), termed 'Hy's Law' must be reported as an SAE.
    a. *Note: Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.*
    b. The following are required if this criterion is met:
        i. Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies and quantitative total immunoglobulin G (IgG or gamma globulins).
        ii. Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week).[13]
        iii. Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen): quantitative hepatitis B DNA and hepatitis delta antibody. *NOTE: if hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus where needed.*[14]
2. ALT ≥ 8 x ULN.
3. ALT ≥ 5 x ULN but < < 8 x ULN persists for ≥ 2 weeks.
4. ALT ≥ 3 x ULN if associated with symptoms (new or worsening) believed to be related to hepatitis (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash, or eosinophilia).
5. ALT ≥ 5 x ULN but < 8 x ULN and cannot be monitored weekly for ≥ 2 weeks.

7.1.5 Other Criteria

Other criteria that may or may not require permanent discontinuation of study medication include but are not limited to AE, lack of efficacy, protocol deviation, non-compliance, study, or site closed/terminated, investigator discretion, or subject withdrawal of consent.

7.1.6 Discontinuation of the Study

If the Sponsor discontinues or terminates the study, all subjects will be permanently discontinued from study medication and should complete the Early Withdrawal/Termination procedures described in Table 1 and Section 7.2 as soon as possible.

7.2 Subject Discontinuation/Withdrawal from the Study

A subject may withdraw from the study at any time at his/her own request or may be withdrawn from administration of study medication and from all study participation at the discretion of the Investigator at any time for safety, behavioral, compliance, or administrative reasons. See the SoA (Table 1) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

- If the subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the study center study records.

If a subject is withdrawn prior to completion of the study, every attempt should be made to have the subject complete the Early Withdrawal/Termination procedures in the SoA (Table 1) as soon as possible and the End of Study follow-up phone call (Section 6.8).

7.3 Lost to Follow-up

A subject will be considered lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study center.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The study center must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to be lost to follow-up and will be discontinued from the study.

8.0 STUDY ASSESSMENTS AND PROCEDURES

Subjects may not complete any screening procedures unless all prohibited medications/therapy described in Section 6.7.2 have been withheld for the defined time interval.

Study procedures and their timing are summarized in the SoA (Table 1).

Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study medication.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a Screening Log to record details of all subjects screened and to confirm eligibility or record reasons for screen failure, as applicable.

Procedures conducted as part of the subject's routine clinical and obtained before signing of the ICF may be utilized for the screening process or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Table 1).

See Section 5.4 for specific information to be collected for screen failures.

8.1 Visits

Planned timepoints for all assessments are provided in the SoA (Table 1).

8.1.1 Visit 1

8.1.1.1 Informed Consent

Informed consent must be obtained according to the informed consent process described in Appendix 2.

8.1.1.2 Demographic Variables

Demographic variables will be recorded. These include date of birth, age, gender, race, ethnicity.

8.1.1.3 COPD Assessment Test (CAT™)

Site staff will review the CAT form and provide instructions to the subject. The CAT will be completed on paper by the subject per the instructions in Section 8.2. The completed CAT will be logged into the eCRF by the study team.

- The order should be CAT followed by the mMRC.

8.1.1.4 Modified Medical Research Council Dyspnea Scale (mMRC)

The mMRC dyspnea scale is a questionnaire that measures COPD symptoms and defines symptom burden (refer to Appendix 5).[15] Site staff will administer/interview the subject to complete the mMRC dyspnea scale questionnaire and record the score in the eCRF.

8.1.1.5 Medical, Medication and Smoking History

A history of relevant current or past medical conditions, surgical history, COPD history, and smoking history will be obtained:

- Medical history, relevant surgical history and medical conditions will be recorded. *Note: Minor surgical procedures (e.g., tonsillectomy, appendectomy) performed more than 5 years prior to screening do not need to be recorded.*
- COPD history will be recorded and includes COPD diagnosis history and COPD exacerbation history.
- Current and prior medications will be recorded (Section 6.7.3).
- COPD type (emphysema and/or chronic bronchitis), as assessed by the investigator or medical professional). Chronic bronchitis is defined as "regular production of sputum for 3 or more months in 2 consecutive years (in the absence of other conditions that may explain it)".[1]
- Smoking history (current or former) will be recorded. Former smokers are defined as those who have stopped smoking for at least 6 months. Pack years calculation: [number of pack years = (number of cigarettes per day / 20) × number of years smoked (e.g., 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years)]

Note: Medical and COPD condition(s) identified during screening will be documented as medical history and not as an AE(s) unless the condition worsens during the study and meets the definition of an AE.

8.1.1.6 Eligibility Criteria

Subject eligibility will be assessed for all inclusion criteria (Section 5.1) and exclusion criteria (Section 5.2).

8.1.2 Visit 2

Medical and COPD history and concomitant medications will be reviewed, and any changes recorded. It will be confirmed that each subject meets all inclusion criteria and no exclusion criteria prior to the dispensing of study equipment and study medication.

8.1.2.1 Vital Signs

Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

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

8.1.2.2 Height and Weight

Height in centimeters (cm), weight in kilograms (kg), and body mass index will be measured and recorded.

8.1.2.3 Physical Examination

A physical examination will include assessments of the Cardiovascular, Respiratory, Gastrointestinal, and Neurological systems.

Investigators should pay special attention to clinical signs to ensure subjects have had no previous serious physical or mental illness(es). Refer to Note at the end of Section 8.1.1.5.

8.1.2.4 Urine Pregnancy Test

A urine pregnancy test will be conducted only on women of childbearing potential (refer to Appendix 4).

8.1.2.5 Spirometry Assessment

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.

Spirometry will be obtained that meets or exceeds the ATS minimal performance recommendations.[12]

- Prior to the spirometry measurement, the site staff will train each subject on how to perform acceptable spirometry maneuvers.
- Acceptable spirometry efforts should have a satisfactory start of test and end of forced expiration (plateau in the volume-time curve) and be free from artifacts due to cough, glottic closure, early termination, poor effort, obstructed mouthpiece, equipment malfunction, or other reason.[12]
- For FEV_1 and FVC determinations, at least 3 but no more than 8 acceptable spirometry efforts should be obtained.
- The largest FEV_1 and FVC from the 3 acceptable efforts should be recorded, even if they do not come from the same effort.

Subjects should refrain from smoking and/or caffeinated beverages prior to spirometry as follows:

- No smoking for at least 1-hour prior to spirometry assessment.
- Abstain from drinking caffeinated beverages (e.g., tea, coffee) for 2 hours prior to spirometry assessment.

8.1.2.6 Study Equipment Dispensed

Subjects will be trained in the use of the PARI LC Sprint nebulizer and PARI PRONEB Max Aerosol Delivery System (compressor), which will be used for inhalation of study medication during treatment (Section 6.1).

Site staff will review the nebulizer information and instructions provided by the manufacturer with the subject (e.g., Instructions for Use, located in the Pharmacy Manual). The subject will receive hands on training on the use of the nebulizer which will coincide with administering of the first dose of study medication (Section 6.3.1). The nebulizer and equipment will be taken home (Section 6.1).

8.1.2.7 Study Medication Dispensed

Study Medication will be dispensed (Sections 6.2 and 6.3.2): 6 weeks supply of ensifentrine (3 mg).

8.1.2.8 Study Medication Dosed (in-clinic)

Subject will be administered first dose of Study Medication in-clinic during training on the use of the nebulizer and compressor (Section 6.3.1).

8.1.2.9 Safety Assessment

Subjects will be assessed for any adverse events per instructions in Section 8.3.2.

8.1.3 Visit 3

Visit 3 will take place at Week 6 (42 ± 3 days after Visit 2). The following will occur:

- The CAT will be completed on paper (Section 8.2), concomitant medication reviewed and any changes recorded, and vital signs will be taken (Section 8.1.2.1).
- Unused Study Medication will be collected and assessed for compliance per Section 6.6.
- Study Medication will be dispensed: 6 weeks supply of ensifentrine (3 mg). A new nebulizer cup may be dispensed, if needed.
- Subjects will be assessed for any adverse events per instructions in Section 8.3.2.

8.1.4 Visit 4

Visit 4 will take place at Week 12 (42 ± 3 days after Visit 3). The following will occur:

- The CAT will be completed on paper (Section 8.2), concomitant medication reviewed and any changes recorded, and vital signs will be taken (Section 8.1.2.1).
- Unused Study Medication will be collected and assessed for compliance per Section 6.6.
- Study equipment (Section 6.1) will be collected.

- Subjects will be assessed for any adverse events per instructions in Section 8.3.2.

8.1.5 Telephone Follow-up

The final study contact is a follow-up telephone call 7 ± 3 days after Visit 4 (or EW/T). The following will occur:

- Concomitant medication will be reviewed, and any changes recorded.
- Subjects will be asked about any adverse events per instructions in Section 8.3.2.

8.2 Efficacy Assessment

Planned timepoints for all efficacy assessments are provided in the SoA (Table 1).

The CAT™ is a one-page, 8-item questionnaire suitable for completion by patients diagnosed with COPD. When completing the questionnaire, individuals rate their experience on a 6-point scale, ranging from 0 (no impairment) to 5 (maximum impairment) with a scoring range of 0-40. Higher scores indicate greater disease impact. Refer to Appendix 5.

The CAT will be completed on paper and must be the first assessment completed at Visits 1, 3 and 4 to avoid influencing the subject's response. At Visit 1, the order should be CAT followed by the mMRC.

All questions must be answered, and the subject should not be told their results. It is recommended that the questionnaire be administered at the same time of day at each visit. Answers to each question will be logged into the eCRF by the study team.

Adequate time must be allowed to complete all items on the questionnaire; the questionnaire must be reviewed for completeness and, if necessary, the subject should be encouraged to complete any missing items.

8.3 Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Table 1).

8.3.1 Vital Signs

Vital signs should be obtained prior to study medication dosing, as applicable.

Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

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

8.3.2 Adverse Event Assessment

The method of detecting AEs will be performed as described in Section 8.4 and Appendix 3.

8.4 Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

AEs will be reported by the subject.

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study medication or study procedures, or that caused the subject to discontinue the study (Appendix 3).

As stated in Section 8.1.1.5, 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.

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

AEs and SAEs will be collected from time of first dose of study medication through the follow-up contact.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 3. The Investigator will submit any updated SAE data to the Sponsor designee within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study medication or study participation, the Investigator must promptly notify the Sponsor.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

8.4.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.4.3 Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study medication under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study medication under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators, as necessary.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.4 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, through the follow-up contact, or the subject is lost to follow-up (as defined in Section 7.3). Further information on follow-up of AEs and SAEs is given in Appendix 3.

8.4.5 Pregnancy

Details of all pregnancies in female subjects will be collected after the start of study medication and until 30 days after the last dose of study medication.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4.6 Adverse Events of Special Interest

Adverse events of special interest have not been identified for ensifentrine.

8.4.7 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Disease-related events and/or disease-related outcomes should generally not be recorded or reported as an adverse event.

COPD exacerbations are an expected disease-related outcome, unless the exacerbations manifest in an unusual or uncharacteristic manner. COPD exacerbations including daily expected COPD symptoms (e.g., dyspnea, chest tightness, wheezing, cough, sputum, that are not associated with the dosing event) will not be collected as an AE unless they meet the definition of an SAE.

8.4.8 Device Incidents

The Investigator, or responsible person according to local requirements (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device incidents to the IRB/IEC, device manufacturer, or regulatory authorities, as required.

A device incident is defined as an incident related to the failure of a medical device, deterioration in its effectiveness, or inadequacy in its labeling or directions that led to the death or serious deterioration in health of a subject, user, or other person, or could do so were it to recur.

8.5 Treatment of Overdose

An overdose is defined as a dose greater than the total daily doses prescribed in this study which results in clinical signs and symptoms. These should be recorded by the investigator on the AE/SAE pages.

In the event of an overdose the investigator should use clinical judgement in treating the overdose and contact the study Medical Monitor. Verona Pharma is not recommending specific treatment guidance for overdose and toxicity management.

8.6 Data Monitoring Committee

There are no plans to include a Data Monitoring Committee for this study. Ensifentrine has demonstrated to have a safety profile similar to placebo in subjects with COPD.

9.0 STATISTICAL CONSIDERATIONS

Further details of the analyses to be performed can be found in the Statistical Analysis Plan (SAP).

9.1 Statistical Hypotheses

The aim of this study is to quantify both improvement CAT scores and responder proportions in subjects with moderate/severe COPD treated with ensifentrine (3 mg) for 12-weeks. No formal statistical tests will be performed. Study conclusions will be based on two-sided unadjusted 95% confidence intervals for estimated change and derived proportions.

9.2 Sample Size Determination

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 provides 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 provides 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 provides the ability to demonstrate the upper 95% confidence interval for a mean change from baseline estimate does not exceed 2 units.

9.3 Statistical Methods

In general, unless stated otherwise, continuous variables will be summarized using descriptive statistics (number of subjects, mean, standard deviation [SD], median, minimum, and maximum values) and for categorical (nominal) variables, the number and percentage of subjects will be used.

In general, unless stated otherwise, continuous variables will be summarized using descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum values) and for categorical (nominal) variables, the number and percentage of subjects will be used.

9.3.1 Populations for Analyses

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.

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 Safety Analysis Set (SAS) will consist of all subjects who were administered the study medication at Visit 2.

9.3.2 Statistical Analyses

Continuous endpoints will be summarized as change from baseline using a mixed model for repeated measures with model terms for time and background therapy, and with baseline included as a covariate. Within subject error will be modeled using an unstructured covariance matrix, and Kenward-Roger method will be used to estimate degrees of freedom. Least square mean estimates, standard errors, and corresponding 95% confidence limits will be presented at each post-treatment time of assessment.

Response frequencies will be summarized by negative binomial regression with model terms for time and background therapy, and with baseline included as a covariate. Within subject correlation in responder status will be modeled using an unstructured covariance matrix. Response proportions, standard errors, and corresponding 95% confidence limits will be generated from estimated frequencies and presented for each post-treatment time of assessment.

9.3.3 Efficacy Analyses

Analysis will be based on the FAS.

Continuous variables will be summarized both for the absolute value and for change from baseline using descriptive statistics (N, mean, median, SD, minimum, and maximum), generated separately as well as overall.

Results will provide the number of subjects included in each analysis, estimated least square means and corresponding standard errors and 95% confidence intervals (CIs).

Total score data will be used for the change from baseline CAT analysis and the responder analysis.

Individual CAT item score (8-items) will be used for the change from baseline item-level analysis.

An analysis of the proportion of subjects with an improvement from baseline in CAT score of 2 or more will be summarized by visit and analyzed using negative binomial regression.

CAT total score and the individual item scores will be listed for each visit (items: Cough, Mucus, Chest Tight, Breathless, Limited Activities, Confident, Sleep and Energy). A plot of the least square means change from baseline in total score over time will be presented (based on the MMRM analysis).

Additional details will be provided in the SAP.

9.3.4 Safety Analyses

Safety analysis will be descriptive and based on the SAS including all treated subjects.

AEs will be analyzed using quantitative and qualitative measures. Treatment emergent adverse events (TEAEs) will be summarized by treatment for all AEs, related AEs, SAEs, deaths, AEs leading to discontinuation of study medication or to withdrawal from study, AEs of different severity and AEs of different chronicity.

TEAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC) and preferred term (PT) for each treatment. Adverse events will be included in subject listings. Seriousness, relatedness, and outcome will be identified in subject listings.

Vital signs will be summarized as change from baseline values for each parameter. Vital signs will be included in subject listings. Abnormal values and marked abnormalities will be identified in subject listings.

9.3.5 Other Analyses

Subject disposition including total number of screened subjects, number of completers, withdrawn subjects (including reason for withdrawal) and subjects included in each analysis set will be summarized overall. Subject disposition will be included in subject listings.

The number of subjects with major protocol deviations will be summarized by type and category of violation overall. Major protocol deviations will be included in subject listings.

Demographic and baseline characteristics will be summarized using descriptive statistics overall. Demographic and baseline characteristics will be included in subject listings.

Medical history will be coded using MedDRA and summarized by SOC and PT for each sequence and overall. Medical history will be provided in subject listings.

Prior medications will denote medications used prior to the first dose of study medication. Prior medications will be summarized and provided in subject listings. Prior medications will be provided in subject listings.

Concomitant medications will denote medications started prior to but continuing after receipt of study medication. Concomitant medications will be summarized separately by Anatomical Therapeutic Chemical (ATC) levels 2 and 4. Concomitant medications will be included in subject listings.

Compliance to study medication will be computed based on the number of ampules/foil pouch count dispensed and unused ampules/foil pouches returned. Non-compliance will

be defined as a compliance value less than 70% over the full study period. Compliance will be summarized overall.

9.3.6 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.

9.4 Interim Analyses

There will be no formal interim analysis in the study.

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Appendix 1 Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
ATS	American Thoracic Society
BID	Twice daily
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CV	Coefficient of variation
eCRF	Electronic case report form
ERS	European Respiratory Society
FAS	Full analysis set
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
IB	Investigator's brochure
ICF	Informed consent form
ICS	Inhaled corticosteroid(s)
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LABA	Long-acting β2-agonist
LAMA	Long-acting muscarinic antagonist
LDPE	Low-density polyethylene
MedDRA	Medical Dictionary for Regulatory Activities
PDE	Phosphodiesterase
PT	Preferred term
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SD	Standard deviation
SoA	Schedule of Activities
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States
Verona	Verona Pharma plc.
WOCBP	Women of Childbearing Potential

Appendix 2 Regulatory, Ethical, and Study Oversight Consideration

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
    - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
    - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and regulatory authority approval, when applicable, before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to subjects.
- The Investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
    - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
    - Providing oversight of the conduct of the study at the study center and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, EU Clinical Trials Directive 2001/20/EC (if applicable), and all other applicable local regulations.
- After reading the protocol, the Principal Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or designee. The study will not start at any study center at which the Investigator has not signed the protocol.

Adequate Resources

The Investigator is responsible for supervising any individual or party to whom the Investigator delegates study-related duties and functions conducted at the study center.

If the Investigator/institution retains the services of any individual or party to perform study related duties and functions, the Investigator/institution should ensure this individual, or party is

qualified to perform those study-related duties and functions and should implement procedures to ensure the integrity of the study-related duties and functions performed and any data generated.

Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Insurance

Financial arrangements are detailed in the Investigator Agreement between the Sponsor and Investigator.

The Sponsor will arrange clinical study insurance to compensate subjects for any potential injury or death caused by the study.

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the subject and/or the subject's legally authorized representative and answer all questions regarding the study.
- Subjects must be informed that their participation is voluntary. Subjects will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the subject was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- A copy of the original ICF(s) must be provided to the subject or the subject's legally authorized representative.
- ICF New Information: New information since the time of the original consent can be presented to subjects in format(s) or method(s) including, but not limited to those listed below unless excluded by local requirements:
    - Revised consent document
    - Addendum to consent
    - Memo or other communication to subjects
    - Orally by phone or in person

Documentation of the method the new information was presented to the subject along with the name of the site staff member and date the new information was presented to the subject must be documented in the subject's source document.

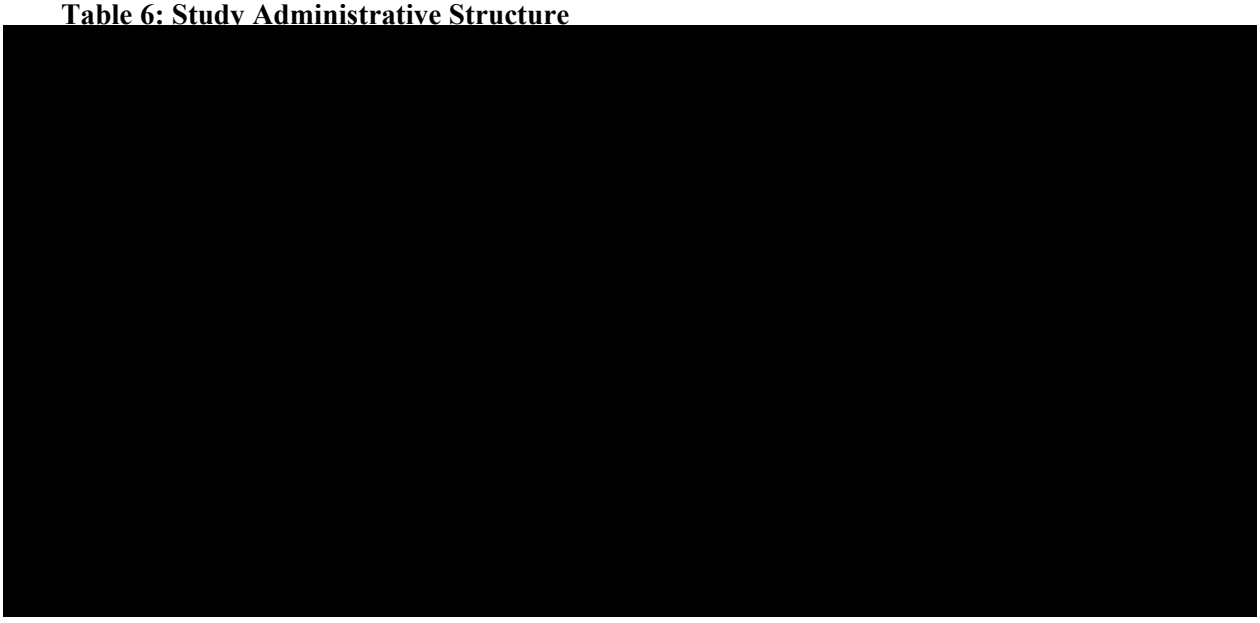
Data Protection

- Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.
- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

Administrative Structure

The study administration structure is in Table 6. Medical Monitor and 24-hour urgent medical contact information is in Table 7.

Table 6: Study Administrative Structure



[redacted]

Dissemination of Clinical Study Data

For studies conducted in the United States, the results of the study are required to be reported on clinicaltrials.gov no later than 1 year after the primary completion date of the clinical study, which is defined as the date of final data collection for the primary outcome measure.

Data Quality Assurance

- All subject data relating to the study will be recorded on printed or eCRFs unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct for each subject by physically or electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered into the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized study center personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Source Documents

The Investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the study center's subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the Investigator's study center.
- Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in ICH E6(R2) Section 1.51.

Study and Study Center Closure

The Sponsor reserves the right to close the study center or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study centers will be closed upon study completion. A study center is considered closed when all required documents and study supplies have been collected and a study center closure visit has been performed.

The Investigator may initiate study center closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study center by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of subjects by the Investigator.
- Discontinuation of further study medication development.

Publication Policy

The data generated by this study are the confidential information of the Sponsor.

Appendix 3 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

Definition of AE

- An AE is any untoward medical occurrence in a subject or subject, temporally associated with the use of study medication, whether or not considered related to the study medication.
- *NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study medication.*

Events Meeting the AE Definition

- Any abnormal laboratory test results (e.g., hematology, clinical chemistry) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study medication administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study medication or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

  "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure should be assessed using the AE/SAE definitions.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

a) Results in death.

b) Is life-threatening.

The term 'life-threatening' in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c) Requires inpatient hospitalization or prolongation of existing hospitalization.

In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the 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. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) Results in persistent disability/incapacity.

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e) Is a congenital anomaly/birth defect

f) Other situations:

- 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.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow-up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF. Each event must be recorded separately.
- It is **not** acceptable for the Investigator to send photocopies of the subject's medical records to Sponsor/Sponsor's designee in lieu of completion of the Verona Pharma /AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by groups such as the Sponsor/Sponsor's designee, Health Authority, or Ethics Committee. In this case, all subject identifiers, with the exception of the subject/patient number, will be redacted on the copies of the medical records before submission to records to the Sponsor/Sponsor's designee.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort, and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.

- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Chronicity

- Single occasion: Single event with limited duration.
- Intermittent: Several episodes of an event, each of limited duration
- Persistent: Event which remained indefinitely.

Assessment of Causality

The Investigator is obligated to assess the relationship between study medication and each occurrence of each AE/SAE. The AE must be characterized as either 1) a reasonable possibility of causality or 2) no reasonable possibility of causality:

- Reasonable possibility: There is a clear temporal relationship between the study intervention and the event onset; and the event is known to occur with the study intervention or there is a reasonable possibility that the study intervention caused the event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the event.
- No reasonable possibility: There is no evidence suggesting that the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established (e.g., event is consistent with medical history).

All efforts should be made to classify the AE according to the above categories.

The Investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study medication administration will be considered and investigated.

The Investigator will also consult the Investigator's Brochure (IB) in his/her assessment.

For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor/Sponsor's designee. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor/Sponsor's designee.

The Investigator may change his/her opinion of causality considering follow-up information and send a SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Action and Outcome

- Action taken with study medication (none, study medication stopped, study medication temporarily interrupted)
- Other actions (none, concomitant medication, study discontinuation, hospitalization, other)
- The outcome and date of outcome according to the following definitions:
  - Recovered or resolved (adverse event disappeared)
  - Recovering or resolving (subject is recovering)
  - Not recovered or not resolved (adverse event remains without signs of improvement)
  - Recovered or resolved with sequelae (adverse event has resulted in permanent disability or incapacity)
  - Fatal
  - Unknown (only applicable if subject has been lost to follow-up)
- Seriousness (yes or no)

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor/Sponsor's designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor/Sponsor's designee with a copy of any postmortem findings including histopathology and/or autopsy report, as applicable local regulatory requirements will allow.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to the Sponsor/Sponsor's Designee within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting to Sponsor/ Sponsor's Designee via Paper Form

- The Medical Monitor contact information can be found in Appendix 2 (Table 7).
- The primary mechanism for reporting an SAE to the Sponsor/Sponsor's designee will be the paper SAE reporting form.
- The SAE reporting form should be sent by fax to the fax number which appears on the form. As an alternative, the completed SAE reporting form can be scanned and sent as an attachment via email to: VeronaSafety@ubc.com.
- Initial notification via telephone or email does not replace the need for the Investigator to complete and sign the SAE pages within the designated reporting time frames.

Appendix 4 Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenopausal female with 1 of the following:

   a) Documented hysterectomy.

   b) Documented bilateral salpingectomy.

   c) Documented bilateral oophorectomy. Note: Documentation can come from the study center personnel's: review of the subject's medical records, medical examination, or medical history interview.

2. Postmenopausal female:

   a) Postmenopausal females are defined as amenorrhoeic for greater than 1 year with an appropriate clinical profile, e.g., age appropriate, > 45 years, in the absence of hormone replacement therapy.

Contraception Guidance

Male Subjects

- Male subjects with female partners of childbearing potential are eligible to participate if they agree to ONE of the following from the first dose up to 30 days after the last dose of study medication:
  - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.
  - Agree to use a male condom plus partner use of a contraceptive method with a failure rate of < 1% per year as described in Table 8 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
- In addition, male subjects must refrain from donating sperm for the duration of the study and for 30 days after the last dose of study medication.
- Male subjects with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the study and for 30 days after the last dose of study medication.

Female subjects

Female subjects of childbearing potential are eligible to participate if they are not breastfeeding and agree to use a highly effective method of contraception consistently and correctly as described in the table below, during the study starting at Visit 1 and for at least 30 days after the last dose of study treatment.

Table 8: Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of < 1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Contraceptive Methods That Are User Independent [a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) Bilateral tubal occlusion.
Vasectomized partner *A vasectomized partner is a highly effective birth control method provided that the partner is the sole male sexual partner of the WOCBP, and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.*
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies. [b]Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilized during the treatment period and for at least 30 days after the last dose of study treatment.

Pregnancy Testing:

- WOCBP should only be included after a negative pregnancy test during screening is conducted prior to study medication dispensing.
- Additional pregnancy testing should be performed at times specified in the SoA (Section 1.3).
- Pregnancy testing should be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

Collection of Pregnancy Information

Male subjects with partners who become pregnant

The Investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in the study.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

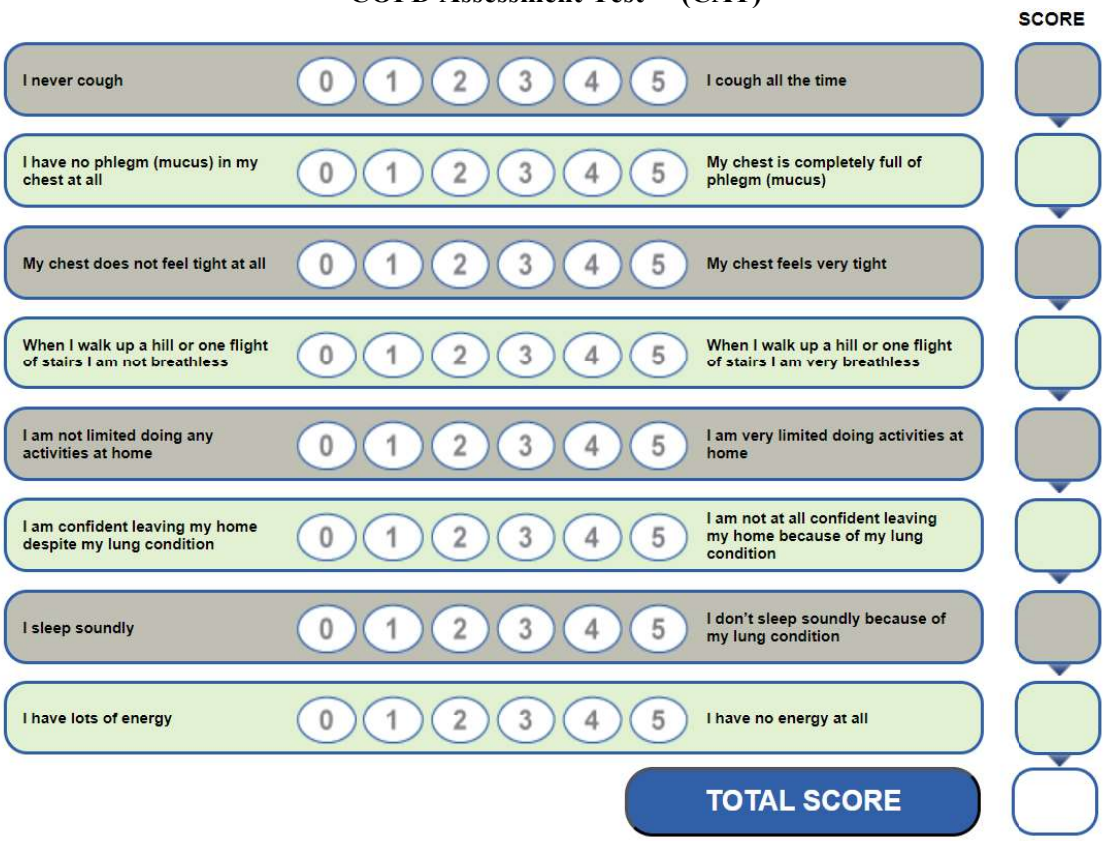
Female subjects who become pregnant

- The Investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor/Sponsor Designee within 24 hours of learning of a subject's pregnancy.
    - The Medical Monitor contact information can be found in Appendix 2 (Table 7).
    - The primary mechanism for reporting Pregnancy to the Sponsor/Sponsor's designee will be the paper Pregnancy reporting form.
    - The Pregnancy reporting form should be sent by fax to the fax number which appears on the form. As an alternative, the completed form can be scanned and sent as an attachment via email to: VeronaSafety@ubc.com.
- Any female subject who becomes pregnant while participating in the study will discontinue study medication. The subject will be approached and asked to consent to being followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the subject and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will be no longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. For SAE reporting, refer to Appendix 3.
- Any post-study pregnancy related SAE considered reasonably related to the study medication by the Investigator will be reported to the Sponsor as described in Section 8.4.5. While the Investigator is not obligated to actively seek this information in former subjects, he or she may learn of an SAE through spontaneous reporting.

Appendix 5 Questionnaires

The COPD Assessment Test™ was developed by a multi-disciplinary group of international experts in COPD supported by GSK. The CAT is self-administered on paper. CAT, COPD Assessment Test, and the CAT logo are trademarks of the GSK group of companies. GlaxoSmithKline Services Unlimited. Registered in England.[3–5]

COPD Assessment Test™ (CAT)



https://www.catestonline.org/patient-site-test-page-english.html

Accessed 01April2024.

CAT score	Level of Impact
31 - 40	Very High Impact
21 - 30	High Impact
10 - 20	Medium Impact
< 10	Low Impact

The modified Medical Research Council (mMRC) Dyspnea Scale (From ATS News 1982; 8:12-16.8).[15] The mMRC is based off the MRC breathlessness score first published by Fletcher, et al.[16]

Site staff will administer/interview the subject to complete the mMRC dyspnea scale questionnaire.

mMRC Grade	Description
0	Not troubled with breathlessness except with strenuous exercise
1	Troubled by shortness of breath when hurrying on the level or walking up a slight hill
2	Walks slower than people of the same age on the level because of breathlessness or has to stop for breath when walking at own pace on the level
3	Stops for breath after walking about 100 yards or after a few minutes on the level
4	Too breathless to leave the house or breathless when dressing or undressing

Signature of Investigator

PROTOCOL TITLE:	A Study Assessing the Effect of Ensifentrine on CAT™ Scores over 12 Weeks in Subjects with Moderate to Severe COPD
PROTOCOL NO:	RPL554-CO-303
VERSION:	4.0
VERSION DATE:	19 August 2024

This protocol is a confidential communication of Verona Pharma plc. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from the Sponsor.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the study center where the study will be conducted. Return the signed copy to the Sponsor.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator Date