Verona Pharma

CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase III Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Ensifentrine over 24 Weeks in Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease.
Protocol Number:	RPL554-CO-302
Version:	5.0
Amendment Number:	4.0
Investigational Product:	Ensifentrine
Short Title:	A Phase III randomized, placebo-controlled study to evaluate the efficacy and safety of ensifentrine over 24 weeks in patients with chronic obstructive pulmonary disease.
Study Phase:	III
Sponsor Name:	Verona Pharma plc
Legal Registered Address	3 More London Riverside London, SE1 2RE UK
Regulatory Agency Identifying Number(s):	EudraCT Number: 2020-002069-32 US IND Number: 133146
Date of Protocol:	30 April 2021 (replaces Version 4.0, dated 17 July 2020)

Sponsor Signatory:

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

[redacted]

Medical Monitor name and contact information can be found in Section 11.2.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Table 1 Document History

Protocol Version	Amendment	Date	Substantial - timings	Region
Version 1.0	Original Protocol	28-May-2020	Original Protocol	Global
Version 2.0	Amendment 1.0	22-June-2020	Yes – prior to initial regulatory submissions	Global
Version 3.0	Amendment 2.0	26-Jun-2020	Yes– prior to initial regulatory submissions	Global
Version 4.0	Amendment 3.0	17-Jul-2020	Yes– prior to initial regulatory submissions	Global
Version 5.0	Amendment 4.0	30-Apr-2021	Yes – during enrollment	Global

Protocol Version 2.0, Amendment 1.0: 22June-2020

Overall Rationale for the Amendment:

The protocol is amended to address minor administrative items (spelling, punctuation, spaces and Table numbering), clarifications, and substantial changes to add an ECG exclusion criteria, spirometry at Week 24, optional rather than mandatory COVID-19 testing, and adding a section on Treatment After the End of Study.

Table 2 Description of Changes in the Amendment

Section # and Name	Description of Change	Brief Rationale
Section 1.3, Schedule of Activities, Register Visit in IRT Section 8.5.2, Interactive Response Technology	Registration in IRT will not be required at Week 18. This is revised to "Register in IRT" with the word "visit" removed. Section 8.5.2 revised to note that information would only be entered into the IRT at specified visits.	Administrative change to align with IRT system.
Section 1.3, Screening Spirometry	The timing of pre-and post-bronchodilator spirometry testing was revised. Pre-bronchodilator testing will be conducted prior to dosing with albuterol/salbutamol.	Administrative change to allow an appropriate window

	Post-bronchodilator testing should be conducted between 15 and 30 minutes following administration of albuterol/salbutamol	within to collect the assessments.
Section 1.3, eDiary Site Activation Activities	Assessments deleted.	Administrative change. Assessments not necessary.
Section 1.3, Footnote 4	Added to the X for the Early Termination visit for Blinded Study Medication Dosing in the Clinic. Added language to indicate that dosing should be performed "if possible".	Administrative change.
Section 1.3, Patient Contact Day Prior to Spirometry Visits and Footnote 8	Week 24 assessment added. Footnote 8 was amended to note additional detail regarding the expected timing of the contact "Either 3 or 4 days", study medication, and other medication withholding prior to the clinic visit. This was also amended to note that patients would be reminded to fill out their paper diary during the Patient Contact prior to the spirometry visits.	Substantial change. Additional patient contact required to align with added spirometry at Week 24.
Section 1.3, Patient Contact Day Prior to Pharmacokinetic Assessments and Footnote 19	Patient contact and Footnote 19 deleted and combined with Footnote 8.	Substantial change. Only one patient contact is needed.
Section 1.3, Spirometry Inhalation Observation & Training	Week 24 assessment added.	Substantial change. Additional assessment required to align with added spirometry at Week 24.
Section 5.2, Exclusion #8	Sleep apnea was changed to "unstable" sleep apnea.	Administrative change. Clarification.

Section 1.3, Chest X-ray and Footnote 6 Section 5.2, Exclusion #22 Section 8.1.7, Chest X-ray	The language "unless restricted by local requirements" was changed to "**For subjects in Germany**, if a CXR or CT scan is not available in the 12 months prior to Screening, the subject is not eligible for the study".	Administrative change. To clarify requirements for Germany regarding chest X-ray.
Section 1.3, Schedule of Activities, Spirometry (pre-dose); Spirometry 0-4 hours post-dose Synopsis Section 1.4, Schedule of Spirometry and In-Clinic Dosing Section 2.1, Study Rationale Section 4.2, Scientific Rationale for Study Design	Pre-dose and 0-4 hour post-dose spirometry assessments added at Week 24. Synopsis and study rationale revised to note that spirometry would be collected over 24 weeks rather than 12. Footnote 1 added to Week 24.	Substantial change. Additional duration of effect desired.
Section 1.3, Footnote 14 Section 6.7.2, Table 7 Section 8.1.16, Dispense Rescue Medication Section 8.4.2, Electrocardiogram	It was noted that albuterol/salbutamol should be withheld for at least 4 hours prior to ECG assessments.	Administrative change for clarify intent.
Section 1.3, Laboratory Tests	Amended to clarify that serum pregnancy testing was included in laboratory testing. Footnote 15 linking to pregnancy testing information added.	Administrative change to clarify when serum and urine pregnancy testing would be conducted.
Section 1.3, Pregnancy Test for Women and Footnote 15	Amended to clarify that only urine testing would be conducted at specified assessments. Footnote 15: the following language was added "A urine test	Administrative change to clarify when serum and urine pregnancy testing would be conducted,

Section 11.3, Clinical Laboratory Tests Section 11.8, Contraceptive Guidance and Collection of Pregnancy Information	will be conducted on all women prior to dosing at Visit 1." Section 11.3: the following language was deleted "Pregnancy testing will be performed and assayed in the central laboratory." The language "WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive pregnancy test." was revised to "WOCBP should only be included after a negative highly sensitive pregnancy test."	and to clarify other potentially ambiguous language.
Section 1.3, Dispense Rescue albuterol/ salbutamol	Dispensing of rescue albuterol/salbutamol was deleted at Week 24	Administrative change to correct an error.
Section 1.3, COVID-19 Test and Footnote 16 Section 8.1.10.2, COVID-19 Section 8.4.3.1, COVID-19	Changed COVID-19 testing requirement to optional and based on local requirements.	Substantial change. Sites have indicated that COVID site risk is managed locally.
Section 5.3, Randomization Criteria #4 Section 7.1.3, Electrocardiogram Withdrawal Criteria Section 11.5, ECG Withdrawal Criteria	In this statement, "In the event that the central ECG reviewer discovers a clinically significant ECG abnormality on the Visit 1 ECG, the patient will be discontinued from the study." The words "clinically" and "from the study" were deleted from the sentence. Clarifications were made to note that the central reviewer would make a determination on significant abnormalities, while clinically significant abnormalities would be	Administrative change to clarify significant and clinically significant abnormalities, and allow flexibility for patients to withdraw from treatment and stay in the study.

	determined per Investigator's discretion.	
Section 6.1.2, Dosing at Home, Blinded Study Medication Administration, 4th bullet. Section 1.3, Patient Contact Day Prior to Spirometry Visits and Footnote 8 Section 1.4, Schedule of Spirometry and In-Clinic Dosing	The bullet originally stated, "The date, start time, and the end time of blinded study medication nebulization should be recorded in the patient diary." The 4th bullet has been revised to state, "One the evening Prior to the Week 6,Week 12, and Week 24 Visits: On a patient paper diary, the patient will record the date, the start time of nebulization, and the end time of nebulization for the evening dose of blinded study medication". Footnote 8 was amended to note that patients would be reminded to fill out their paper diary during the Patient Contact prior to the spirometry visits. The following language was added in Table 4 as a Note: "For pre-dose spirometry conducted between 11.5 and 12 hours after the patients evening dose the day prior to the visit, the paper diary with the evening dosing completion time should be consulted."	Clarification change to more accurately reflect the dosing information required just prior to the Week 6, Week 12, and Week 24 (or Early Term/Withdrawal visits where 12-hour spirometry will be performed).
Synopsis, Overall Design Section 4.1, Overall Design Section 6.2, Section 6.7.2, Section 6.7.3, Section 8.2, Section 11.2, Section 11.3, Tables 5 to 14.	In reference to 'long-acting β2 agonist,' the word 'agonist' was misspelled. Tables 3 to 12 were updated to numbers 5 to 14.	Administrative change to correct a spelling error and Table numbering due to Amendment.

Section 6.7.1, Rescue Medication 6.7.1.1, Documentation of Rescue Medication Use	The sentence "Rescue medication will be sourced by the study center and dispensed at each visit as needed." Was deleted, and the word "study" was added prior to albuterol/salbutamol. The following language was added "After Screening, use of Rescue Medication will not be recorded in the concomitant medication page of the eCRF." The example was also updated to include number of puffs and to delete "route" in bullet 2.	Administrative change to allow for flexible sourcing of rescue medication.
6.7.3, Table 8	"Systemic" and "parenteral" were added to "Oral steroid therapies". Footnote 1 was inserted "Except for the treatment of COPD exacerbations during the study (Section 11.6). Localized corticosteroid injections are permitted".	Administrative change. Clarification.
Section 6.7.4.1, Recording of Rescue Medication and/or LAMA or LABA Medications	3rd bullet: removed descriptive text in the parenthesis "(eg, morning dose and evening dose, [both if on a twice-daily regimen])."	Administrative change.
Section 6.8, Treatment After the End of Study	This section was added along with the following language: "There are no plans to provide post-study treatment, including study medication for compassionate use following study completion. At the end of the treatment period (Visit 5 or Visit 9 or early termination), patients may resume conventional COPD therapy as prescribed by the investigator or other physician.	Substantial change. Missing section was in error.

	Medications initiated after the end of study treatment should not be entered into the eCRF except for those given for a serious adverse event (SAE)."	
Section 8.3.1, Spirometry	The word "judgement" was replaced by "determination".	Administrative change.
Section 8.3.2, COPD Exacerbation Assessment	The language stating that exacerbations would be based on symptoms reported in the eDiary was removed.	Administrative change to correct an error.
Section 8.3.3.6, Evaluating-Respiratory Symptoms Questionnaire Section 1.3 and Footnote 12 Section 8.1.13, Electronic Diary Activities Section 8.5.4, Electronic Diary Activities	Clarified that the E-RS is derived from the EXACT-PRO. This assessment is clarified as E-RS/EXACT-PRO.	Administrative change. Clarification.
Section 8.4.2, Electrocardiogram	The following language "determination of an acceptable endpoint measurement(s) will override judgement by the investigative site." was revised to: "interpretation of the measurement(s) will override the interpretation by the investigative site, if consensus is not reached."	Administrative change. Clarification.
Section 8.5.8, Dispense/Collect Rescue Albuterol/Salbutamol	Corrected to note that rescue medication would be dispensed at specified visits rather than each study visit.	Administrative change. Corrected inconsistency.
8.5.10.2, Recording of Medications and Information Specific to the Pharmacokinetic	Recording of the nebulization end time was added. Collection of Medication name, dose (eg. Dose unit, route, schedule/frequency) was added	Administrative change to correct omissions and clarify language.

Procedures and Sample Analysis and Table 10	to Table 10, along with other administrative edits.	
Section 8.6.1, Site Level Disaster Plan	The text was revised to indicate it is 'recommended' that investigative sites prepare a written disaster plan for this study. The requirement for a written disaster plan to be prepared "before the site initiation visit is conducted" has been deleted.	Administrative change to recommend rather than require investigative sites to prepare a Disaster Plan for the study.
Section 9.4.3, Other Analyses	The text "The outcome of COVID-19 tests will be summarized by treatment group and occasion" was removed.	Administrative change to reflect optional COVID-19 testing.
Section 11.4, ECG Exclusion Criteria	Added "QTcF ≥ 480 msec when RBBB is present"	Substantial change recommended by a Cardiology consultant.
Section 11.11, Country Specific Requirements	The following language was added: "Germany: a CXR or CT scan must be available in the 12 months prior to Screening for eligibility."	Administrative change to align with Eligibility language clarification.

Protocol Version 3.0, Amendment 2.0: 26-June-2020

Overall Rationale for the Amendment:

The protocol is amended to remove the requirement for pregnancy testing in all women and to only perform pregnancy testing on women of childbearing potential.

Description of Changes in the Amendment

Section # and Name	Description of Change	Brief Rationale
Section 1.3, Footnote 15	The current instruction 'Pregnancy testing will be conducted on all women' will be changed to 'Pregnancy testing will be	To remove the requirement for pregnancy testing in all women.

	conducted on women of childbearing potential.'	
Section 7.1.5, Positive pregnancy test in females	Changed 'all women' to 'women of childbearing potential.'	To remove the requirement for pregnancy testing in all women.
Section 11.3, Table 13	Changed the first footnote to state women 'of childbearing potential.'	To remove the requirement for pregnancy testing in all women.
Section 11.8, Contraceptive guidance and collection of pregnancy information	The definition of non-childbearing potential in post-menopausal women was clarified: Additional detail was added to the text in 3.(a) to indicate that 'postmenopausal females are defined as amenorrhoeic for greater than 1 year with an appropriate clinical profile, eg, age appropriate, > 45 years, in the absence of hormone replacement therapy.' Language indicating FSH testing or hormonal birth control withdrawal was deleted.	To clearly define the definition of post-menopausal women.
11.12, Signature of Investigator	Version number and version date updated to reflect version 3.0 and version date 26Jun2020.	To match the version number and version date for this amendment.

Protocol Version 4.0, Amendment 3.0: 17-July-2020

Overall Rationale for the Amendment:

The protocol is amended to reorder the secondary endpoint testing hierarchy, to remove an evening dosing requirement at early termination visits with 12-hour spirometry, to revise 'Events Meeting the AE Definition', to clarify COVID-19 testing as optional, to make minor clarifications to the pharmacokinetic section, to correct a minor document formatting issue, and to clarify the protocol version and amendment numbers.

Description of Changes in the Amendment

Section # and Name	Description of Change	Brief Rationale
Synopsis, Secondary Endpoints Section 3.2.2, Secondary Endpoints Section 9.0, Statistical Considerations: - Sections 9.1 Statistical Hypotheses - Section 9.4.1 Efficacy Analysis	The order of the secondary endpoints has changed to raise the testing hierarchy of 'SGRQ total score at Week 24 (change from baseline)' and to lower the testing hierarchy of 'The proportion of St. George's Respiratory Questionnaire (SGRQ) responders at Week 24'.	To elevate the continuous variable in the testing hierarchy.
Section 1.4 Schedule of Spirometry and In-Clinic Dosing	Evening blinded study medication dosing in the Clinic at the Early Term/Withdrawal Visit has been removed.	An evening dose of blinded study medication at the Early Term/Withdrawal Visit is not required.
Appendix 7, Adverse Events: Definition and Procedures for Recording, Evaluating, Follow-up and Reporting. Events Meeting the AE Definition, last bullet.	Removed the last bullet: "The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, 'lack of efficacy' or 'failure of expected pharmacological action' also constitutes and AE or SAE."	This text contradicted the text in the bullet above. "Lack of efficacy" or "failure of expected pharmacological action" are not to be reported as adverse events in this study.
Section 1.3, Schedule of Activities (SoA). COVID-19 Test.	COVID-19 testing was made optional at any time during the study in Protocol Version 2.0. The SoA has been updated to state Optional COVID-19 TEST in the line item and the term "Optional"	Clarification

	has been added to each potential testing timepoint in the SoA.	
Section 8.5.10 Pharmacokinetics. Section 8.5.10.1 Collection of Samples	The volume of whole blood was reduced from 'approximately 8 ml' to 'approximately 4 ml.'	A clarification based on current blood volume requirements.
Section 8.5.10 Pharmacokinetics. Section 8.5.10.2 Recording of Medications and Information Specific to the Pharmacokinetic Procedures and Sample Analysis, Pharmacokinetic (PK) eCRF module	Pharmacokinetic (PK) eCRF: The title of this paragraph was changed from "Pharmacokinetic (PK) eCRF module" to "Collection of medication and associated information in the eCRF." The 2nd bullet, sub-bullet 3 was deleted.	A clarification to more accurately reflect that the information will be captured in more than one eCRF module. Sub-bullet 3 is not required.
Section 8.1.8 Spirometry Assessment	A formatting issue in the previous amendment caused the text associated with Section 8.1.7 to become part of the header for Section 8.1.8 Spirometry Assessment. This formatting issue has been corrected.	Formatting correction
Protocol Amendment Summary of Changes Table 1 Document History and the description of each amendment.	In previous changes to the protocol, the term *Protocol Amendment* was used to describe the updated *Protocol Version* number. The text references to protocol version and amendment has been updated and corrected.	Clarification

Protocol Version 5.0, Amendment 4.0: 30-Apr-2021

Overall Rationale for the Amendment:

The protocol is amended to allow some patients with stable use of inhaled corticosteroids, reorder the secondary endpoint testing hierarchy and add additional endpoints, to update the handling of missing data in the statistical analysis, to incorporate contents of Protocol clarification letters dated 29Sep2020 and 5Nov2020, to revise exclusion criteria relating to hepatitis B and C, and to revise and clarify prohibited medication requirements regarding chronic use of antibiotics and beta-blockers, and to update and clarify

requirements for stable use of maintenance therapy in Inclusion #8. Minor spelling errors, formatting corrections were also made.

Description of Changes in the Amendment

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities 8.5.6 ~~Inhalation and Observation and~~ Training for Spirometry	"Inhalation Observation" deleted Footnotes 4 and 19: Clarified that PK sampling should only be drawn at early termination and visits for patients who took blinded study medication within 48 hours of the visit. Footnote 8: Added ICS to withholding Footnote 17: Added "rescue medication may be dispensed at the time of signing the Informed Consent, if this occurs prior to commencement of screening assessments." Footnote 18: Added "if allowed per local site practices, otherwise the study supplied compressors will not be retrieved and collected."	Clarification. To eliminate unnecessary collection of PK samples in patients not taking study medication. To note allowance of ICS requires the same withholding as LAMA and LABA To ensure patients who require rescue medication prior to screening procedures have access to it. To note that due to COVID, sites may not be able to collect study compressors.
1.4 Schedule of Spirometry and In-Clinic Dosing with Blinded Study Medication	Footnote 1 added for Evening Dosing: "Patients may be discharged from the clinic after Week 12 assessments are complete to self-administer their evening dose of study medication. If administered in the clinic, the Week 12 evening dose must be administered by unblinded site staff."	To clarify that patients may be discharged for their evening dose at home at the Week 12 visit.

2.2 Background	Updated IB version from 19 to 20, 2021 (or more current version, if applicable)	IB version update.
2.3 Benefit/Risk Assessment	Updated with results from completed pre- and post-natal development definitive study "There were no effects of ensifentrine on fertility and reproductive performance in female rats and no effects on pre- and post-natal development in female rats or offspring (Study 8438109)." Updated IB version from 19 to 20, 2021 (or more current version, if applicable)	Updated with recent results from the completed pre- and post-natal development study. IB version update.
3.2.2 Secondary Endpoints 9.1 Statistical Hypothesis 1.1 Synopsis	Average FEV1 AUC (0-4h) at week 12 was demoted to secondary endpoint #5.	Endpoint reordering results in morning trough FEV1 at week 12 to be promoted to secondary endpoint #4.
3.2.3 Other Endpoints 1.1 Synopsis	Average FEV1 AUC (6-12h) at week 12 was added	Endpoint added to evaluate the effects in the second half of the dosing interval.
4.1 Overall Design 4.2 Scientific Rationale for Study Design 1.1 Synopsis	Allowance and withholding periods for ICS were added: "Up to 20% of patients are allowed to take inhaled corticosteroids during the study under certain provisions (see Sections 6.7.2 and 6.7.3)." LABA and LAMA monotherapy was changed to LABA and LAMA therapy. Withholding periods were updated to include LAMA/ICS and LABA/ICS.	Updated to note allowance of ICS under certain provisions. Stable ICS use in a subgroup is not expected to impact study endpoints or safety assessment of ensifentrine.
5.1 Inclusion Criteria	#8: Statement clarified: Patients taking maintenance LAMA or	Duration prior to screening updated

	LABA therapy must demonstrate "~~stable~~ regular use of ~~the~~ maintenance LAMA or LABA therapy, in any form, for at least 2 ~~3~~ months prior to Screening and agree to continue use of their current permitted LAMA or LABA medication for the duration of the study."	from 3 to 2 months, which still allows 3 months stable use prior to baseline. Clarifies "in any form" to note that the exact same background medication is not required during this interval.
5.2 Exclusion Criteria	#12: Added: "Note: Chronic stable hepatitis B and C is not exclusionary if the patient otherwise meets study entry criteria." #19 and #20 relating to specific exclusion of Hepatitis B and C were deleted.	Language changed to allow for stable chronic hepatitis B and C to be allowed if the subject meets other study criteria.
5.2 Exclusion Criteria	#25: added *nebulized*: "blinded nebulized study medication"	To clarify that patients that have received nebulized blinded study medication in a prior study are excluded.
5.3 Randomization Criteria	Inclusion #1: added "at Visit 1"	Clarification.
5.3 Randomization Criteria	Exclusion #4: Reworded to include: "assessed *before the patient is randomized*." "After a patient has been randomized, ECG withdrawal criteria (Section 11.5) will apply. In the event that the central ECG reviewer discovers a significant ECG abnormality *meeting ECG withdrawal criteria* on the Visit 1 ECG in 2 of 3 triplicate measurements, the patient ~~will~~may be discontinued.	To clarify that ECGs assessed prior to randomization are subject to ECG Exclusion Criteria, while ECGs assessed after randomization (even if they were conducted prior) are subject to ECG withdrawal criteria.

		Abnormalities should be confirmed in 2 of 3 triplicates.
5.3 Randomization Criteria	Exclusion #5: Added: "as assessed at Screening Visit 0 (e.g. including overreads or lab values obtained after the day of Screening)."	Clarification.
6.1.1 Dosing in the Clinic	Deleted: ~~this includes morning and evening doses on the 12 hour clinic day (week 12).~~ Added: Patients may be discharged from the clinic after Week 12 assessments are complete to self-administer their evening dose of study medication. If administered in the clinic, the Week 12 evening dose must be administered by unblinded site staff.	Updated to allow patient dosing at home the evening of the Week 12 visit.
6.1.2 Dosing at Home	Added "(and ICS, if applicable)"	To clarify order of dosing at home in patients on ICS.
6.7.2 Permitted Rescue and Background Medications	Added: "Any vaccine that is recommended by the patient's healthcare provider is permitted during the study (e.g. COVID, influenza, pneumonia), and should be recorded in the eCRF.	Clarification.
6.7.2 Permitted Rescue and Background Medications	Table 7: The table was updated to include ICS use, and the following language "Stable use of ICS is permitted IF the patient has been taking the ICS at least 4 weeks prior to Screening (Visit 0) AND the patient is also taking maintenance LAMA or LABA. ICS should not be initiated or discontinued during the study. ICS monotherapy and high dose ICS (e.g. >1000 mcg of	Updated to note allowance of ICS under certain provisions. Stable ICS use in a subgroup is not expected to impact study endpoints or safety assessment of ensifentrine.

	fluticasone propionate or equivalent) is not allowed." *"Dual LAMA/LABA therapy is not allowed"* Language to clarify that ICS is subject to withholding prior to spirometry also added.	
6.7.3 Prohibited Medication/Therapy	Table 8: Oral systemic or parenteral steroid therapies ~~for COPD~~ Added: Antibiotics for lower respiratory tract infection: 6 weeks prior to screening and prohibited during the study[1]. Chronic use of antibiotics is not allowed 6 weeks prior to or during the study. Added: ICS (e.g. ICS monotherapy and patients in the no background therapy stratum). High dose ICS (e.g. >1000 mcg fluticasone propionate or equivalent) Added: Ipratropium (including combinations with albuterol/salbutamol) Added: Nebulized LAMA or LABA *or ICS*. For patients in the no maintenance therapy stratum: 4 weeks prior to screening and prohibited during the study. For patients in the LAMA/LAMA stratum: 1 week prior to screening and prohibited during the study (e.g. patient should switch from nebulizer to dry powder or metered dose inhaler therapy).	Edits to clarify prohibited medications, certain ICS use in certain groups, nebulized therapy restrictions and to add exclusion for oral beta agonists, which can cause bronchodilation. The exclusion of oral beta blockers was deleted as it was determined that this would not impact safety of patients or efficacy endpoints.

	Added: Oral beta$_2$-agonists: one week prior to screening and prohibited during the study. Deleted: ~~non-selective oral beta blockers: 1 week prior to screening and prohibited during the study.~~	
6.7.4 Recording Use of Concomitant Medication 8.5.4 Electronic Diary Activities	Clarified recording of ICS use.	Clarification.
7.1.3 Electrocardiogram Withdrawal Criteria 8.4.2.2 Clinically Significant Abnormality 11.5 Appendix 5 Electrocardiogram Withdrawal Criteria	Added in 7.1.3: "All ECGs conducted or overread after a patient has been randomized will be subject to ECG Withdrawal Criteria (Section 11.5). Patients ~~will~~ may be discontinued" "and in consideration with the patients medical history and baseline ECG measurements" "The intent of the triplicate ECG measurement is to differentiate abnormalities from artifact. Abnormalities should be confirmed in 2 of 3 measurements." Language added for consistency in 8.4.2.2 and 11.5.	To clarify that ECGs assessed after randomization (even if they were conducted prior) are subject to ECG withdrawal criteria. The decision to withdraw a patient should be informed by the patients medical history and baseline ECGs. Abnormalities should be confirmed in 2 of 3 triplicates.
7.3.1 Early Termination/Withdrawal Procedures	Added: and ICS	To clarify patients should continue ICS if possible and follow withholding procedures.
8.1.10.1 Viral Serology	Added: "Chronic stable hepatitis B and C is not exclusionary if the patient otherwise meets study entry criteria." Deleted: ~~and evaluated per Exclusion criteria 19~~	Clarified to align with Exclusion #12.

	~~and 20. Viral serology may not be repeated.~~	
8.1.15 Nebulizer Equipment Training 8.5.5 Nebulizer Equipment Training	Language added to clarify that Instructions for Use will constitute nebulizer equipment training at Screening and hands on training will occur at Visit 1.	Clarification.
8.3.1 Spirometry	Withholding periods were updated to include LAMA/ICS and LABA/ICS.	Clarification.
8.3.3 Health Outcomes	Clarified that the healthcare utilization assessment can be done at any time during the visit.	Clarification.
8.4.1 Vital Signs	Added: The mode of temperature collection should be noted in the source (e.g. oral, forehead, etc). Deleted: ~~Oral~~	Clarification.
8.4.2 Electrocardiogram	Added: It is recommended that ECG assessments should be obtained after patients have rested for approximately 5 minutes.	Clarification.
8.5.11 Genotyping/Phenotyping	Edit: “will be” changed to “may be” stored for up to 1 year. Deleted: ~~However, genetic research may be extended to other genes that might affect ensifentrine PK (eg, other drug metabolizing enzymes, drug transporters) if the results from the clinical study cannot be explained by the current level of drug metabolism and PK understanding, or if patients with outlying PK behavior are observed. Therefore, a blood sample will be collected for deoxyribonucleic acid (DNA) analysis for genotyping.~~	Clarification. Language deleted as additional genotyping will not be conducted.

9.4.1 Efficacy Analysis 9.4.4 Missing Data	Missing data handling approach was clarified: All data collected after treatment withdrawal will be used in the analysis. Remaining missing data will primarily be imputed using multiple imputation based on baseline characteristics and data collected at post-randomization visits. A sensitivity analysis will also be conducted.	Revised approach following FDA feedback.
9.4.1 Efficacy Analysis	ICS use added as a subgroup	Alignment with ICS allowance.
11.9 Appendix 9 Liver Safety	Added: "Investigators may at their discretion refer patients meeting liver safety criteria below to a specialist who may determine the appropriate or medically necessary additional or confirmatory laboratory tests or procedures as required by the protocol or otherwise deemed necessary (e.g. liver imaging)." Deleted "~~Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.~~"	Clarification.

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1.0 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

A Phase III Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Ensifentrine over 24 Weeks in Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease.

Short Title:

A Phase III randomized, placebo-controlled study to evaluate the efficacy and safety of ensifentrine over 24 weeks in patients with chronic obstructive pulmonary disease.

Rationale

Verona Pharma plc. is developing inhaled nebulized ensifentrine for the maintenance treatment of chronic obstructive pulmonary disease (COPD). RPL554-CO-302 is one of the two Phase III confirmatory studies for the inhaled nebulized ensifentrine suspension formulation in patients with COPD.

The two confirmatory studies RPL554-CO-301 and RPL554-CO-302 are planned as randomized, double-blind, parallel-group, placebo-controlled studies intended to provide replicate evidence of efficacy in terms of improvements in lung function, symptoms and quality of life and the safety of ensifentrine compared to placebo in patients with moderate to severe COPD.

Ensifentrine is a dual inhibitor of phosphodiesterase (PDE)3 and PDE4 which has demonstrated both bronchodilator and anti-inflammatory effects in clinical studies (Singh 2018, 2020 and Franciosi 2013). No dual inhibitors of PDE3 and PDE4 are currently approved for the treatment of COPD. As such, both studies are placebo-controlled to assess the treatment effect of ensifentrine as a novel treatment for patients with COPD. The dose of 3 mg twice daily was informed by two Phase IIb studies in patients with COPD. The first study evaluated ensifentrine as monotherapy and the second study assessed ensifentrine as an add-on to tiotropium. Both studies showed that the 3 mg dose had an optimal benefit:risk profile. Because ensifentrine provides bronchodilation via its inhibition of PDE3 and PDE4, lung function endpoints are key endpoints for the evaluation of efficacy in patients with COPD. Additional endpoints validated in patients with COPD will inform on effects of ensifentrine on symptoms and quality of life from this dual mechanism of action. A treatment duration of 12 weeks is considered sufficient to demonstrate the bronchodilator effects, while a duration of 24 weeks will inform on symptom improvement. Ensifentrine has demonstrated in Phase II studies additional meaningful bronchodilation when added on to current standard of care beta-agonist and muscarinic antagonist therapies.

RPL554-CO-301 will enroll approximately 800 patients with moderate to severe COPD in 2 subsets. The 24-week subset will enroll approximately 400 patients randomized 1:1 ensifentrine (3 mg): placebo and the 48-week subset will enroll approximately 400 patients randomized 3:1 in order to minimize the number of patients assigned to placebo over 48 weeks. The assessments in each subset are identical over the first 24 weeks. The 48-week subset will continue to assess long-term safety in this subset of patients.

Study RPL554-CO-302 is planned as a 24-week study that will enroll 800 patients and be randomized 5:3 to ensifentrine (3 mg): placebo and is otherwise identical to the first 24 weeks of RPL554-CO-301. This study will assess population pharmacokinetic (PK) via sparse sampling in all patients.

Both studies will assess lung function, symptoms, and quality of life over 24 weeks. Safety and tolerability will be assessed over 24 or 48 weeks.

Objectives and Endpoints

Objectives

Primary Objective

The primary objective of this study is to evaluate the efficacy of ensifentrine on lung function compared to placebo over a 12-hour dosing interval in patients with moderate to severe chronic obstructive pulmonary disease (COPD).

Secondary Objectives

- To evaluate the effect of ensifentrine on other lung function parameters.
- To evaluate the effect of ensifentrine on COPD symptoms.
- To evaluate the effect of ensifentrine on health-related quality of life.

Other Objectives

- To evaluate the effect of ensifentrine on moderate/severe COPD exacerbations.
- To evaluate the effect of ensifentrine on health utility and healthcare resource utilization. (HRU)
- To characterize the pharmacokinetics of ensifentrine in patients with COPD.
- To evaluate the effect of ensifentrine on inflammatory biomarkers

Safety Objective

To evaluate the safety and tolerability of ensifentrine over 24 Weeks.

Endpoints

Primary Endpoint

Average forced expiratory volume in 1 second (FEV_1) area under the curve $(AUC)_{0\text{-}12h}$ post-dose at Week 12 (change from baseline).

Secondary Endpoints

- Peak FEV_1 over 4 hours post-dose at Week 12 (change from baseline).
- Evaluating-Respiratory Symptoms (E-RS) Total Score at Week 24 (change from baseline as a weekly average).
- SGRQ total score at Week 24 (change from baseline).
- Morning trough FEV_1 at Week 12 (change from baseline).
- Average FEV_1 $AUC_{0\text{-}4h}$ post-dose at Week 12 (change from baseline).
- The proportion of St. George's Respiratory Questionnaire (SGRQ) responders at Week 24.
- Rescue medication use at Week 24 (change from baseline).
- Transitional Dyspnea Index (TDI) at Week 24.
- Evening trough FEV_1 at Week 12 (change from baseline).
- Peak FEV1, morning and evening trough FEV_1, FEV_1 $AUC_{0\text{-}4h}$, E-RS Total Score, SGRQ responder analysis, and TDI at other Study Visits (change from baseline).
- SGRQ total score at Weeks 6 and 12 (change from baseline).
- Rescue medication use at Weeks 6 and 12 (change from baseline).

Other Endpoints

- Moderate/severe COPD exacerbation frequency over 24 Weeks (this individual study and pooled with data from study RPL554-CO-301).
- Time to first moderate/severe COPD exacerbation over 24 Weeks (this individual study and pooled with data from study RPL554-CO-301).
- Study withdrawal before 24 Weeks.
- EuroQol-5-Domain Questionnaire (EQ-5D-5L) at Week 12 (change from baseline).
- Healthcare Resource Utilization (HRU) over 24 Weeks.
- Average FEV_1 $AUC_{6\text{-}12h}$ post-dose at Week 12 (change from baseline).

- Ensifentrine concentrations following sparse sample collection at Weeks 6, 12, and 24.
- Patient genotype/phenotype including but not limited to cytochrome P-450 (CYP)2C9 and CYP2D6 metabolic activity.
- Interleukin (IL)-6, IL-8, and C-reactive protein at Weeks 12 and 24.

Safety Endpoints

- Incidence of adverse events (AEs)
- Vital signs
- Electrocardiogram (ECG)
- Laboratory tests

Overall Design

RPL554-CO-302 is a multicenter, randomized, double blind, parallel group, placebo controlled study to determine the efficacy and safety of ensifentrine 3 mg twice daily (BID) for 24 weeks, administered via nebulizer vs. placebo in patients 40 to 80 years of age with moderate to severe COPD (FEV_1 30% – 70% of predicted, FEV_1/forced vital capacity [FVC] ratio <0.7, with documented COPD symptoms).

Up to 50% of patients recruited will be using stable background maintenance as *either* long-acting muscarinic antagonist (LAMA) *or* long-acting β2 agonist (LABA) maintenance therapy for 24 weeks and all patients will be provided with rescue albuterol/salbutamol for use as needed during the study. Up to 20% of patients are allowed to take inhaled corticosteroids during the study under certain provisions (see Sections 6.7.2 and 6.7.3). Washout of patients on stable background maintenance LAMA or LABA monotherapy for the sole purpose of study eligibility is not recommended.

Randomization will be stratified by two different factors: stable background maintenance LAMA or LABA therapy use (yes or no) and cigarette smoking (current or former). Patients will be randomized 5:3 to receive ensifentrine (3 mg):placebo for 24 weeks. Patients in the stable background maintenance LAMA or LABA therapy stratum must withhold Twice-Daily LAMA or LABA (or LAMA/ICS or LABA/ICS) for 24 hours and Once-Daily LAMA or LABA (or LAMA/ICS or LABA/ICS) for 48 hours prior to initiation of any spirometry. All patients must withhold short acting bronchodilator (SABA) rescue medication for at least 4 hours prior to initiation of any spirometry.

All sites will use standardized spirometry and electrocardiogram (ECG) equipment provided by a central vendor and all spirometry and ECGs will be over-read by the blinded central vendor.

Patients will be screened for eligibility before entering a 28-day run-in period to ensure a stable COPD treatment regimen and to collect baseline information on symptoms and

rescue medication use. Permitted rescue and background medications and the condition of their use during the study are described in Section 6.7.2. Prohibited medications and the prohibited time intervals prior to Screening are described in Section 6.7.3.

Patients completing the run-in period and meeting all entry and Randomization Criteria will be randomized. The two different stratification factors will be applied at randomization. Details on blinded study medication and administration are provided in Section 6. The Study Schematic is shown in Section 1.2.

During the treatment period, patients will complete all assessments and procedures as outlined in the Schedule of Activities (SoA, Section 1.3) for 24 weeks. Patients completing treatment will complete a Follow-up within 4 to 10 days of the last scheduled study visit.

Patients meeting the withdrawal criteria during the study or who withdraw from the study for other reasons will be discontinued and requested to complete the Early Termination/ Withdrawal Procedures and complete a Follow-up within 4 to 10 days of the Early Termination/Withdrawal Visit.

Patients who permanently discontinue double blind study medication may remain in the study and follow the assessments and procedures as noted in Section 7.2.

Number of Investigators and Study Centers

Approximately 151 Investigators and study centers are expected to participate in this study.

Number of Patients

Approximately 800 randomized patients are planned.

Treatment Groups and Duration

Randomization will be stratified by two different factors: background maintenance LAMA or LABA therapy use (yes or no) and cigarette smoking (current or former). Patients will be randomized active to placebo 5:3 for 24 weeks. The background therapy stratum will be capped at 50%. Patients in the background therapy stratum are expected to continue their background maintenance LAMA or LABA therapy daily throughout the duration of the study, with the exception of withholding 24 or 48 hours prior to spirometry as previously described.

The approximately 800 patients meeting the Randomization Criteria will be randomized to receive the following treatments in a 5:3 ratio:

Treatment Arm 1: Ensifentrine Nebulized Suspension; 3 mg BID

Treatment Arm 2: Ensifentrine Placebo Nebulized BID

Overall, 500 patients will be randomized to ensifentrine and 300 patients will be randomized to placebo.

All blinded study medications will be double-blind and administered using the inhaled route via a standard jet nebulizer supplied by the Sponsor. Nebulization time should be approximately 5 minutes but no longer than 10 minutes.

Statistical Methods

Efficacy analysis will primarily be performed on the modified intent-to-treat (mITT) population including all patients randomized and treated in the study. All tests will be two-sided at a 5% significance level. Secondary efficacy endpoints intended for label claims will be tested in a strict hierarchical order to preserve the alpha level.

Primary endpoint, change from baseline in FEV_1 $AUC_{0\text{-}12h}$ at Week 12, will be compared between treatments using an analysis of covariance (ANCOVA) model adjusting for treatment, region, background medication strata, smoking status, and baseline FEV_1. Patients will be included in analysis as randomized. Missing data will be imputed to get as close to the mITT population as possible. Primary choice of imputation will be based on data collected at early termination visits or at visits performed after treatment withdrawal and, when no such data available, by the average change in the opposite treatment group as randomized to.

Safety analysis will be descriptive and based on the safety set including all randomized and treated patients. Safety analysis will be by actual treatment received.

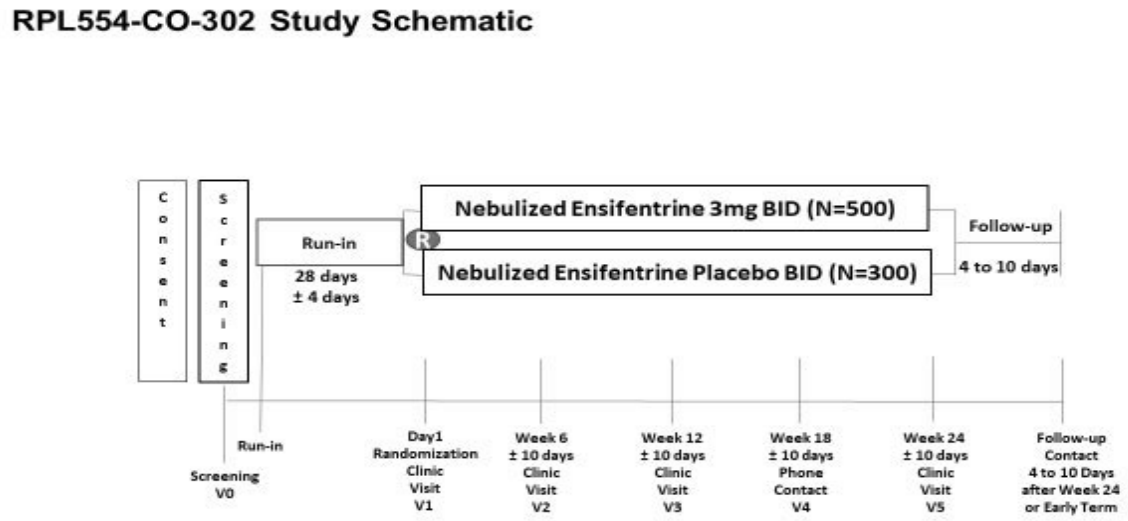
The pharmacokinetics of ensifentrine will be characterized by nonlinear mixed effects modeling based on sparse sampling. The population PK (and population PK-PD, if performed) analyses will be performed in accordance with a separate modeling data analysis plan and will be reported outside of the clinical study report.

Sample Size

Approximately 800 patients will be randomized. The standard deviation for the change in peak FEV_1 is estimated to be 250 mL. With a 2-sided test at a 5% significance level and 500 vs. 300 evaluable patients in the two groups, there will be an 90% power to detect a true difference of 59 mL between the treatments.

1.2 Schema

Figure 1: Study Schematic



1.3 Schedule of Activities

Table 3: Schedule of Activities

			Procedures for Patients Completing 24-Weeks of Treatment						Procedures for Early Term/Withdrawal	
Study Assessments and Procedures	**Screening 1 day Clinic Visit[1]**	**Run-in Period**	**Day 1 (Rand) Clinic Visit[1]**	**Week 6 Clinic Visit[1,2]**	**Week 12 Clinic Visit[1,2]**	**Week 18 Phone Contact**	**Week 24 Clinic Visit [1,2]**	**Follow up Phone Contact[3]**	**Early Term/ Withdrawal[4]**	**Follow up Phone Contact[3]**
		28 Days ± 4 Days		**± 10 Days**	**± 10 Days**	**± 10 Days**	**± 10 Days**	**4 to 10 Days after Week 24**	**ET/ Withdrawal**	**4 to 10 Days After Early Term**
	V0	**Run-in**	**V1**	**V2**	**V3**	**V4**	**V5**			
Basic Procedures										
Written Informed Consent[5]	X									
Demographics	X									
Medical/COPD/Smoking and Surgical History	X									
Inclusion/Exclusion Criteria	X									
Chest X-ray (if CXR or CT Scan not available in past 12 months)[6]	X									
Screening Spirometry (pre- and post-bronchodilator dose)[7,9]	X									
mMRC	X		X							
Nebulizer Equipment Training	X		X							
Concomitant Medication Assessment	X		X	X	X	X	X	X	X	X
Register in IRT	X		X	X	X		X		X	
Randomization Criteria / Randomization			X							

Table 3: Schedule of Activities

			Procedures for Patients Completing 24-Weeks of Treatment						Procedures for Early Term/Withdrawal	
Study Assessments and Procedures	**Screening 1 day Clinic Visit[1]**	**Run-in Period**	**Day 1 (Rand) Clinic Visit[1]**	**Week 6 Clinic Visit[1,2]**	**Week 12 Clinic Visit[1,2]**	**Week 18 Phone Contact**	**Week 24 Clinic Visit [1,2]**	**Follow up Phone Contact[3]**	**Early Term/ Withdrawal[4]**	**Follow up Phone Contact[3]**
		28 Days ± 4 Days		**± 10 Days**	**± 10 Days**	**± 10 Days**	**± 10 Days**	**4 to 10 Days after Week 24**	**ET/ Withdrawal**	**4 to 10 Days After Early Term**
	V0	**Run-in**	**V1**	**V2**	**V3**	**V4**	**V5**			
Efficacy Assessments and Associated Procedures										
Patient Contact Day Prior to Spirometry Visits[8]			X	X	X		X		X	
COPD Exacerbation Assessment			X	X	X	X	X	X	X	X
Spirometry Training[9]	X		X	X	X		X		X	
Spirometry (pre-dose)[10]			X	X	X		X		X	
Spirometry 0-4 hours post dose[10]			X	X			X			
Spirometry 0-12 hours post dose[10]					X				X	
Health Outcomes[11]										
SGRQ			X	X	X		X			
EQ-5D-5L			X		X					
BDI			X							
TDI				X	X		X			
Healthcare Utilization Assessment	X		X	X	X	X	X	X	X	X
Patient Perception Survey								X		X

Table 3: Schedule of Activities

			Procedures for Patients Completing 24-Weeks of Treatment						Procedures for Early Term/Withdrawal	
Study Assessments and Procedures	**Screening 1 day Clinic Visit[1]**	**Run-in Period**	**Day 1 (Rand) Clinic Visit[1]**	**Week 6 Clinic Visit[1,2]**	**Week 12 Clinic Visit[1,2]**	**Week 18 Phone Contact**	**Week 24 Clinic Visit [1,2]**	**Follow up Phone Contact[3]**	**Early Term/ Withdrawal[4]**	**Follow up Phone Contact[3]**
		28 Days ± 4 Days		**± 10 Days**	**± 10 Days**	**± 10 Days**	**± 10 Days**	**4 to 10 Days after Week 24**	**ET/ Withdrawal**	**4 to 10 Days After Early Term**
	V0	**Run-in**	**V1**	**V2**	**V3**	**V4**	**V5**			
Issue eDiary to Patients Eligible to Enter Run-in	X									
Assess eDiary and E-RS Compliance (E-RS/EXACT-PRO will be on eDiary)[12]			X	X	X	X	X		X	
Collect eDiary							X		X	
Safety Assessments										
Vital Signs[13]	X		X	X	X		X		X	
12-Lead ECG (pre-dose)[14]	X		X	X	X		X		X	
12-Lead ECG (1.5 hours post dose)[14]			X	X	X		X		X	
Physical Examination	X									
AE Assessment			X	X	X	X	X	X	X	X
Laboratory Assessments										
Laboratory Tests Haematology, Chemistry (non-fasting), Pregnancy Test (serum) [15]	X		X				X		X	
Urine Pregnancy Test for Women[15]			X	X	X					
Viral Serology for hepatitis	X									
Optional COVID-19 Test[16]	**Optional**		**Optional**	**Optional**	**Optional**		**Optional**		**Optional**	

Table 3: Schedule of Activities

			Procedures for Patients Completing 24-Weeks of Treatment						Procedures for Early Term/Withdrawal	
Study Assessments and Procedures	**Screening 1 day Clinic Visit[1]**	**Run-in Period**	**Day 1 (Rand) Clinic Visit[1]**	**Week 6 Clinic Visit[1,2]**	**Week 12 Clinic Visit[1,2]**	**Week 18 Phone Contact**	**Week 24 Clinic Visit [1,2]**	**Follow up Phone Contact[3]**	**Early Term/ Withdrawal[4]**	**Follow up Phone Contact[3]**
		28 Days ± 4 Days		**± 10 Days**	**± 10 Days**	**± 10 Days**	**± 10 Days**	**4 to 10 Days after Week 24**	**ET/ Withdrawal**	**4 to 10 Days After Early Term**
	V0	**Run-in**	**V1**	**V2**	**V3**	**V4**	**V5**			
Blinded Study Medication, Rescue Medication, Nebulizers and Compressor										
Blinded Study Medication Dosing in Clinic[17]			X	X	X		X		X[4]	
Dispense study supplied nebulizer and compressor (Compressor dispensed at Day 1 only) [17]			X	X	X		X			
Dispense Blinded Study Medication[17]			X	X	X					
Collect Blinded Study Medication and Assess Compliance[17]				X	X		X		X	
Dispense Rescue albuterol/salbutamol[17]	X		X	X	X					
Collect Rescue albuterol/salbutamol[17]			X	X	X		X		X	
Collect Study Supplied Compressor (Week 24 or Early Term as applicable)[18]							X		X	
Pharmacokinetics, Pharmcogenomics and Biomarker Collection										
Pharmacokinetic Sampling[19]				X	X		X		X	
Pharmacogenomic Sample[20]			X							
Biomarker Sample[21]			X		X		X			

NOTE: Information and Details on most of the Study Assessments and Procedures can be found in Section 8.0.

1. No visit procedures may be completed until the informed consent has been obtained (at or prior to Screening Visit 0) and unless all rescue medication (albuterol/salbutamol), LAMA or LABA medication (if applicable), have been withheld for the time periods defined in Section 8.3.1.2. Request patients withhold caffeine and smoking as per Section 8.3.1.2.
2. See Section 8.6 for disaster contingency details.
3. For Follow-up, a phone contact is preferred over a clinic visit unless a clinic visit is required by the IRB/IEC or other local requirement.
4. The early termination (ET)/ withdrawal visit should be conducted as soon as possible as per the early termination/withdrawal procedures in Section 7.3.1. If possible, patients should remain on blinded study medication through the early termination visit (Section 7.3.1). PK sampling should be drawn at ET only for patients who have taken blinded study medication within 48 hours of the ET/withdrawal visit.
5. Informed consent must be obtained by the process described in Section 11.2. Consent may be obtained prior to the Screening Visit but must be obtained prior to any study procedures.
6. Chest X-Ray should be obtained at Screening unless a CXR or a CT Scan obtained within the past 12 months are available. **For subjects in Germany,** if a CXR or CT scan is not available in the 12 months prior to Screening, the subject is not eligible for the study. (Section 8.1.7).
7. Screening spirometry: Pre-bronchodilator testing will be conducted prior to dosing with albuterol/salbutamol. Post-bronchodilator testing should be conducted between 15 and 30 minutes following administration of albuterol/salbutamol as per instructions in Sections 8.1.8 and 8.3.1.
8. Either 3 or 4 days prior to a scheduled in-clinic visit where spirometry is scheduled and blinded study medication will be administered, site staff will contact the patient (phone or text preferred), reminding them to take their blinded study medication, and to fill out their paper diary *for two full calendar days* prior to Week 6, 12 and 24 visits (See Section 8.5.10.2). Patients will be reminded that prior to the clinic visit, they should withhold their nebulized study medication the morning of the visit as this will be dosed in the clinic, withhold rescue medication (albuterol/salbutamol) at least 4 hours prior to their visit and withhold their LAMA or LABA medication, and ICS (if applicable) until the end of the clinic visit. Request patients withhold caffeine and smoking as per Section 8.3.1.2. In addition, patients will also be reminded to bring their paper diary and remaining unused blinded study medication to the clinic visit to the attention of the unblinded site staff member. If a foil pouch is opened but the blinded study medication is not opened/not used, the patient should be instructed to seal the opened foil pouch (eg, tape) before returning it to the clinic (See Section 6.0 for details).
9. See Section 8.3.1.1 for details on Spirometry Training.
10. See Section 1.4, Schedule of Spirometry and In-Clinic Dosing with Blinded Study Medication. See Section 8.3.1 for instructions on spirometry. See Section 7.3.1.1 for spirometry procedures at Early Term/Withdrawal.
11. Health Outcomes: After completion of the mMRC at Randomization/Visit 1, the Health Outcome questionnaires and indexes should be completed in the order presented (Section 8.3.3).

12. The E-RS/EXACT-PRO will be completed by the patient each evening in the eDiary (see details in Section 8.5.4). eDiary compliance will be visually reviewed by site staff at each on-site clinic visit and via discussion with the patient during phone contact and/or flexible visits when patients are unable come into the clinic. Patients with poor compliance should be instructed by the site staff to improve compliance.
13. Vital signs: See Section 8.1.5 and Section 8.4.1 for details.
14. At Day 1/Randomization/Visit 1 prior to dosing (pre-dose), triplicate ECGs must be performed. Patients should refrain from caffeine, smoking and albuterol/salbutamol prior to ECGs for the withholding periods described in Section 5.4.1 and Section 8.4.2. See Section 8.4.2 for instructions on ECG. See Section 7.3.1.1 and Section 7.3.1.2 for ECG procedures at Early Term/ Withdrawal.
15. Pregnancy Testing: Pregnancy testing will be conducted on women of childbearing potential. A urine test will be conducted prior to dosing at Visit 1. Instructions in Section 7.1.5, Section 8.7.5 and Section 11.8 should be followed for Women with a positive pregnancy test after randomization.
16. A COVID-19 test for active disease is optional. COVID-19 testing should follow local requirements (Section 11.3). If conducted, the test may be done within 7 days of the visit or at the visit. In addition, a COVID-19 test may be conducted anytime a patient is suspected/exhibiting signs of active disease. If a COVID-19 test is positive for active disease, see Section 7.1.6
17. Information on blinded study medication, dosing and compliance, rescue medication, nebulizers and compressor can be found in Section 6.0. The end time of blinded study medication nebulization is when a slight sputtering sound from the nebulizer is heard. This will be considered Time 0 for the purposes of scheduling all post-dose study procedures (Section 6.1.1). Rescue medication may be dispensed at the time of signing the Informed Consent, if this occurs prior to commencement of screening assessments.
18. Collect study supplied compressor if allowed per local site practices, otherwise study supplied compressors will not be returned and collected.
19. Pharmacokinetic Sampling: Pharmacokinetic (PK) sample collection schedule will be different between even and odd numbered sites as described in Section 8.5.10.1, and should only be drawn for patients who have taken blinded study medication at least 48 hours prior to the visit
20. Patients will be invited to participate in optional genetic research. The pharmacogenomic sample should be collected on Day 1 but may be collected at any time during the study. See Section 8.5.11.
21. The biomarker samples should be collected from all patients pre-dose. See Section 8.5.12 and Section 11.3.

Abbreviations: AE=Adverse Event; BDI=Baseline Dyspnea Index; COPD=Chronic Obstructive Pulmonary Disease; CT=Computed Tomography; COVID=Corona Virus Disease; CXR=Chest X-Ray; eDiary=Electronic Diary; ECG=Electrocardiogram; EQ-5D-5L=EuroQol Questionnaire; E-RS=Exact-Respiratory Symptoms; ET=Early Term; IEC=Independent Ethics Committee; IRB=Institutional Review Board; IRT=Interactive Response Technology; LABA= Long-acting β2 agonist; LAMA= Long-acting muscarinic antagonist; IL=Interleukin; mMRC=Modified Medical Research Council Dyspnoea Scale; PK=Pharmacokinetic; Rand=Randomization; SGRQ=St. George Respiratory Questionnaire; TDI=Transitional Dyspnea Index; V=Visit.

1.4 Schedule of Spirometry and In-Clinic Dosing with Blinded Study Medication

Table 4: Schedule of Spirometry and In-Clinic Dosing with Blinded Study Medication

Every effort should be made to initiate spirometry according to these timings:	**Visit 1** **Randomization**	**Week 6** **Visit 2**	**Week 12** **Visit 3**	**Week 24** **Visit 5**	**Early Term/Withdrawal**
Pre-Dose Spirometry	*Two separate timepoints* within 40 minutes prior to dosing.	Within 40 minutes prior to dosing *AND between 11.5 and 12 hours after the patients evening dose the day prior to this visit.*	Within 40 minutes prior to dosing *AND between 11.5 and 12 hours after the patients evening dose the day prior to this visit.*	Within 40 minutes prior to dosing *AND between 11.5 and 12 hours after the patients evening dose the day prior to this visit.*	Within 40 minutes prior to dosing *AND between 11.5 and 12 hours after the patients evening dose the day prior to this visit (if applicable).*
Morning Blinded Study Medication Dosing in the Clinic	Time: Between 6 AM and 10 AM	Time: Between 6 AM and 10 AM	Time: Between 6 AM and 10 AM	Time: Between 6 AM and 10 AM	Time: Between 6 AM and 10 AM
Post-Dose Serial Spirometry	30 min, 1, 2, and 4 hours post-dose.	30 min, 1, 2, and 4 hours post-dose.	30 min, 1, 2, 4, 6, 8 hours and the 12 hour pos-dose spirometry should not start prior to 11.5 hours.	30 min, 1, 2, and 4 hours post-dose.	30 min, 1, 2, 4, 6, 8 hours and the 12 hour post-dose spirometry should not start prior to 11.5 hours.
Evening Blinded Study Medication Dosing[1]	None	None	Time: After completion of the 12-hour spirometry and between 6 PM and 10 PM	None	None

Note: Additional details on information contained in this table can be found in Section 6.0 and Section 8.3.1. For pre-dose spirometry conducted between 11.5 and 12 hours after the patients evening dose the day prior to the visit, the paper diary with the evening dosing completion time should be consulted.

[1]Patients may be discharged from the clinic after Week 12 assessments are complete to self-administer their evening dose of study medication. If administered in the clinic, the Week 12 evening dose must be administered by unblinded site staff.

2.0 INTRODUCTION

2.1 Study Rationale

Verona Pharma plc. is developing inhaled nebulized ensifentrine for the maintenance treatment of chronic obstructive pulmonary disease (COPD). RPL554-CO-302 is one of the two Phase III confirmatory studies for the inhaled nebulized ensifentrine suspension formulation in patients with COPD.

The two confirmatory studies RPL554-CO-301 and RPL554-CO-302 are planned as randomized, double-blind, parallel-group, placebo-controlled studies intended to provide replicate evidence of efficacy in terms of improvements in lung function, symptoms and quality of life and the safety of ensifentrine compared to placebo in patients with moderate to severe COPD.

RPL554-CO-301 will enroll approximately 800 patients with moderate to severe COPD in 2 subsets. The 24-week subset will enroll approximately 400 patients randomized 1:1 ensifentrine (3 mg): placebo and the 48-week subset will enroll approximately 400 patients randomized 3:1 in order to minimize the number of patients assigned to placebo over 48 weeks. The assessments in each subset are identical over the first 24 weeks. The 48-week subset will continue to provide long-term safety data in this subset of patients.

Study RPL554-CO-302 is planned as a 24-week study that will enroll 800 patients and be randomized 5:3 to ensifentrine (3 mg): placebo and is otherwise identical to the first 24 weeks of RPL554-CO-301. This study will assess population PK via sparse sampling in all patients.

Both studies will assess lung function, symptoms, and quality of life over 24 weeks. Safety and tolerability will be assessed over 24 or 48 weeks.

2.2 Background

Ensifentrine is a selective dual phosphodiesterase (PDE)3 and PDE4 inhibitor which has clinically demonstrated bronchodilation and anti-inflammatory activity following inhaled dosing. This novel mechanism of action represents an important potential additional treatment option for patients with moderate to severe COPD, and other respiratory indications such as asthma and cystic fibrosis whose disease is manifest by airways obstruction and inflammation. As a potential new treatment for COPD, this new mechanism of action can 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. Ensifentrine is first being developed as an inhaled suspension formulation for delivery via a nebulizer for patients with COPD.

Ensifentrine has been studied in the nebulizer formulation in 15 clinical trials involving more than 1250 subjects. The initial nebulizer solution formulation was used in the first five clinical trials between 2009 and 2014.

Ten clinical studies have been completed with ensifentrine delivered in a nebulized suspension format. The two most recent of the ten studies, 4-week Phase IIb study RPL554-CO-205 and Phase 1 study RPL554-PK-102, were performed using an optimized variant of the suspension formulation in which the phosphate buffer loading in the vehicle was reduced ten-fold. This optimized formulation, referred to as the 'low phosphate' formulation, is the proposed Phase III and to-be-marketed formulation.

In the clinical studies performed to date, ensifentrine has demonstrated pronounced bronchodilator effects in healthy subjects and in patients with COPD or asthma. In single-dose studies, ensifentrine alone was as effective as albuterol or ipratropium as a bronchodilator in patients with COPD (RPL554-009-2015; Singh 2018). Ensifentrine has also demonstrated anti-inflammatory effects in a model of COPD-like inflammation in healthy subjects (Franciosi 2013).

A 3-day study was conducted where nebulized ensifentrine or placebo was administered twice daily to patients with COPD as an add-on treatment to tiotropium (Spiriva®; RPL554-CO-202). In this study, statistically significant and clinically meaningful improvements in bronchodilation were seen compared to placebo. In addition, ensifentrine significantly reduced residual lung volumes and increased the speed of onset of the bronchodilator effect to under 5 minutes.

In the first completed 4 week dose-ranging, 403-patient Phase IIb study, RPL554-CO-203, four dose levels of nebulized ensifentrine (0.75, 1.5, 3, and 6 mg) were administered twice daily to patients with moderate to severe COPD not taking additional maintenance bronchodilator therapies. All doses of ensifentrine met the primary endpoint, showing a statistically significant increase in peak FEV_1 vs placebo ($p<0.001$) with placebo-corrected changes from baseline >200 mL in peak FEV_1 after 4 weeks of dosing. In addition, statistically significant improvements in average FEV_1 over 12 hours were observed at all doses after the first administration, and this effect was sustained over 4 weeks. Notably, statistically significant and clinically meaningful improvements in total COPD symptoms were shown using the Evaluating Respiratory Symptoms in COPD (E-RS™: COPD) measure, a validated daily assessment of stable COPD symptoms. Ensifentrine showed a meaningful reduction in symptoms on the total score and all subscales of the E-RS at or near the minimal clinically important difference (MCID) of each.

In a second recently completed 4 week dose-ranging, 413-patient Phase IIb study, RPL554-CO-205, with ensifentrine or placebo added on to maintenance tiotropium, 4 dose levels (0.375, 0.75, 1.5, and 3 mg) of ensifentrine or placebo were administered twice daily to patients with moderate to severe COPD who remained symptomatic and with impaired lung function following a 2 week tiotropium run-in. All doses of

ensifentrine met the primary endpoint, showing a statistically significant increase in peak FEV_1 (all $p<0.05$) which was sustained over 4 weeks. For the two highest doses, 1.5 and 3 mg, increases in peak FEV_1 were observed >100 mL compared to placebo after 4 weeks of dosing. In addition, a statistically significant and meaningful improvement in average FEV_1 over 12 hours was shown with the 3 mg dose at Week 4 (87 mL, $p=0.0111$). Notably, statistically significant and clinically meaningful improvements in health-related quality of life as measured by St. George's Respiratory Questionnaire (SGRQ)-COPD (Meguro, 2007) were observed at Week 4 with the 1.5 and 3 mg doses of ensifentrine added onto tiotropium (placebo-corrected; both $p<0.05$), which exceeded the MCID for both doses.

Overall, ensifentrine was well tolerated in the 15 clinical studies conducted to date, with adverse event (AE) incidence and severity generally similar to those in the placebo-treated group. Serious adverse events (SAEs) have been uncommon and there is no apparent pattern in the SAEs reported to date.

Verona Pharma is developing nebulized ensifentrine as a maintenance therapy for patients with COPD. Information on the background of ensifentrine as described in this section can be found in the Verona Pharma plc. Ensifentrine Clinical Investigators Brochure (IB) v. 20.0, 2021 (or more current version, if applicable), unless otherwise cited.

2.3 Benefit/Risk Assessment

No significant medical risks to patients 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 patients 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. Otherwise, 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 anti-inflammatory 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 patients with COPD and the overall favorable safety profile in studies to date, the benefit/risk profile of ensifentrine is considered positive.

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 v. 20.0, 2021 (or more current version, if applicable).

3.0 OBJECTIVES AND ENDPOINTS

3.1 Objectives

3.1.1 Primary Objective

The primary objective of this study is to evaluate the efficacy of ensifentrine on lung function compared to placebo over a 12-hour dosing interval in patients with moderate to severe COPD.

3.1.2 Secondary Objectives

- To evaluate the effect of ensifentrine on other lung function parameters.
- To evaluate the effect of ensifentrine on COPD symptoms.
- To evaluate the effect of ensifentrine on health-related quality of life.

3.1.3 Other Objectives

- To evaluate the effect of ensifentrine on moderate/severe COPD exacerbations.
- To evaluate the effect of ensifentrine on health utility and healthcare resource utilization (HRU).
- To characterize the pharmacokinetics of ensifentrine in patients with COPD.
- To evaluate the effect of ensifentrine on inflammatory biomarkers.

3.1.4 Safety Objective

To evaluate the safety and tolerability of ensifentrine over 24 Weeks.

3.2 Endpoints

3.2.1 Primary Endpoint

Average forced expiratory volume in 1 second (FEV_1) area under the curve $(AUC)_{0\text{-}12h}$ post-dose at Week 12 (change from baseline).

3.2.2 Secondary Endpoints

- Peak FEV_1 over 4 hours post-dose at Week 12 (change from baseline).
- Evaluating-Respiratory Symptoms (E-RS) Total Score at Week 24 (change from baseline as a weekly average).
- SGRQ total score at Week 24 (change from baseline).

- Morning trough FEV_1 at Week 12 (change from baseline).
- Average FEV_1 $AUC_{0\text{-}4h}$ post-dose at Week 12 (change from baseline).
- The proportion of St. George's Respiratory Questionnaire (SGRQ) responders at Week 24.
- Rescue medication use at Week 24 (change from baseline).
- Transitional Dyspnea Index (TDI) at Week 24.
- Evening trough FEV_1 at Week 12 (change from baseline).
- Peak FEV_1, morning and evening trough FEV_1, FEV_1 $AUC_{0\text{-}4h}$, E-RS Total Score, SGRQ responder analysis, and TDI at other Study Visits (change from baseline).
- SGRQ total score at Weeks 6 and 12 (change from baseline).
- Rescue medication use at Weeks 6 and 12 (change from baseline).

3.2.3 Other Endpoints

- Moderate/severe COPD exacerbation frequency over 24 Weeks (this individual study and pooled with data from study RPL554-CO-301).
- Time to first moderate/severe COPD exacerbation over 24 Weeks (this individual study and pooled with data from study RPL554-CO-301).
- Study withdrawal before 24 Weeks.
- EuroQol-5-Domain Questionnaire (EQ-5D-5L) at Week 12 (change from baseline).
- Healthcare Resource Utilization (HRU) over 24 Weeks.
- Average FEV_1 $AUC_{6\text{-}12h}$ post-dose at Week 12 (change from baseline).
- Ensifentrine concentrations (sparse sample collection) at Weeks 6, 12, and 24.
- Patient genotype/phenotype including but not limited to cytochrome P-450 (CYP)2C9 and CYP2D6 metabolic activity.
- Interleukin (IL)-6, IL-8, and C-reactive protein at Weeks 12 and 24.

3.2.4 Safety Endpoints

- Incidence of AEs
- Vital signs
- Electrocardiogram (ECG)
- Laboratory tests

4.0 STUDY DESIGN

4.1 Overall Design

RPL554-CO-302 is a multicenter, randomized, double blind, parallel group, placebo controlled study to determine the efficacy and safety of ensifentrine 3 mg twice daily (BID) for 24 weeks administered via nebulizer vs. placebo in patients 40 to 80 years of age with moderate to severe COPD (FEV_1 30% – 70% of predicted, FEV_1/forced vital capacity (FVC) ratio <0.7, with documented COPD symptoms).

Up to 50% of patients recruited will be using stable background maintenance as *either* long-acting muscarinic antagonist (LAMA) *or* long-acting β2 agonist (LABA) maintenance therapy for 24 weeks and all patients will be provided with rescue albuterol/salbutamol for use as needed during the study. Up to 20% of patients are allowed to take inhaled corticosteroids during the study under certain provisions (see Sections 6.7.2 and 6.7.3). Washout of patients on stable background maintenance LAMA or LABA monotherapy for the sole purpose of study eligibility is not recommended.

Randomization will be stratified by two different factors: stable background maintenance LAMA or LABA therapy use (yes or no) and cigarette smoking (current or former). Patients will be randomized 5:3 to receive ensifentrine (3 mg):placebo for 24 weeks. Patients in the background maintenance LAMA or LABA therapy stratum must withhold Twice-Daily maintenance LAMA or LABA (or LAMA/ICS or LABA/ICS) for 24 hours and Once-Daily maintenance LAMA or LABA (or LAMA/ICS or LABA/ICS) for 48 hours prior to initiation of any spirometry. All patients must withhold short acting bronchodilator (SABA) rescue medication for at least 4 hours prior to initiation of any spirometry.

All sites will use standardized spirometry and ECG equipment provided by a central vendor and all spirometry and ECGs will be over-read by the blinded central vendor.

Patients will be screened for eligibility before entering a 28-day run-in period to ensure a stable background maintenance LAMA or LABA bronchodilator medication regimen and to collect baseline information on symptoms and rescue medication use. Permitted rescue and background medications and the condition of their use during the study are described in Section 6.7.2. Prohibited medications and the prohibited time intervals prior to Screening are described in Section 6.7.3

Patients completing the run-in period and meeting all entry and Randomization Criteria will be randomized. The two different stratification factors will be applied at randomization. Details on blinded study medication and administration are provided in Section 6.0. The Study Schematic is shown in Section 1.2.

During the treatment period, patients will complete all assessments and procedures as outlined in the Schedule of Activities (Section 1.3) for 24 weeks. Patients completing treatment will complete a Follow-Up within 4 to 10 days of the last scheduled study visit.

Patients meeting the withdrawal criteria during the study or who withdraw from the study for other reasons will be discontinued and requested to complete the Early Termination/ Withdrawal Procedures and complete a Follow-Up within 4 to 10 days of the Early Termination/ Withdrawal Visit.

Patients who permanently discontinue double blind study medication may remain in the study and follow the assessments and procedures as noted in Section 7.2.

4.2 Scientific Rationale for Study Design

Verona Pharma plc is developing inhaled nebulized ensifentrine for the maintenance treatment of COPD. RPL554-CO-301 is one of the two Phase III confirmatory studies for the inhaled nebulized ensifentrine suspension formulation in patients with COPD.

The two confirmatory studies RPL554-CO-301 and RPL554-CO-302 are planned as randomized, double-blind, parallel-group, placebo-controlled studies intended to provide replicate evidence of efficacy in terms of improvements in lung function symptoms and quality of life and safety of ensifentrine compared to placebo in patients with moderate to severe COPD.

Ensifentrine is a dual inhibitor of PDE3 and PDE4 which has demonstrated both bronchodilator and anti-inflammatory effects in clinical studies (Singh 2018, 2020 and Franciosi 2013). No dual inhibitors of PDE3 and PDE4 are currently approved for the treatment of COPD. As such, both studies are placebo-controlled to assess the treatment effect of ensifentrine as a novel treatment for patients with COPD. The dose of 3 mg twice daily was informed by two Phase IIb studies in patients with COPD. The first evaluated ensifentrine as monotherapy and the other added on to tiotropium which showed that the 3 mg dose had an optimal benefit:risk profile. Because ensifentrine provides bronchodilation via its inhibition of PDE3 and PDE4, lung function endpoints are key endpoints for the evaluation of efficacy in patients with COPD. Additional endpoints validated in patients with COPD will inform on effects on symptoms and quality of life from this dual mechanism of action. A treatment duration of 12 weeks is considered sufficient to inform on bronchodilator effects, while a duration of 24 weeks will inform on symptom improvement.

Ensifentrine has demonstrated in Phase II studies additional meaningful bronchodilation alone or when added on to current standard of care beta-agonist and muscarinic antagonist therapies. Symptom and quality of life improvement has been shown over 4 weeks as monotherapy or added on to tiotropium.

In RPL554-CO-301 and RPL554-CO-302, up to 50% of patients recruited will be using stable background maintenance as *either* LAMA *or* LABA maintenance therapy and all patients will be provided with rescue albuterol/salbutamol for use as needed during the study. Up to 20% of patients are allowed to take inhaled corticosteroids during the study under certain provisions (see Sections 6.7.2 and 6.7.3). Washout of patients on stable

background maintenance LAMA or LABA monotherapy for the sole purpose of study eligibility is not recommended to ensure a population with stable COPD is enrolled.

Randomization in RPL554-CO-301 will be stratified by three different factors: treatment duration (48 or 24 weeks), stable background maintenance LAMA or LABA therapy use (yes or no), and cigarette smoking (current or former). The 48 weeks strata will be randomized active to placebo 3:1, and the 24 weeks strata will be randomized active to placebo 1:1. The 48-week subset is intended to inform on the long-term safety of ensifentrine vs placebo and the 3:1 randomization in this subset is intended to minimize the number of patients randomized to placebo for 48 weeks.

Study RPL554-CO-302 is planned as a 24-week study that will enroll 800 patients and be randomized 5:3 to ensifentrine (3 mg): placebo and is otherwise identical to the first 24 weeks of RPL554-CO-301. This study will assess population PK via sparse sampling in all patients.

Both studies will assess lung function, symptoms, and quality of life over 24 weeks. Safety and tolerability will be assessed over 24 or 48 weeks.

4.3 Justification for Dose

A 3 mg twice daily dose was selected as the Phase 3 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 patients with or without additional bronchodilator background therapy.

A review of safety and tolerability across all COPD studies has shown a safety profile similar to placebo, even when added on top of other bronchodilator therapies:

- 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 patients 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 patients after 4 weeks.
- 24-hour Holter monitoring in 324 patients 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.

4.4 End of Study Definition

A patient is considered to have completed the study if he/she has successfully completed all on-treatment randomized visits and completed the follow-up contact.

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

5.0 STUDY POPULATION

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

5.1 Inclusion Criteria

Informed Consent

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 informed consent form (ICF) and in this protocol.

Age and Sex

2. Age: Patient must be 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 (Section 11.8) from Screening and throughout the study and for at least 30 days after the last dose of blinded study medication.
    - Females are eligible to participate if they are not pregnant, not breastfeeding, and at least one of the following conditions apply:

        a) Not a woman of childbearing potential (WOCBP) as defined in Section 11.8.

        Or

        b) A WOCBP who agrees to follow the contraceptive guidance in Section 11.8 from Screening and throughout the study and for at least 30 days after the last dose of blinded study medication.

Smoking History

4. Smoking History: Current or former cigarette smokers with a history of cigarette smoking ≥10 pack years at Screening (Visit 0) [number of pack years = (number of cigarettes per day / 20) × number of years smoked (eg, 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years)]. Pipe and/or cigar use cannot be used to calculate pack-year history. Former smokers are defined as those who have stopped smoking for at least 6 months prior to Visit 0. Smoking cessation programs are permitted during the study.

COPD Diagnosis, Symptoms, Severity and Maintenance Therapy

5. COPD Diagnosis: Patients with an established clinical history of COPD as defined by the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines (Celli BR, 2004) with symptoms compatible with COPD.
6. COPD Symptoms: A score of ≥2 on the Modified Medical Research Council (mMRC) Dyspnea Scale.

7. COPD Severity:
    a. Pre- and Post-albuterol/salbutamol FEV_1/FVC ratio of <0.70.
    b. Post-albuterol/salbutamol FEV_1 ≥30 % and ≤70% of predicted normal calculated using the National Health and Nutrition Examination Survey III (Hankinson, 1999).
8. Maintenance Therapy: Patients on no maintenance/background therapy or patients on stable maintenance as *either* LAMA *or* LABA therapy are eligible. Patients taking maintenance LAMA or LABA therapy must demonstrate regular use of maintenance LAMA or LABA therapy, in any form, for at least 2 months prior to Screening and agree to continue use of their current permitted LAMA or LABA medication for the duration of the study. Section 6.7.3 lists the medications that are prohibited during the study and the prohibited time intervals prior to Screening. Background maintenance LAMA or LABA bronchodilator therapy will be capped at 50% of patients.

Other Requirements for Inclusion

9. Capable of withholding SABAs for 4 hours prior to initiation of any spirometry. Patients in the maintenance LAMA or LABA therapy stratum must be capable of withholding Twice-Daily maintenance LAMA or LABA for 24 hours and Once-Daily maintenance LAMA or LABA for 48 hours prior to initiation of any spirometry.
10. Capable of using the study nebulizer correctly and complying with all study restrictions and procedures.
11. Ability to perform acceptable spirometry in accordance with ATS/ERS guidelines (Miller 2005).

5.2 Exclusion Criteria

Current Condition or Medical History

1. History of life-threatening COPD including Intensive Care Unit admission and/or requiring intubation.
2. Hospitalizations for COPD, pneumonia, or Corona Virus Disease 2019 (COVID-19) in the 12 weeks prior to Screening and/or a positive COVID-19 test result indicating an active infection at Screening. Patients with COVID-19 antibodies from a previous exposure with no active infection are not excluded.
3. COPD exacerbation requiring oral or parenteral steroids within 3 months of Screening.
4. Previous lung resection or lung reduction surgery within 1-year of Screening.
5. Long term oxygen use defined as oxygen therapy prescribed for greater than 12 hours per day. As needed oxygen use (≤12 hours per day) is not exclusionary.
6. Pulmonary rehabilitation, unless such treatment has been in a stable maintenance phase for 4 weeks prior to Visit 1 and remains stable during the study.

7. Lower respiratory tract infection within 6 weeks of Screening.
8. Other respiratory disorders including, but not limited to, a current diagnosis of asthma, active tuberculosis, lung cancer, sarcoidosis, lung fibrosis, interstitial lung diseases, unstable sleep apnea, known alpha-1 antitrypsin deficiency, core pulmonale, clinically significant pulmonary hypertension, clinically significant bronchiectasis, or other active pulmonary diseases.
9. Major surgery (requiring general anesthesia) in the 6 weeks prior to Screening, lack of full recovery from surgery at Screening, or planned surgery through the end of the study.
10. Historical or current evidence of clinically significant cardiovascular disease defined as any disease that in the opinion of the Investigator would put the safety of the patient at risk through participation or which could affect the efficacy or safety analysis if the disease/condition were to exacerbate during the study, including, but not limited to:
    - Myocardial infarction or unstable angina within 6 months prior to Screening.
    - Unstable or life-threatening cardiac arrhythmia requiring intervention within 3 months prior to Screening.
    - Diagnosis of New York Heart Association (Dolgin 1994) Class III and Class IV heart failure.
11. Chronic uncontrolled disease including, but not limited to, endocrine, active hyperthyroidism, neurological, hepatic, gastrointestinal, renal, hematological, urological, immunological, psychiatric, or ophthalmic diseases that the Investigator believes are clinically significant.
12. Unstable liver disease defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices or persistent jaundice, cirrhosis, known biliary abnormalities (except for Gilbert's syndrome or asymptomatic gallstones). Note: Chronic stable hepatitis B and C is not exclusionary if the patient otherwise meets study entry criteria.
13. 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.
14. Findings on physical examination that an investigator considers to be clinically significant at Screening.

Prior/Concomitant Therapy

15. Use of prohibited medications within the time intervals defined in Section 6.7.3.

History or Suspicion of Drug or Alcohol Abuse

16. Current or history of past drug or alcohol abuse within the past 5 years.

Laboratory and Other Diagnostic Parameters

17. Glomerular Filtration Rate (eGFR) <30 mL/min. The Chronic Kidney Disease Epidemiology Collaboration Creatinine (2009) calculation will be used (Levey, 2009).

18. Alanine aminotransferase (ALT) ≥ 2 x upper limit of normal (ULN), alkaline phosphatase and/or bilirubin > 1.5 x ULN (isolated bilirubin >1.5 x ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).

19. Any other abnormal hematology, biochemistry, or viral serology deemed by an investigator to be clinically significantly abnormal. Abnormal chemistry and/or hematology may be repeated during Screening.

20. Chest X-ray (CXR; posterior-anterior) at Screening, or in the 12 months prior to Screening with clinically significant abnormalities not attributable to COPD. If a CXR within the past 12 months is not available but a computerized tomography (CT) scan within the same time period is available, the CT scan may be reviewed in place of a CXR. **For subjects in Germany**, if a CXR or CT scan is not available in the 12 months prior to Screening, the subject is not eligible for the study.

21. Electrocardiogram (ECG) finding that is significantly abnormal as defined in Section 11.4 on the 12-lead ECG obtained at Screening.

Other Exclusions

22. 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 trial within 30 days prior to Screening.

23. Use of an experimental medical device or participation in a follow-up phase of an experimental medical device clinical trial within 30 days prior to Screening.

24. Intolerance or hypersensitivity to albuterol/salbutamol or ensifentrine (RPL554) or any of its excipients/components.

25. Prior receipt of blinded nebulized study medication in an ensifentrine (RPL554) study.

26. 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.

27. Inability to read, understand, and/or complete questionnaires (in the opinion of the Investigator).

28. A disclosed history or one known to the Investigator of significant non-compliance in previous investigational studies or with prescribed medications.

29. Any other reason that the Investigator considers makes the patient unsuitable to participate.

5.3 Randomization Criteria

Criteria for Inclusion at Randomization

1. Symptoms of COPD: A score of ≥2 on the mMRC Dyspnea Scale at Visit 1.
2. Completion of the e-Diary at least 5 of the last 7 days of the Run-in period.

Criteria for Exclusion from Randomization

1. COPD exacerbation or lower respiratory tract infection between Screening and Randomization (defined as use of any additional treatment other than current treatment and rescue medication and/or emergency department or hospital visit). Patients with a severe COPD exacerbation that requires hospitalization may not be rescreened.
2. Positive COVID-19 result at Screening or between Screening and Randomization.
3. Prohibited medication use between Screening Visit 0 and Visit 1.
4. Significantly abnormal ECG finding as defined in Section 11.4 on the 12-lead ECG obtained at Screening as assessed by the investigator or site medical doctor/medically qualified person OR on the pre-dose ECG obtained at Visit 1 *before the patient is randomized*. After a patient has been randomized, ECG withdrawal criteria (Section 11.5) will apply. In the event that the central ECG reviewer discovers a significant ECG abnormality meeting ECG withdrawal criteria on the Visit 1 ECG in 2 of 3 triplicate measurements, the patient may be discontinued.
5. Did not meet one or more of the Inclusion Criteria (Section 5.1) or met one or more of the Exclusion Criteria (Section 5.2) as assessed at Screening Visit 0 (e.g. including overreads or lab values obtained after the day of Screening).

5.4 Lifestyle Considerations

5.4.1 Caffeine and Tobacco

5.4.1.1 Prior to Spirometry and prior to ECG:

Recommendation/request: Patients should refrain from smoking and/or caffeinated beverages prior to Spirometry and ECGs for the withholding periods below:

- *Smoking:* No smoking for at least 1-hour prior to each spirometry and ECG assessment.
- *Caffeinated Beverages:* Abstain from drinking beverages with high levels of caffeine (eg, tea, coffee) for 2 hours prior to each spirometry and ECG assessment.

5.5 Rescreening

5.5.1 Rescreening Prohibited

Patients who do not meet the following Inclusion Criteria may not be rescreened under any circumstances:

- Inclusion Criteria #5: COPD Diagnosis
- Inclusion Criteria #6: COPD Symptoms
- Inclusion Criteria #7: COPD Severity

5.5.2 Rescreening Permitted if Medical Monitor Approves

Approval from the Medical Monitor must be obtained to rescreen patients other than those for whom rescreening is prohibited (Section 5.5.1). Rescreened patients should be assigned the same patient number as for the initial screening.

5.6 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but were not randomized to receive blinded study medication. See Section 7.1.1 for instructions on managing patients who did not meet the criteria for randomization but were randomized in error.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients 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

Patients will be randomly assigned to receive double-blind study medication (either ensifentrine or placebo) administered using the inhaled route via a standard jet nebulizer (Section 6.2.2) supplied by the Sponsor.

In this protocol the terms 'investigational product,' 'double-blind study medication,' and 'blinded study medication' are the same and refer to the blinded nebulized study medication.

6.1 Administration of Blinded Study Medication

6.1.1 Dosing in the Clinic

The Clinic Visit *MUST BE RESCHEDULED* within 3 days of the scheduled visit if any of the following apply:

- If the rescue medication or maintenance LAMA or LABA medication are not withheld for the time intervals defined in Section 6.7.2.
- If the morning dose of blinded study medication is not withheld.

Dosing Environment

- To avoid cross-contamination, blinded study medication dosing must be conducted in a shielded and well-ventilated environment.
- Patients may be in the same room as other patients who are being dosed on the same day if separated by a partial partition or curtain and if other patients and other staff members cannot visualize the study medication administration by the blinded study site staff member. These measures are in place to protect study medication blinding.

Designated Unblinded Site Staff Member

To maintain the treatment blind, each site will designate an unblinded site staff member not associated with study conduct to administer in-clinic doses.

Dosing Visit Schedule and Time(s) of Day

***Coordination of the timing of spirometry and in-clinic dosing with blinded study medication is critical.* See Section 1.4, for the Schedule of Spirometry and In-Clinic Dosing with Blinded Study Medication.**

Blinded Study Medication Administration

A new PARI LC Sprint® jet nebulizer (study supplied nebulizer), with a PARI Vios® PRO Aerosol Delivery System PARI BOY® compressor or equivalent (study supplied

compressor) will be dispensed to the patient and used to dose the blinded study medication in the clinic and at home.

- Blinded study medication will be administered by inhalation of an aerosol generated by the reusable study supplied nebulizer attached to a study supplied compressor.
- The unblinded site staff member should follow the nebulizer Set-Up instructions provided with the nebulizer and the Pharmacy Manual to prepare and administer the blinded study medication.
- Administration of nebulized blinded study medication will be observed by the unblinded site staff member from start of nebulization until end time of nebulization. The unblinded site staff member MUST administer blinded study medication at all in-clinic dosing times. Patients may be discharged from the clinic after Week 12 assessments are complete to self-administer their evening dose of study medication. If administered in the clinic, the Week 12 evening dose must be administered by unblinded site staff.
- Blinded study medication nebulization time should be approximately 5 minutes and may not exceed 10 minutes.
- The end time of blinded study medication nebulization is when a slight sputtering sound from the nebulizer is heard. This will be considered Time 0 for the purposes of scheduling all post-dose study procedures.
- The date, the start time, and the end time of blinded study medication nebulization will be recorded by the unblinded site staff member in the patient source document and the electronic case report form (eCRF).
- Patients will take their study supplied nebulizer study supplied compressor and instructions home for use during the study. A new study supplied nebulizer(s) will be issued periodically. Only a study supplied nebulizer and a study supplied compressor may be used to administer blinded study medication during the study.

6.1.2 Dosing at Home

Following Visit 1, patients will self-administer their daily morning and evening doses at home at approximately the same times, approximately 12 hours apart, each day for the duration of the study, except for specific clinic visit days when patients will have their doses administered in the clinic.

Prior to Dosing at Home

- Patients in the maintenance LAMA or LABA stratum should take their maintenance LAMA or LABA (and ICS, if applicable) prior to taking blinded study medication.

Blinded Study Medication Administration

- Each patient will follow the Nebulizer Set-Up instructions and blinded study medication label to prepare and self-administer the blinded study medication by inhalation using the reusable study supplied nebulizer attached to the study supplied compressor.

- Blinded study medication nebulization time should be approximately 5 minutes and may not exceed 10 minutes.
- The end time of blinded study medication nebulization is considered to be when a slight sputtering sound from the nebulizer is heard. This will be considered Time 0 for the purposes of scheduling all post-dose study procedures.
- On the evening Prior to the Week 6, Week 12 and Week 24 Visits (or Early Term/Withdrawal visits where 12-hour spirometry will be performed): On a patient paper diary, the patient will record the date, the start time of nebulization, and the end time of nebulization for the evening dose of blinded study medication.

Used Blinded Study Medication

- Patients will be instructed to discard all used ampules of blinded study medication and the open foil pouches that contained the used ampules at home.

Unused Blinded Study Medication

- Patients should be instructed to bring all unused blinded study medication to the clinic at each clinic visit for collection and assessment of medication compliance by the unblinded site staff member.
- If a foil pouch is opened but the blinded study medication is not opened/not used, the patient should seal the opened foil pouch (eg, tape) before returning it to the clinic.

6.2 Investigational Product/Blinded Study Medication

Investigational product/blinded study medication is described in Table 5.

Table 5: Investigational Product/Blinded Study Medication Details

Name:	**Ensifentrine**	**Placebo**
Dosage Formulation:	Nebulizer suspension	Nebulizer solution
Unit Dose:	3 mg	0 mg
Concentration (mg/mL)	1.2 mg/mL	0 mg/mL
Route of Administration	Inhalation	Inhalation
Dosing Instructions:	1 ampule (2.5 mL) per dose	1 ampule (2.5 mL) per dose
Manufacturer	The Ritedose Corporation, Columbia, SC, USA	The Ritedose Corporation, Columbia, SC, USA

The ensifentrine formulation is a sterile suspension of micronized ensifentrine [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.

The placebo is the same as the ensifentrine suspension except that the active ensifentrine ingredient is omitted, [redacted]

and is also supplied as a single unit-dose LDPE translucent ampule overwrapped in a foil pouch.

Both ensifentrine and placebo are manufactured using aseptic manufacturing techniques in accordance with Good Manufacturing Practice GMP guidelines and will be provided to the sites as patient kits.

6.2.1 Blinded Study Medication Dispensing and Formulation Information

Patients will be dispensed blinded study medication kit(s) as per the schedule outlined in the SoA with one exception. If a patient is unable to attend a scheduled visit due to disaster, the instructions for blinded study medication dispensing as outlined in Section 8.6 should be followed.

The blinded study medication formulation constituent and concentrations are described in Table 6.

[redacted]

6.2.2 Medical Devices

1. No Sponsor manufactured medical device is used in this study.
2. Other medical devices provided for use in this study are:
   - PARI LC Sprint nebulizer
   - PARI Vios PRO Aerosol Delivery System, PARI BOY compressor or equivalent
3. Instructions for medical device use are provided in the package insert.
4. Information on medical device incidents and reporting is provided in Section 8.7.8.

6.3 Preparation/Handling/Storage/Accountability

1. Blinded study medication should be stored below 25°C (77°F) and should not be frozen.
2. An investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all blinded study medication received and any discrepancies are reported and resolved before use of the blinded study medication.
3. All blinded study medication must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized study center staff.
4. The temperature should be monitored, and logs maintained in areas where blinded study medication is stored. If temperature conditions have been compromised or any blinded study medication has not been stored appropriately, this should be documented, and the blinded study medication quarantined until the Sponsor has been notified and confirmed whether it may be used.
5. Only patients meeting the Randomization Criteria in the study may receive blinded study medication and only authorized study center staff may supply or administer blinded study medication.
6. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for blinded study medication accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation, and final disposition records).
7. Further guidance and information for the final disposition of unused blinded study medication are provided in the Pharmacy Manual.

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

6.4 Measures to Minimize Bias: Randomization and Blinding

1. Both ensifentrine and placebo pouches and packaging are identical in appearance.
2. Packaging of both ensifentrine and placebo will have a blinded description applied and all packs will have a unique kit number applied for identification.
3. Deliveries of both ensifentrine and placebo will not indicate the actual product but will instead indicate a blinded description.
4. Patients will be randomized to receive either ensifentrine or placebo using an electronic Interactive Response Technology (IRT). The IRT will not indicate the treatment arm during the randomization process but will indicate the unique kit numbers to be dispensed to the patient.
5. Site staff (both blinded and unblinded) will only have access to blinded reports within the IRT.
6. An unblinded site staff member not associated with study conduct will administer in-clinic doses.
7. If more than one patient will be at the clinic at the same time, they will be shielded from each other to prevent cross-contamination or observance of treatment.

Note: Patients may be aware of the appearance when pouring blinded study medication into the nebulizer. Therefore, they should be instructed not to inform site personnel of the appearance of their blinded study medication. Similarly, study personnel are not to discuss the appearance with patients or other site personnel. Patients will be instructed to return unused blinded study medication (ie, unopened or unused blinded study medication in taped foil pouches) only to the unblinded site staff at their next visit. The investigator will need to confirm and document that the blinding procedures have/have not been maintained for each patient throughout the study. See Data Quality Assurance in Section 11.2).

6.5 Emergency Unblinding

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

Unblinding that occurs for any other reason, including unintentional unblinding, will be documented and promptly reported to the Sponsor and Medical Monitor.

6.6 Blinded 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 each visit, prior to dispensing blinded study medication, previously dispensed unused blinded study medication (ie, unopened or unused blinded study medication in taped foil pouches) will be retrieved by the unblinded site staff member and compliance assessed. Patients 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 patient source document.

Noncompliance is defined as taking less than 70% of blinded 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.

6.7.1 Rescue Medication

Study albuterol/salbutamol should be used for rescue use. If study rescue albuterol/salbutamol cannot be dispensed at a scheduled clinic visit, the medication may be dispensed alternatively according to local requirements (Section 8.6). If at any time during the study albuterol/salbutamol is unavailable in a given country or region, the Medical Monitor must be contacted to discuss and approve alternative rescue medication (Section 8.6).

6.7.1.1 Documentation of Rescue Medication Use

- Documentation of albuterol/salbutamol during the 3 months prior to Screening 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."
- Rescue albuterol/salbutamol used during clinic visits where spirometry will be conducted should be recorded in a module provided in the eCRF for each specific spirometry visit. Details (eg, dose (number of puffs), date, and time of administration) will be recorded.
- Rescue albuterol/salbutamol used at all other times after Screening will be documented in the eDiary (eg, number of puffs per day).
- After Screening, use of Rescue Medication will not be recorded in the concomitant medication page of the eCRF.

6.7.2 Permitted Rescue and Background Medications

Permitted rescue and background medications are provided in Table 7.

Any vaccine that is recommended by the patient's healthcare provider is permitted during the study (e.g. COVID, influenza, pneumonia), and should be recorded in the eCRF.

Table 7: Permitted Rescue and Background Medications

Medication	Condition
Albuterol/salbutamol	Used as rescue medication as needed during the study. Must be withheld for at least 4 hours prior to spirometry.[1] Should be withheld for at least 4 hours prior to ECGs.
Either LAMA or LABA	Patients entering the study on a maintenance regimen of either LAMA or LABA therapy will be required to remain on that regimen at a stable dose for the duration of the study. *Dual LAMA/LABA therapy is not allowed.* Stable ICS use is allowed along with a LAMA or LABA maintenance regimen if it was initiated at least 4 weeks prior to Screening. ICS monotherapy is not allowed. Must withhold prior to spirometry: Twice-Daily maintenance LAMA or LABA (or LAMA/ICS or LABA/ICS) for 24 hours, and Once-Daily maintenance LAMA or LABA (or LAMA/ICS or LABA/ICS) for 48 hours, including at Visit 1.[1] The maintenance LAMA or LABA (or LAMA/ICS or LABA/ICS) therapy should resume once all spirometry for a given visit has been completed.
No maintenance or background therapy	Patients entering the study on no maintenance background therapy will not be allowed to initiate background maintenance therapy for COPD (ie, maintenance LAMA or LABA therapy, or ICS therapy) for the duration of the study.
Inhaled corticosteroids (ICS)	Stable use of ICS is permitted IF the patient has been taking the ICS at least 4 weeks prior to Screening (Visit 0) AND the patient is also taking maintenance LAMA or LABA. ICS should not be initiated or discontinued during the study. ICS monotherapy and high dose ICS (e.g. >1000 mcg of fluticasone propionate or equivalent) is not allowed.
[1]If the withholding periods are not met the visit should be rescheduled to be held within 3 days of the scheduled visit. Abbreviations: COPD=chronic obstructive pulmonary disease; LAMA= long-acting muscarinic antagonist; LABA= long-acting β2 agonist	

6.7.3 Prohibited Medications/Therapy

Prohibited medications and therapies are provided in Table 8.

Table 8: Prohibited Medications/Therapy

Medication	Time Interval
Oral, Systemic or Parenteral Steroid Therapies	3 months prior to Screening Visit and prohibited during the study.[1]
Antibiotics for lower respiratory tract infection	6 weeks prior to Screening Visit and prohibited during the study.[1] Chronic use of antibiotics is not allowed 6 weeks prior to or during the study.
Inhaled Corticosteroids (ICS) (e.g. ICS monotherapy and patients in the no maintenance therapy stratum) High dose ICS (e.g. >1000 mcg of fluticasone propionate or equivalent)	4 weeks prior to Screening Visit and prohibited during the study.
Oral leukotriene inhibitors (i.e. montelukast, zafirlukast, zileuton)	48 hours prior to Screening Visit and prohibited during the study.
Theophylline and PDE4 inhibitor (e.g. roflumilast, apremilast, crisaborole)	48 hours prior to Screening Visit and prohibited during the study.
Terbutaline	1-day prior to Screening Visit and prohibited during the study.
Ipratropium (including combinations with albuterol/salbutamol)	6 hours prior to Screening Visit and prohibited during the study.
LAMA/LABA combination products	4 weeks prior to Screening Visit and prohibited during the study.
Nebulized LAMA or LABA or ICS For patients in the no maintenance therapy stratum: For patients in the LAMA or LABA stratum:	 4 weeks prior to Screening Visit and prohibited during the study. 1-week prior to Screening Visit and prohibited during the study (e.g. patient should switch from nebulized to dry powder or metered dose therapy)
LAMA Excluded ONLY for patients in the no maintenance therapy stratum	4 weeks prior to Screening Visit and prohibited during the study.[2]
LABA Excluded ONLY for patients in the no maintenance therapy stratum	4 weeks prior to Screening Visit and prohibited during the study.[2]
Oral beta$_2$-agonists	1-week prior to Screening Visit and prohibited during the study.

[1]Except for the treatment of COPD exacerbations during the study (Section 11.6). Localized corticosteroid injections (eg, intra-articular and epidural), intranasal and topical corticosteroids are permitted.

[2]Washout of patients on stable background maintenance LAMA or LABA monotherapy for the sole purpose of study eligibility is not recommended.

Abbreviations: COPD=chronic obstructive pulmonary disease; ICS=inhaled corticosteroids; LAMA= long-acting muscarinic antagonist; LABA= long-acting β2 agonist; PDE4= phosphodiesterase 4

6.7.4 Recording Use of Concomitant Medications

6.7.4.1 Recording of Rescue Medication and/or LAMA or LABA Medications, and ICS (if applicable)

- Rescue medication (albuterol/salbutamol) use during the study should be recorded as described in Section 6.7.1.
- Use of LAMA or LABA medications, and ICS (if applicable) during the 3 months prior to Screening 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).
  - For patients in the maintenance LAMA or LABA therapy stratum, the end date for LAMA or LABA, and ICS (if applicable) should be documented as "Ongoing."
  - For patients not in the maintenance LAMA or LABA therapy stratum, the actual end date should be documented, if applicable.
- For patients in the maintenance LAMA or LABA therapy stratum, the LAMA or LABA (or LAMA/ICS or LABA/ICS) medication used during the study should be recorded in the eDiary only.
- See Section 8.5.10.2 for information to be collected for PK.

6.7.4.2 Recording of Medications <u>other than</u> Rescue Medication and/or LAMA or LABA or ICS Medications

All COPD medications used within 3 months prior to Screening will be recorded in the eCRF. All non-COPD medications will be recorded in the eCRF starting at Screening 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.

6.7.4.3 Recording of Medications and Information Specific to the Pharmacokinetic Procedures and Sample Analysis:

See Section 8.5.10.2 for recording of medications and information specific to the PK procedures and sample analysis.

6.8 Treatment After the End of Study

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

At the end of the blinded study medication treatment period (Visit 5 or Visit 9 or early termination), patients 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 serious adverse event (SAE).

7.0 DISCONTINUATION OF BLINDED STUDY MEDICATION AND PATIENT DISCONTINUATION/ WITHDRAWAL

7.1 Discontinuation of Blinded Study Medication

Patients who permanently discontinue blinded study medication are not required to withdraw from the study unless they test positive for COVID-19 active disease. If a patient must permanently discontinue blinded study medication for reason(s) other than testing positive for COVID-19 active disease, the patient should complete the "Patient Discontinuation/Withdrawal from the Study" assessments described in Section 7.3 as soon as possible. In addition, every effort should be made by the investigator/staff to keep the patient in the study to collect important efficacy and safety data as detailed in Section 7.2.

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

See the SoA (Section 1.3) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1 Does Not Meet Criteria for Randomization

If a patient who does not meet the Randomization Criteria is inadvertently randomized and receives blinded study medication, the Medical Monitor must be contacted and will consult with the Sponsor to determine if the patient may continue, must be discontinued from blinded study medication and/or discontinued from the study.

7.1.2 Liver Chemistry Stopping Criteria

Discontinuation of blinded study medication for abnormal liver function should be considered by the Investigator when a patient meets one of the conditions outlined in Section 11.9 or if the Investigator believes that it is in best interest of the patient.

7.1.3 Electrocardiogram Withdrawal Criteria

All ECGs conducted or overread after a patient has been randomized will be subject to ECG Withdrawal Criteria (Section 11.5). Patients may be discontinued from blinded study medication if they experience a significant abnormality(ies) on their ECG including, but not limited to those listed in the ECG Withdrawal Criteria, Section 11.5, and in consideration with the patient's medical history and baseline ECG measurements. Clinically significant abnormalities as determined by the Investigator may also result in patient discontinuation from study medication per the Investigator's judgement. Triplicate ECGs (over a brief period of time) should be performed on patients experiencing a

significant abnormality on their ECG or other clinically significant abnormality as determined by the Investigator. The intent of triplicate ECG measurements is to differentiate significant abnormalities from artifact. Abnormalities should be confirmed in 2 of 3 triplicate ECG measurements.

7.1.4 COPD Exacerbation Withdrawal Criteria

Guidelines for identifying COPD exacerbation in this study and conditions for study continuation or withdrawal due to COPD exacerbation can be found in Section 11.6.

7.1.5 Positive Pregnancy Test in Females

Women who are pregnant or breastfeeding are not eligible to participate. Pregnancy testing is being conducted in women of childbearing potential at Screening and at other times specified in the SoA (Section 1.3).

Women exhibiting a positive pregnancy test (Section 11.3) during the study will be discontinued from blinded study medication and followed-up per the Collection of Pregnancy Information guidelines in Section 8.7.5 and Section 11.8.

7.1.6 Positive COVID-19 Test Indicating an Active Infection

Patients with a positive COVID-19 test result indicating an active infection will be required to discontinue blinded study medication and will be required to withdraw from the study.

7.1.7 Other Criteria

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

7.2 Study Participation After Discontinuation of Blinded Study Medication

Patients may permanently discontinue blinded study medication before the end of the study if they choose to or at the investigator's discretion.

Patients who permanently discontinue blinded study medication are not required to withdraw from the study unless they test positive for COVID-19 active disease. Patients who have permanently discontinued blinded study medication but do not test positive for COVID-19 active disease and have not withdrawn consent may continue in the study and complete all remaining protocol specified visits.

The Investigator must document the reason for discontinuation of blinded study medication in the eCRF.

Ideally, patients who have permanently discontinued blinded study medication will continue to attend scheduled clinic visits and complete important efficacy and safety assessments. However, if this is not possible then the investigator will encourage the patient to select one of the three options below to participate in as much of the study as they are willing (or able) to participate:

7.2.1 Reduced Assessments

The patient continues to follow the SoA (Section 1.3) and completes only the following assessments:

- Spirometry
- SGRQ
- COPD exacerbation
- AE
- Concomitant medication

7.2.2 Combination of Phone Contact and Reduced Assessments

The site contacts the patient by phone per the SoA (Section 1.3) to complete the following assessments:

- COPD exacerbation
- SAE
- Concomitant medication

In addition, the patient returns to the clinic at Week 24 to complete the following assessments:

- Spirometry
- SGRQ
- COPD exacerbation
- SAE
- Concomitant medication

7.2.3 Phone Contact Only

The site contacts the patient by phone per the SoA (Section 1.3) to complete the following assessments:

- COPD exacerbation
- SAE
- Concomitant medication

7.3 Patient Discontinuation/Withdrawal from the Study

A patient may withdraw from the study at any time at his/her own request, may permanently discontinue blinded study medication but wish to remain in the study, or may be withdrawn from administration of blinded study medication or from all study participation at the discretion of the Investigator at any time for safety, behavioral, compliance, or administrative reasons. See the SoA (Section 1.3) 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 patient 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 patient 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.

7.3.1 Early Termination/Withdrawal Procedures

If a patient is withdrawn prior to the Week 12 visit, every attempt should be made to have the patient complete the early termination/ withdrawal procedures in the SoA (Section 1.3) as soon as possible.

- If possible, patients should remain on blinded study medication and their maintenance LAMA or LABA medication and ICS (if applicable), follow the withholding procedures prior to Spirometry in Section 8.3.1.2, and should refrain from smoking or caffeinated beverages as recommended in Section 5.4.1.1.
- Patients unable to remain on blinded study medication and/or their maintenance LAMA or LABA medications and ICS (if applicable) should still complete the early termination/ withdrawal visit as soon as possible.

7.3.1.1 12-Hour Spirometry and 1.5 Hour ECG Procedures

For patients who are withdrawn prior to completing the Week 12 visit only, every attempt should be made to have the patient complete the 12-hour spirometry procedures and the ECG procedures at the early termination/withdrawal visit unless consent is withdrawn or the patient is being withdrawn for safety reasons precluding this assessment.

Patients who Continued Blinded Study Medication

Patients who have continued administration of their blinded study medication should complete the spirometry and ECG procedures as follows:

- Spirometry: Pre-dose and 0-12-hour post-dose assessments as per Section 1.4 and Section 8.3.1.
- ECG: Pre-dose and 1.5-hour post-dose ECG procedures as per Section 8.4.2.

Patients who Discontinued Blinded Study Medication

Patients who have discontinued blinded study medication prior to the early termination/ withdrawal visit may optionally complete spirometry and ECG assessments at the early termination visit if they have not already completed the Week 12 assessments. These patients will not be dosed with blinded study medication. If possible, patients should start spirometry between 6 am and 10am, withhold rescue medication and/or maintenance LAMA or LABA medications for the time period specified in Section 6.7.2, and refrain from caffeinated beverages and/or smoking for the time period specified in Section 5.4.1. The spirometry and ECG procedures should be completed as follows:

- Spirometry: Serial spirometry at 0-hour, 30 min, and 1, 2, 4, 6, 8, and 12 hours.
- ECG: 12-lead ECG at 0-hour and 1.5 hours.
- Note: If a patient completed only one of the serial 12-hour spirometry or 1.5-hour ECG procedures at Week 12, they may optionally complete the other one (the one not completed at Week 12) at this visit.

7.3.1.2 Single 12-Lead ECG

Patients who early term/withdraw after Week 12 and are not completing either the pre-dose and 1.5-hour or the 0-hour and 1.5-hour ECG assessments described in Section 7.3.1.1 will complete a single 12-lead ECG as per Section 8.4.2.

7.4 Lost to Follow-up

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

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

- The study center must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether the patient wishes to and/or should continue in the study.

- Before a patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study.

8.0 STUDY ASSESSMENTS AND PROCEDURES

- Patients may not complete any Screening Visit Procedures including the Spirometry Assessment unless all prohibited medications/therapy described in Section 6.7.3 have been withheld for the defined time interval.
- Study procedures and their timing are summarized in the SoA (Section 1.3).
- 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 patient should continue or discontinue blinded 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 patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for Screening failure, as applicable.
- Procedures conducted as part of the patient's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for Screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- The maximum amount of blood collected from each patient over the duration of the study, including any extra assessments that may be required, will not exceed 300 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- See Section 5.6 for specific information to be collected for screen failures.

8.1 Screening Assessments and Procedures

8.1.1 Informed Consent

Informed consent must be obtained according to the Informed Consent Process described in Section 11.2.

8.1.2 Demographic Variables

Demographic variables will include items such as age, sex, ethnicity, body mass index, and race.

8.1.3 Medical/Surgical/ COPD/ and Smoking History

A history of relevant current or past medical conditions, surgical history, COPD history, and smoking history (current or former [yes or no]) will be obtained.

- Minor surgical procedures (eg, tonsillectomy, appendectomy) performed more than 5 years prior to Screening Visit 0 do not need to be recorded.
- COPD history will include COPD exacerbation history and 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 three or more months in two consecutive years (in the absence of other conditions that may explain it [GOLD, 2020])."
- Former smokers are defined as those who have stopped smoking for at least 6 months prior to Screening Visit 0.

Medical and COPD condition(s) identified during the Screening Visit 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.

8.1.4 Prior/Concomitant Medications/Therapies

A history of prior medications used will be obtained and recorded as described in Section 6.7.4.

8.1.5 Vital Signs

Vital signs will be completed at Screening per the instructions in Section 8.4.1. In addition, height in centimeters (cm), weight in kilograms (kg), and body mass index will also be measured and recorded at Screening.

8.1.6 Electrocardiogram

12-Lead ECGs will be completed per the instructions in Section 8.4.2.

8.1.7 Chest X-Ray

A CXR (posterior-anterior) will be obtained at Screening or obtained within 12 months prior to Screening. If a CXR within the past 12 months is not available but a CT scan within the same time period is available, the CT scan can be reviewed in place of a CXR.

For subjects in Germany, if a CXR or CT scan is not available in the 12 months prior to Screening, the subject is not eligible for the study, as this assessment will not be conducted at the Screening visit.

8.1.8 Spirometry Assessment

Spirometry at Screening will be completed per the instructions in Section 8.3.1.

8.1.9 Modified Medical Research Council Dyspnea Scale

The mMRC dyspnea scale is a questionnaire that measures COPD symptoms and defines symptom burden at Screening (Fletcher, 1960). Site staff will administer/interview the patient to complete the mMRC dyspnea scale questionnaire.

8.1.10 Clinical Laboratory Assessments

Clinical laboratory tests will be conducted per the instructions in Section 8.4.3. Abnormal chemistry and/or hematology may be repeated during Screening/Run-in.

8.1.10.1 Viral Serology

Viral serology for HBsAg, anti-HBc, anti-HBs, and Hepatitis C Virus will be obtained at Screening. Chronic stable hepatitis B and C is not exclusionary if the patient otherwise meets study entry criteria.

8.1.10.2 COVID-19

Testing for COVID-19 may optionally be completed (Section 11.3) prior to spirometry and following local requirements. Patients with a positive COVID-19 test result indicating an active infection at Screening or anytime between Screening and Randomization will be excluded.

Patients with a positive COVID-19 antibody test from a past exposure who do not exhibit symptoms of an active COVID-19 infection are eligible to participate in the study.

8.1.11 Physical Examination

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

Investigators should pay special attention to clinical signs to ensure patients have had no previous serious illness(es).

8.1.12 Inclusion/Exclusion Criteria

Patient eligibility will be assessed using the inclusion criteria (Section 5.1) and exclusion criteria (Section 5.2).

8.1.13 Electronic Diary Activities

Electronic Diary training will be conducted and the eDiary will be issued for use during the study. Patients will be instructed to enter their daily symptoms (E-RS:COPD/EXACT-PRO questionnaire), rescue medication (puffs per day), and maintenance LAMA or LABA medication (if applicable) into the eDiary each day.

8.1.14 Interactive Response Technology

Patients will be registered in the IRT system (See Section 8.5.2).

8.1.15 Nebulizer Equipment Training

See Section 8.5.5 for details on nebulizer equipment training. At the Screening Visit, site staff will review the information and instructions provided by the manufacturer with the patient (e.g. Instructions for Use, located in the Pharmacy Manual). Hands-on training with the nebulizer equipment will not occur until the Randomization Visit.

8.1.16 Dispense Rescue Medication

Rescue medication (albuterol/salbutamol) will be dispensed for use as needed during the study but must be withheld for at least 4 hours prior to spirometry and should be withheld for at least 4 hours prior to ECGs. See Section 6.7.2 for additional details.

8.2 Randomization Criteria Assessment– Day 1

The criteria for Randomization are described in Section 5.3.

8.3 Efficacy Assessments

Planned timepoints for all efficacy assessments are provided in the SoA (Section 1.3).

8.3.1 Spirometry

Spirometry will be obtained using spirometry equipment provided by the central spirometry vendor that meets or exceeds the American Thoracic Society minimal performance recommendations [Miller, 2005].

The central spirometry vendor will provide a spirometry manual with additional instructions and details.

All Spirometry will be reviewed and over-read by the central spirometry vendor and the spirometry vendors determination of acceptable endpoint measurements will override determination by the investigative site.

- Acceptable spirometry efforts should have a satisfactory start of test and end of test (plateau in the volume-time curve) and be free from artifacts due to cough, early termination, poor effort, obstructed mouthpiece, equipment malfunction, or other reason [Miller, 2005].
- 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.

8.3.1.1 Spirometry Training

Prior to the first spirometry measurement at each clinic visit requiring Spirometry, the site staff will train each patient on how to perform acceptable spirometry maneuvers according to instructions provided by the central spirometry vendor.

8.3.1.2 Spirometry must be performed as follows:

- ***Coordination of the timing of spirometry and in-clinic dosing with blinded study medication is critical.* See Section 1.4, for the Schedule of Spirometry and In-Clinic Dosing with Blinded Study Medication.**
- Spirometry Start Time: between 06:00 am and 10:00 am.
- Health Outcomes: Complete health outcome assessments as described in Section 8.3.3 prior to spirometry.
- Withhold the Following or Reschedule the Visit*:
  - *Blinded Study Medication*: Blinded study medication must be withheld until pre-dose spirometry is completed.
  - *Rescue Medication:* Albuterol/salbutamol must be withheld for ≥4 hours.
  - *Maintenance LAMA or LABA medications (or LAMA/ICS or LABA/ICS, if applicable):* Must withhold Twice-Daily medications for 24 hours and Once-Daily medications for 48 hours prior to spirometry.

  If the withholding periods above are not met, the visit should be rescheduled to be held within 3 days of the scheduled visit.

- Recommendation/ Request: Patients should refrain from smoking and/or caffeinated beverages prior to Spirometry and ECGs for the withholding periods below:
  - *Smoking: No smoking for at least 1-hour prior to each spirometry assessment.*
  - *Caffeinated Beverages: Abstain from drinking beverages with high levels of caffeine (eg, tea, coffee) for 2 hours prior to each spirometry assessment.*

8.3.2 COPD Exacerbation Assessment

Guidelines for Identifying COPD Exacerbations for this study are located in Section 11.6.

8.3.3 Health Outcomes

The schedule for all health outcomes assessments are provided in the SoA (Section 1.3).

During Study Visits

All patient reported outcomes administered during study visits should be administered at the beginning of a study visit before any physical activity or spirometry, except for Healthcare Utilization assessment, which can be done at any point during the visit. The following is the recommended order *as applicable for a given visit*:

- mMRC
- SGRQ
- EQ-5D-5L
- Baseline/Transitional Dyspnea Index (BDI)/TDI

8.3.3.1 St. George's Respiratory Questionnaire

The SGRQ Patient Reported Outcome (PRO) measure is designed to assess health-related quality of life in patients with COPD in terms of symptoms, daily activity limitation, and psychosocial well-being (Jones, 1991). The SGRQ is completed by the patient.

8.3.3.2 EuroQol-5-Domain Questionnaire

The EQ-5D-5L questionnaire is a standardized instrument designed to measure health utility in terms of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (Szende, 2014). The EQ-5D-5L questionnaire is completed by the patient.

8.3.3.3 Baseline Dyspnea Index/Transitional Dyspnea Index

The BDI is used to measure the severity of dyspnea in patients at baseline (Mahler, 1984). Mahler also developed the TDI which measures changes in patient dyspnea from baseline. The instruments are scored based on ratings for functional impairment, magnitude of task, and magnitude of effort. The BDI and TDI are administered by site staff via patient interview.

8.3.3.4 Healthcare Utilization

All unscheduled visits to a physician office, visits to urgent care, visits to emergency department, and hospitalizations for any cause and/or related to COPD will be recorded in the eCRF. In addition, visits and contacts that are due to a COPD exacerbation will be assessed at each clinic visit and recorded in the exacerbation form of the eCRF.

8.3.3.5 Patient Perception Survey

At the Follow-up contact, the study site will survey each patient regarding patient perception of their study treatment assignment.

At Home

8.3.3.6 Evaluating-Respiratory Symptoms Questionnaire

The E-RS is a PRO instrument derived from the EXACT-PRO designed to collect data to quantify the severity of respiratory symptoms across domains of breathlessness, chest symptoms and cough/sputum in patients with COPD and evaluate treatment benefit (EXACT 2013). The E-RS is an electronic instrument to be completed by the patient in the form of the EXACT-PRO in the eDiary each evening before bedtime.

8.4 Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA, Section 1.3.

8.4.1 Vital Signs

- Vital signs should be obtained prior to blinded study medication dosing at all visits.
- Temperature in Celsius, pulse rate, blood pressure, and respiratory rate will be assessed. The mode of temperature collection should be noted in the source (e.g. oral, forehead, etc).
- 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, respiratory rate, and pulse measurements should be obtained after the patient has been at rest for at least 5 minutes in the supine position and located in a quiet setting without distractions (eg, television, cell phones).

8.4.2 Electrocardiogram

12-lead ECG will be obtained using standardized ECG equipment provided by the centralized vendor. Albuterol/salbutamol should be withheld for at least 4 hours prior to ECG assessments. It is recommended that ECG assessments should be obtained after patients have rested for approximately 5 minutes.

- The central ECG vendor will provide an ECG manual with additional instructions and details.
- All ECGs will be reviewed and over-read by the central ECG vendor and the ECG vendors interpretation of the measurement(s) will override the interpretation by the investigative site, if a consensus is not reached.

8.4.2.1 Day 1/Randomization/Visit 1: Triplicate ECGs at Pre-Dose

At Day 1/Randomization/Visit 1 prior to dosing (pre-dose), triplicate ECGs (over a brief period of time) must be performed.

8.4.2.2 Clinically Significant Abnormality

Review the ECG Withdrawal Criteria. If a clinically significant ECG abnormality is identified post-randomization, even if the assessment was pre-dose, the ECG Withdrawal Criteria in Section 11.5 should be reviewed and triplicate ECGs (over a brief period of time) should be performed to confirm the abnormality in 2 of 3 measurements.

8.4.2.3 Recommendation/ Request

Patients should refrain from smoking and/or caffeinated beverages prior to ECGs for the withholding periods below:

- *Smoking:* No smoking for at least 1-hour prior to each ECG assessment.
- *Caffeinated Beverages:* Abstain from drinking beverages with high levels of caffeine (eg, tea, coffee) for 2 hours prior to each ECG assessment.

8.4.3 Clinical Laboratory Assessments

See Section 11.3 for the list of clinical laboratory tests to be performed and additional instructions.

8.4.3.1 COVID-19

Testing for COVID-19 may optionally be completed. Patients with a positive COVID-19 test result indicating an active infection anytime during the study will be withdrawn.

8.4.4 Adverse Event Assessment

The method of detecting AE will be performed as described in Section 8.7 and Section 11.7.

8.5 Other Assessments and Procedures

Planned timepoints for all other assessments and procedures are provided in the SoA, Section 1.3.

8.5.1 Concomitant Medication Assessment

Patients must be queried for concomitant medication use at each contact (clinic visit or phone contact). Concomitant medications must be documented in the eCRF. Concomitant medications/therapy and documentation are described in Section 6.7. The list of permitted rescue and background medications is provided in Section 6.7.2. The list of prohibited medications/therapy is provided in Section 6.7.3.

8.5.2 Interactive Response Technology

Sites will enter information into the IRT at specified visits. All patients consented will be assigned a patient identification number upon signing of the informed consent.

8.5.3 Randomization

Patients meeting all inclusion criteria (Section 5.1) and all Randomization Criteria (Section 5.3) and meeting none of the exclusion criteria (Section 5.2) will be randomly assigned to blinded study medication via the IRT (Section 8.5.2) at Visit 1.

8.5.4 Electronic Diary Activities

Electronic Diary (eDiary) training will be conducted. Patients will be instructed to enter their daily symptoms (E-RS:COPD/EXACT-PRO questionnaire), administration of their blinded study medication (morning and evening), rescue medication (puffs per day), and maintenance LAMA or LABA medication, or LAMA/ICS or LABA/ICS (if applicable) into the eDiary each day. Electronic Diary compliance will be visually reviewed by the site staff at each clinic visit or discussed with the patient via phone contact and/or when patients are unable to come into the clinic. Patients with poor compliance should be instructed by the site staff to improve eDiary compliance.

8.5.5 Nebulizer Equipment Training

Patients and site staff will be trained on use of the PARI LC Sprint nebulizer and PARI Vios PRO Aerosol Delivery System, and the PARI BOY compressor or equivalent which will be used for inhalation of blinded study medication during the study period. Once the site staff has been trained, they will review the information and instructions provided by the manufacturer with the patient (e.g. Instructions for Use, located in the Pharmacy Manual). Hands on training with the nebulizer will occur at randomization with administration of the first dose of blinded study medication.

8.5.6 Training for Spirometry

Training for spirometry maneuvers will be conducted by the site staff as per the guidelines in the spirometry manual provided by the central spirometry vendor.

8.5.7 Blinded Study Medication Dosing in the Clinic

Blinded study medication dosing in the clinic will be conducted as described in Section 6.1.1.

8.5.8 Dispense/Collect Rescue Albuterol/Salbutamol

Albuterol/salbutamol will be dispensed/collected at specified visit for use as needed. See Section 6.7.1 for additional detail.

8.5.9 Dispense/Collect Blinded Study Medication

Blinded study medication will be dispensed/collected at clinic visits that include Spirometry.

8.5.10 Pharmacokinetics

All randomized patients will participate in pharmacokinetics.

8.5.10.1 Collection of Samples

A limited (sparse) sampling strategy to collect samples of whole blood will be implemented for the determination of ensifentrine in human plasma for PK assessment. Blood samples for the determination of plasma concentrations ensifentrine will be taken by venipuncture or indwelling catheter at the times specified in the SoA (Section 1.3). Up to 7 blood samples will be collected from each patient across visits at Weeks 6, 12, 24, and/or early termination visit. A sparse sampling collection scheme will be followed with sample collection times being different between even and odd numbered sites. The PK collection timepoints and associated windows are detailed by visit in Table 9 below:

Table 9: PK Collection Timepoints and Window Relative to Ensifentrine Dosing

Visit Number	Visit Week	Odd Sites [a]	Even Sites [a]
2	6	1.5 hours[b] 4 (± 1) hours	1.0 (± 0.5) hours 2.5 (± 0.5) hours
3	12	0.5 (± 0.25) hours 3 (± 0.5) hours 6 to 8 hours	Pre-dose (-0.5 hours) 4 to 6 hours 8 to 12 hours
5	24	Pre-dose (-0.5 hours) 1.0 (± 0.5) hours	Pre-dose (-0.5 hours) 1.5 hours[b]
ET/ withdrawal		At the time of visit [c]	At the time of visit [c]

a. Sample collection range is provided for samples scheduled on Week 12 at ≥ 4 hours to provide flexibility for collection at the later sampling time points.

b. The samples scheduled at 1.5 hours post-dose should be collected immediately (within 10 minutes) following the simultaneously scheduled ECG collection.

c. This sample should only be collected if the patient has received ensifentrine within the last 48 hours.

Abbreviations: ET=early termination; ECG=electrocardiogram; PK=pharmacokinetic

Approximately 4 mL of whole blood per time point for PK will be collected. The exact date/time of each blood sample collection will be recorded in the patient's eCRF. Blood samples for PK analyses should be collected in appropriate blood collection tubes as defined in the PK laboratory manual. The Sponsor or designee will provide the Investigator with a manual containing details for the preparation of blood samples to be collected. Detailed sample collection, labeling, storage, and shipment information will be described in the Laboratory Manual.

8.5.10.2 Recording of Medications and Information Specific to the Pharmacokinetic Procedures and Sample Analysis

Paper Diary

In addition to the information on blinded study medication, LAMA and/or LABA medication, and rescue albuterol/salbutamol collected in the e-Diary (Section 8.5.4) and concomitant medication information collected as described in Section 6.7, the information in Table 10 will be collected by the patient on a paper diary for the two (2) full calendar days prior to each PK collection visit. This information will be transcribed into the PK eCRF module, the concomitant medication eCRF module, or both, as applicable:

Table 10: Recording of Medications and Information Specific to Pharmacokinetics

Medication and Time Period	Collect
For all medications that are administered for the 2 full calendar days immediately prior to each PK collection visit:	Medication name, dose (eg. Dose unit, route, schedule/frequency) Start Date and Start Time Date and Time of all doses taken prior to collection of the PK Sample
Blinded study medication administered the morning and the evening for the two full calendar days immediately prior to the PK collection visit:	Date Nebulization Start Time Nebulization End Time Any missed or partially administered (eg, nebulization not complete) blinded study medication administration timepoints within 2 days prior to a PK collection visit.
Abbreviations: PK=pharmacokinetic	

Collection of medication and associated information in the eCRF

Medication and associated information collected in eCRF modules will include, but not be limited to the following information:

- Subject Number/Visit Number/Study Week
- All medications administered for the 2 calendar days immediately prior to each PK collection visit and administered during the PK collection visit:
  - Medication information including but not limited to the medication name, dose, dose unit, route, schedule/frequency
  - The start date and start time or 'continuing.' 'Continuing' can be selected if:
    - 1) the medication name, dose, dose unit, route, schedule/frequency are documented exactly the same as documented in the concomitant medication eCRF,
    - 2) the start date is prior to the 2 days before the PK collection visit, and
  - The stop date(s) and stop time(s) of the last dose taken prior to collection of a PK sample at any PK collection sampling timepoint on the day of a PK collection visit.
- Blinded study medication history for the 2 calendar days immediately prior to each PK collection visit which includes, but are not limited to the details below:
  - The start date, nebulization start time, and nebulization end time of blinded study medication each morning and each evening.
  - Response to the question at each dosing time "Was administration of the blinded study medication completed (yes/ no)?" If the response is "no," the reason for interruption should be documented.
  - Response to the question "Were there any missed or partially administered (eg, nebulization not complete) blinded study medication administration timepoints (yes or no)?" If the response is "yes," the length of the interruption should be recorded in minutes and the reason for the interruption should be documented.

- Dosing of blinded study medication during each PK collection visit must include the following information as applicable for a given PK collection visit:
  - Morning Dose:
    - The start date and nebulization start time of blinded study medication.
    - Response to the question "Was administration of the blinded study medication completed (yes/ no)?" If the response is "no," the reason for interruption should be documented.
- PK Sample Collection
  - The date and time of each PK blood sample collected for PK analysis must be recorded.

8.5.10.3 Determination of Drug Concentration

Samples for the determination of plasma PK for ensifentrine will be analyzed on behalf of the Sponsor using appropriate validated analytical methods. Full details of the bioanalytical methods will be described in a separate Bioanalytical Report. All samples from patient assigned to treatment with ensifentrine during the study that are within the known stability of ensifentrine at the time of planned analysis by the bioanalytical laboratory will be analyzed; samples obtained from placebo patients will not be analyzed. Drug concentration information that may unblind the study will not be reported to study centers or blinded personnel until the study has been unblinded. Only the bioanalytical laboratory and unblinded biostatistician(s) who generate the randomization schedule may be unblinded to patient treatment assignment prior to database lock (DBL).

8.5.11 Genotyping/ Phenotyping

Genetic variation may impact a patient's response to study treatment, susceptibility to, and severity and progression of disease. Variable response to study treatment may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated.

Since it is known that ensifentrine is metabolized by cytochrome P450 (CYP) isozymes 2C9 (primary) and also 2D6, assessment of genetic variation will include the assessment of CYP2C9 phenotype and CYP2D6 phenotype of patients.

The results of this pharmacogenetic research will be reported separately and will not form part of the Clinical Study Report (CSR).

Approximately 8 mL of blood for DNA isolation will be collected from patients who have consented to participate in the genotyping/phenotyping analysis component of the study. Participation is optional. Patients who do not wish to participate in the genotyping/ phenotyping research may still participate in the study.

In the event of DNA extraction failure, a replacement genotyping/phenotyping blood sample may be requested from the patient. Signed informed consent will be required to

obtain a replacement sample unless it was included in the original genotyping/ phenotyping consent.

These samples may be stored for up to 1-year after the genotyping/ phenotyping analysis has been completed.

Details on processes for collection and shipment and destruction of these samples can be found in the genotyping/phenotyping laboratory instructions.

8.5.12 Biomarker Collection

Collection of samples for other biomarker research is also a part of this study. Approximately 10 mL of blood for biomarker research is required and will be collected from all patients in this study as specified in the SoA (Section 1.3).

Analysis of interleukin (IL)-6, IL-8, and C-reactive protein (CRP) will be conducted to evaluate the effect of ensifentrine on inflammatory biomarkers (Section 11.3).

8.6 Disaster Contingencies

Prospective planning is required for this study due to the increased risk of a regional or global disaster (eg pandemic, natural disaster, terrorism).

8.6.1 Site-Level Disaster Plan

It is recommended that investigative sites prepare a written Disaster Plan for this study which describes how the site will manage patient activities and procedures in the event that site is not operating normally, site equipment is not available, and/or patient(s) cannot attend an in-clinic study visit. This written Disaster Plan could include but not be limited to a description of how the following activities and procedures will be conducted for remote visits or phone/video contact:

- Phlebotomy collection
- Vital signs collection
- Blinded study medication distribution
- Rescue albuterol/salbutamol distribution

8.6.2 Unscheduled Visit

8.6.2.1 Blinded Study Medication and/or Rescue Medication

If blinded study medication and/or rescue albuterol/salbutamol cannot be dispensed at a scheduled clinic visit or if a patient will likely run out before attending a scheduled clinic visit, the medication may be dispense alternatively in line with according to local requirements.

Blinded study medication and/or rescue medication can be collected, and compliance can be assessed at the next in-clinic visit.

8.6.2.2 Study Supplied Nebulizer Replacement

If a study supplied nebulizer cannot be distributed at a scheduled clinic visit or if the study supplied nebulizer requires replacement before attending a scheduled clinic visit, the study supplied nebulizer may either be picked-up by the patient directly outside the clinic, sent to the patient's home via trackable mail/postal service (unless restricted by local requirements), or given to the patient at the next scheduled visit.

8.6.2.3 Other Contingencies

- eDiary: In the event of a problem with the eDiary or the paper diary for recording of medications and information specific to the PK procedures and sample analysis, a replacement eDiary and/or paper diary may either be picked-up by the patient directly outside the clinic or sent to the patients home according to local requirements.
- Rescue medication (albuterol/salbutamol): In the event that albuterol/salbutamol is in short supply/not available in a given country or region, another medication may be substituted following consultation and approval by the Medical Monitor (unless restricted by local requirements).
- COVID-19 Testing for Active Disease: A COVID-19 test may be conducted anytime a patient is suspected/exhibiting signs of active disease. If a COVID-19 test is positive for active disease, see Section 7.1.6 for next steps and Section 8.7.9 for AE and other reporting.
- Information relating to disruption of study participation due to COVID-19 will be captured in the eCRF (eg, reason for implementation of contingency measures, reason for missing data and relationship to COVID-19).

8.7 Adverse Events

The definitions of an AE or SAE can be found in Section 11.7.

Adverse events will be reported by the patient.

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 blinded study medication or study procedures, or that caused the patient to discontinue the study (Section 11.7).

As stated in Section 8.1.3, medical and COPD condition(s) identified during the Screening Visit 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.

8.7.1 Time Period and Frequency for Collecting AE and SAE Information

AEs and SAEs will be collected from time of first dose of blinded study medication through the follow-up contact with one exception. Serious Adverse Events assessed as related to study participation (eg, study treatment, protocol-mandated procedures, invasive tests or change in existing therapy) will be collected from the time of consent through the follow-up contact.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Section 11.7. 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 patient has been discharged from the study, and he/she considers the event to be reasonably related to the blinded study medication or study participation, the Investigator must promptly notify the Sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 11.7.

8.7.2 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 patient is the preferred method to inquire about AE occurrences.

8.7.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs, will be followed until resolution, stabilization, the event is otherwise explained, through the follow-up contact, or the patient is lost to follow-up (as defined in Section 7.4). Further information on follow-up of AEs and SAEs is given in Section 11.7.

8.7.4 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 patients and the safety of a blinded 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 blinded 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.

8.7.5 Pregnancy

- Details of all pregnancies in female patients will be collected after the start of blinded study medication and until 30 days after the last dose of blinded 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 Section 11.8.
- Abnormal pregnancy outcomes (eg spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.7.6 Adverse Events of Special Interest

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

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

COPD exacerbations are an expected disease-related outcome. COPD exacerbations will not be collected as an AE unless they meet the definition of an SAE. COPD exacerbations should be captured on the COPD exacerbation eCRF (See Section 11.6).

8.7.8 Medical Device Incidents (Including Malfunctions)

The PARI LC Sprint nebulizer and PARI Vios PRO Aerosol Delivery System, and PARI BOY compressor or equivalent are being provided for use in this study for administration of blinded study medication.

In order to fulfill regulatory reporting obligations worldwide, the Investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with such devices.

The definition of a medical device incident, examples of incidents, and instructions for documenting and reporting medical device incidents are provided in Section 11.10.

Medical Device incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 11.7.

8.7.8.1 Time Period for Detecting Medical Device Incidents

- Medical device incidents or malfunctions of the device that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the Investigator learns of any incident at any time after a patient has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the Investigator will promptly notify the Sponsor.
- The method of documenting Medical Device Incidents is provided in Section 11.10.

8.7.8.2 Follow-up of Medical Device Incidents

- All medical device incidents involving an AE will be followed and reported in the same manner as other AEs (see Section 11.7). This applies to all patients, including those who discontinue blinded study medication.
- The Investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the incident.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the Investigator.

8.7.8.3 Prompt Reporting of Medical Device Incidents to Sponsor/Sponsor Representative

- Medical device incidents will be reported to the Sponsor/Sponsor's designee within 24 hours after the Investigator determines that the event meets the protocol definition of a medical device incident.
- The Medical Device Incident Report Form will be sent to the Sponsor/Sponsor's designee by the same method as used for SAE reporting (Section 11.7).
- Contacts for Medical Device Incident reporting are the same as SAE reporting and can be found in Section 11.2 on the Medical Monitor Contact Information Page.

8.7.8.4 Regulatory Reporting Requirements for Medical Device Incidents

- The Investigator will promptly report all incidents occurring with any medical device provided for use in the study in order for the Sponsor/Representative to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- The Investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/IEC.

8.7.9 COVID-19 Positive for Active Disease

An AE/SAE of positive COVID-19 active disease should be documented as any AE/SAE occurring in this study would be documented per the guidance throughout this section (Section 8.7). In addition, local guidelines for reporting COVID-19 to local and/or health authorities should be followed.

8.8 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.

9.0 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The aim of this study is to show superiority of ensifentrine over placebo regarding selected efficacy measures. The null hypothesis to be tested for each endpoint will be that there is no difference between ensifentrine and placebo, against the alternative hypothesis that ensifentrine is better than placebo. All tests will be two-sided at a 5% significance level. Primary and key secondary endpoints used for claims will be tested in a sequential order to preserve the alpha level. Testing will stop once a not significant result is achieved. Test order will be FEV_1 $AUC_{0\text{-}12h}$ at 12 weeks, peak FEV_1 at 12 weeks, weekly mean E-RS total symptom score at week 24, SGRQ total score at Week 24, morning trough FEV_1 at Week 12, FEV_1 $AUC_{0\text{-}4h}$ at 12 weeks and proportion of SGRQ responders at 24 weeks.

9.2 Sample Size Determination

Approximately 800 patients will be randomized. The standard deviation for the change in FEV_1 $AUC_{0\text{-}12h}$ is estimated to be 250 mL. With a 2-sided test at a 5% significance level and 500 vs. 300 evaluable patients in the two groups, there will be an 90% power to detect a true difference of 59 mL between the treatments. If the withdrawal rate at 24 weeks exceeds 25% overall, additional patients may be randomized to the study to compensate for the loss of data.

9.3 Populations for Analyses

mITT population: will include all patients randomized and treated with blinded study medication in the study. Patients will be handled as randomized in the mITT analyses.

PP population: will include all patients in the mITT without any major/important protocol deviations considered to have an impact on efficacy assessments. Reasons for exclusion will be specified at a Blind Data Review Meeting prior to database lock (DBL) and may include violations of inclusion/exclusion criteria, violations of withdrawal criteria, incorrect randomization, use of prohibited medication and non-compliance.

Safety set: will include all patients randomized and treated in the study. Patients will be handled by actual treatment in the safety analyses.

Pharmacokinetic set: will include all patients randomized to ensifentrine, receive at least one dose of ensifentrine, and have at least one quantified ensifentrine concentration at a scheduled PK time point after the start of dosing without important protocol violations and/or events with potential to affect PK concentrations.

The population PK analysis set will be defined in the modeling analysis plan.

9.4 Statistical Analyses

9.4.1 Efficacy Analyses

Efficacy analysis will primarily be performed on the mITT population. The primary endpoint and key secondary endpoints will also be evaluated using the PP population as a sensitivity analysis. Impact of imputations and various baseline characteristics will also be checked.

The primary endpoint, change from baseline in FEV_1 $AUC_{0\text{-}12h}$ at Week 12, will be compared between treatments using an analysis of covariance (ANCOVA) model adjusting for treatment, region, background medication strata, and smoking status as factors and baseline FEV_1 as covariate. The estimated treatment difference with 95% confidence interval and associated (two-sided) p-value will be presented. Missing data will be imputed to get as close to the mITT population as possible. Primarily imputation will be based on data collected at visits performed after treatment withdrawal or at early termination visits even if outside visit window. When no such data is available, imputation will primarily be done using multiple imputation based on baseline characteristics and secondarily, as a sensitivity analysis, by the average change in the opposite treatment group as randomized to as a worst-case scenario. Further details on the handling of missing data will be given in the Statistical Analysis Plan.

Key secondary endpoints, FEV_1 $AUC_{0\text{-}4h}$, peak FEV_1, morning trough FEV_1, SGRQ total score and weekly mean E-RS total score, and other continuous secondary or exploratory endpoints will be assessed repeatedly during the study and the change from baseline to pre-specified time point of evaluation will be compared by similar ANCOVA models adjusting for treatment, region, background medication strata and smoking status as factors and baseline as covariate. Data collected at visits performed after treatment withdrawal or at early termination visits will be used in the analyses. Remaining missing data will primarily be imputed using multiple imputation based on baseline characteristics and data collected at post-randomization visits. Since assessed repeatedly, in contrast to primary endpoint, these data will also be analyzed for sensitivity by mixed model repeated measures models with treatment, visit and treatment by visit interaction as factors, baseline as covariate, subject as random factor and covariance structure by visit.

The proportion of responders on the SGRQ, patients with an improvement of at least 4 units, will be compared between treatment groups using a logistic regression model with fixed factors treatment, region, and background medication strata, and smoking status. Imputation of missing data will be done similar as for continuous endpoints. A sensitivity analysis will be performed in which patients with missing data at the required visit will be considered non-responder in the analysis.

The time to first COPD exacerbation during the 24 or 48 week treatment period, depending on stratification, will be visualized using a Kaplan-Meier plot and compared between treatment groups using the log-rank test, stratified by region, background medication strata, and smoking status. As a secondary evaluation a Cox's proportional

hazards model will be used with the same factors. Patients without exacerbations will be censored at last day in the treatment period, including period of recording after possible treatment withdrawal. The treatment difference in the Cox model will be expressed as a hazard ratio. Assumption of proportional hazards will be checked. The number of COPD exacerbations during the 24- or 48-week treatment period will be compared between treatments using a negative binomial model adjusting for treatment, region, background medication strata and smoking status and further using the log exposure time as an offset. The treatment difference from the negative binomial model will be expressed as an annualized risk ratio.

Subgroup analyses will be performed for the primary endpoint and selected secondary endpoints by gender, age-class (below or above 65 years), region, background medication strata, smoking status, ICS use, known chronic bronchitis, and FEV_1 reversibility at baseline (≥12% and ≥ 200 mL).

9.4.2 Safety Analyses

Safety analysis will be based on the safety set.

Adverse events will be analyzed using quantitative and qualitative measures. Treatment-emergent adverse events will be summarized by treatment group for all AEs, related AEs, serious adverse events, deaths, adverse events leading to discontinuation of blinded study medication or to withdrawal from study, adverse events of different severity and adverse events of different chronicity. Treatment-emergent adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class and preferred term for each treatment group. For selected adverse events, time to first event will be visualized using Kaplan-Meier plots.

Laboratory data will be summarized by each visit including change from baseline. The number of normal, abnormal not clinically significant and abnormal clinically significant values on each parameter will be summarized for change over study using shift tables. All data will be listed and values outside reference ranges will be highlighted in the listings.

Vital signs and continuous parameters from the ECGs will be summarized by each visit including change from baseline. Values outside pre-specified ranges (low, high) or changes exceeding pre-specified limits will be summarized by visit for each parameter. The number of normal, abnormal not clinically significant and abnormal clinically significant values on the ECG overall evaluation will be summarized for change over study using shift tables. All data will be listed and values outside reference ranges will be highlighted in the listings.

9.4.3 Other Analyses

The patient flow including total number of screened patients, number of randomized patients, completers, withdrawn patients (including reason for withdrawal) and patients

included in each of the analysis sets will be summarized by treatment group and for the total.

The number of patients with major protocol deviations will be summarized by category of violation and by treatment group including subset of major protocol deviation leading to exclusion from the per-protocol set.

Demographic and baseline characteristics will be summarized using descriptive statistics for each treatment group and for the total number of randomized patients. Medical history will be coded using MedDRA and summarized by system organ class and preferred term for each treatment group. Prior medications will denote medications used prior to first dose of study drug independent of if stopped at randomization or not. Concomitant medications will denote medications started prior to but continuing after randomization or medications with a start date at or after the randomization date. Prior and concomitant medications will be summarized separately by Anatomical Therapeutic Chemical (ATC) levels 2 and 4.

Compliance to blinded study medication will be computed based on the number of ampules/foil pouch count dispensed and returned. Non-compliance will be defined as a compliance value less than 70% over the full study period. Secondarily, compliance will also be computed based on recording of study drug intake in the diary.

The impact of COVID-19 on the study participation of all patients will captured on a separate eCRF page and include items such as attendance at in-clinic study visits. Details of presentation will be outlined in the Statistical Analysis Plan.

9.4.4 Missing Data

All data collected after treatment withdrawal will be used in the analyses. Patients withdrawn from study will perform an End-of-Study visit after decision to withdraw the patient has been made. Data collected at such visits will be used for analysis even if outside the visit window for the endpoint. Remaining missing data will primarily be imputed using multiple imputation based on baseline characteristics and data collected at post-randomization visits. In addition, a worst-case scenario using the average change in the opposite treatment group will be used for imputation as a sensitivity analysis. For the responder analysis of SGRQ, patients with no available data for imputation will be considered non-responders as a sensitivity analysis. In exacerbation analyses, patients are included with data collected up to last day in the treatment period/period of recording following treatment withdrawal.

9.4.5 Pharmacokinetics

All reported plasma concentrations will be listed and summarized using appropriate descriptive statistics. Graphical presentations of concentration data will be provided, if appropriate.

Ensifentrine concentrations will be used for a population PK analysis of ensifentrine. The pharmacokinetics of ensifentrine will be characterized by nonlinear mixed effects modeling based on sparse sampling. From the established model, the influence of various demographic covariates (eg, body weight, gender, genotype) and other patient-specific factors on ensifentrine exposure may be assessed. The data from this study may be combined with data collected from other studies for a pooled meta-analysis using modeling and simulation to estimate PK parameters as well as exposure – response (safety) correlations. The population PK (and population PK-PD, if performed) analyses will be performed in accordance with a separate modeling data analysis plan and will be reported outside of the clinical study report.

9.5 Interim Analyses

There will be no formal interim analysis in the study. Blinded data will be monitored continuously and the assumptions for the variability in data checked as well as the withdrawal rate.

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11.0 APPENDICES

11.1 Appendix 1: Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
Anti-HBc	Hepatitis B core antibody
Anti-HBs	Hepatitis B surface antibody
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
ATS	American Thoracic Society
AUC	Area under the curve
AV	Atrioventricular
BDI	Baseline dyspnea index
BID	Twice daily
bmp	Beats per minute
CFR	Code of Federal Regulations
BMI	Body mass index
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CSR	Clinical Study Report
CRP	C-reactive protein
CXR	Chest X-ray
CT	Computed tomography
CV	Coefficient of variation
DBL	Data Base Lock
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
e-Diary	Electronic diary
EQ-5D-5L	EuroQol-5-Domain Questionnaire
E-RS	Evaluating Respiratory Symptoms
ERS	European Respiratory Society
ERT	eResearch Technology
FAS	Full Analysis Set
FEV_1	Forced expiratory volume in 1 second

FSH	Follicle stimulating hormone
FVC	Forced vital capacity
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HRT	Hormonal replacement therapy
HRU	Healthcare resource utilization
IB	Investigator's brochure
IC	Inspiratory capacity
ICF	Informed consent form
ICH	International Council for Harmonisation
ICS	Inhaled corticosteroid(s)
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
IL	Interleukin
INR	International normalized ratio
INN	International Non-proprietary Name
IRB	Institutional Review Board
IRT	Interactive Response Technology
IT	Information technology
LABA	Long-acting β2-agonist
LAHB	Left anterior hemiblock
LAMA	Long-acting muscarinic antagonist
LDPE	Low density polyethylene
LPHB	Left posterior hemiblock
LOCF	Last observation carried forward
LS	Least square
MAD	Multiple ascending dose(s)
MCID	Minimum clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
mMRC	Modified Medical Research Council
MMRM	Mixed model for repeated measures
NYH	New York Health

PDE	Phosphodiesterase
PCR	Polymerase Chain Reaction
PGAC	Patient Global Assessment of Change
PK	Pharmacokinetic(s)
PP	Per-protocol
PT	Preferred term
QoL	Quality of life
QTcF	QT interval corrected for heart rate using Fridericia's formula
QTL	Quality tolerance limit
RBBB	Right bundle branch block
RNA	Ribonucleic Acid
SABA	Short-acting β2 agonists
SAE	Serious adverse event
SAMA	Short-acting muscarinic antagonists
SAP	Statistical analysis plan
SD	Standard deviation
SOA	Schedule of Activities
SOC	System organ class
SGRQ	St George's Respiratory Questionnaire
SUSAR	Suspected unexpected serious adverse reaction
TDI	Transition Dyspnea Index
TEAE	Treatment-emergent adverse event
UK	United Kingdom
ULN	Upper limit of normal
USA	United States of America
WOCBP	Women of Childbearing Potential

DEFINITION OF TERMS

QT interval	The portion of an electrocardiogram between the onset of the Q wave and the end of the T wave.

11.2 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 patients.
- 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 (Section 11.12). 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 patients 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 patient and/or the patient's legally authorized representative and answer all questions regarding the study.
- Patients must be informed that their participation is voluntary. Patients 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 patient 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 patient or the patient's legally authorized representative.
- ICF New Information: New information since the time of the original consent can be presented to patients 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 patients
- Orally by phone or in person

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

Data Protection

- Patients will be assigned a unique identifier by the Sponsor. Any patient records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.
- The patient 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 patient.
- The patient 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.
- The Sponsor/Sponsor's designee will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician, or any other third party, unless required to do so by law.
- Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in case of a medical emergency, the Sponsor or representative physician or an Investigator might know a patient's identity and also have access to his or her genetic data. Also, regulatory authorities may require access to the relevant files.

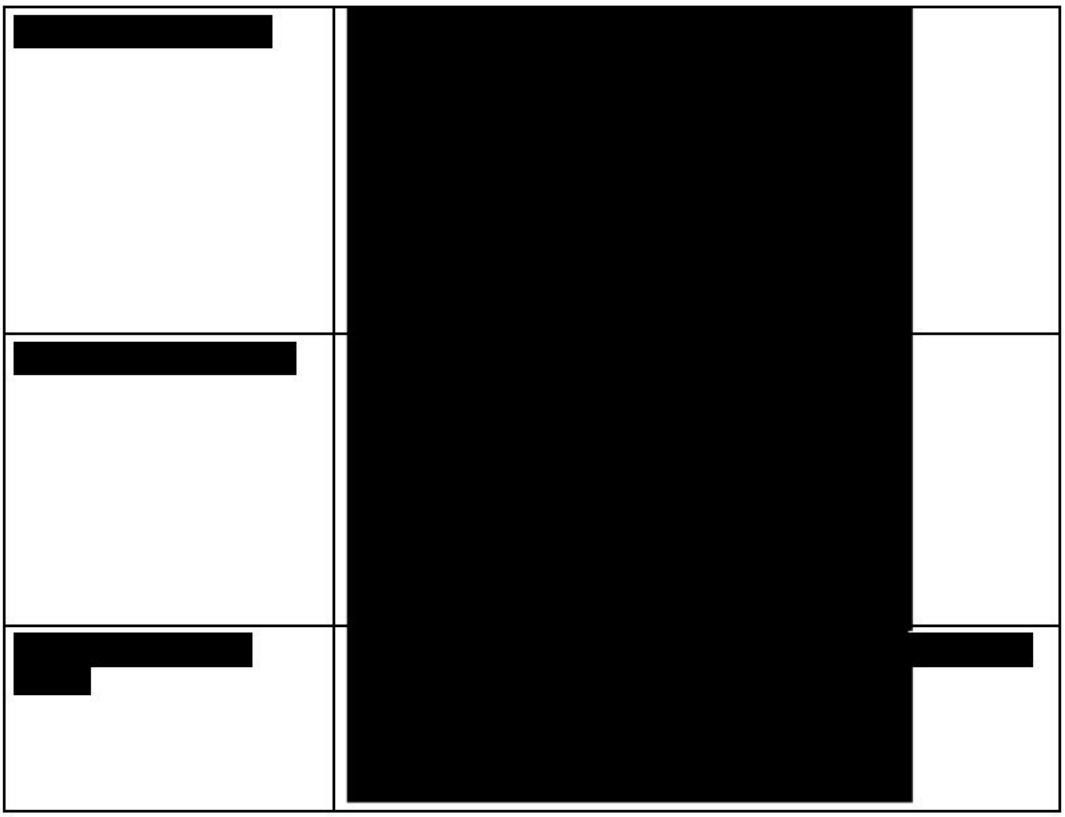
Administrative Structure

The study administrative structure is in Table 11 and the Medical Monitor and the 24-hour urgent medical contact information is in Table 12.

Table 11: Study Administrative Structure

Function	Responsible Organization
Study Operations Management	IQVIA
Medical Monitoring	IQVIA
Safety Reporting	IQVIA
Study Master File	IQVIA
Randomization Code	IQVIA
Data Management	IQVIA
Clinical Supply Management	Verona Pharma plc and IQVIA
Quality Assurance Auditing	Verona Pharma plc
Biostatistics	Verona Pharma plc and IQVIA
Medical Writing	Verona Pharma plc and IQVIA
Laboratory Assessments	Q2 Solutions and IQVIA
Electrocardiogram Collection, Review, and Analysis	eResearch Technology (ERT)

Table 12: Medical Monitor



Dissemination of Clinical Study Data

For studies conducted in the United States, the results of the study are required to be reported on clinical trials.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 patient 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 and will need to confirm that the blinding procedures have or have not been maintained for each patient by physically or electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in 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 patients 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 patients. 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 patient 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 patients by the Investigator.
- Discontinuation of further study medication development.

Publication Policy

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

11.3 Appendix 3: Clinical Laboratory Tests

The tests detailed in Table 13 will be performed by the central laboratory.

- Fasting is not required prior to laboratory testing.
- Laboratory tests should be collected prior to dosing with blinded study medication.

Table 13: Protocol Required Safety Laboratory Assessments

Chemistry	**Hematology**	**Viral Serology**
Albumin	Hemoglobin	Hepatitis B Serology (Markers include HBsAg, anti-HBs, anti-HBc, and others)
Alkaline phosphatase	Hematocrit	Hepatitis C virus antibody
Alanine amino transferase (ALT or SGPT)	Platelet count	
Aspartate amino transferase (AST or SGOT)	WBC count	**Other**
Bilirubin, direct	Leukocyte differential count	Pregnancy test for Women[1]
Bilirubin, indirect	Neutrophils, absolute	COVID-19 testing[2]
Bilirubin, total	Neutrophils, segs (%)	
Calcium	Neutrophils, bands (%)	**Biomarkers**
Chloride	Basophils (%)	IL-6
CO2 content/Bicarbonate	Eosinophils (%)	IL-8
Creatinine	Eosinophils, absolute	C-Reactive Protein (CRP)
Creatine phosphokinase (CPK), total	Lymphocytes (%)	
Gamma glutamyl transferase (GGT)	Monocytes (%)	**Genotyping**
Glucose	RBC count	CYP2C9
Phosphorus		CYP2D6
Potassium		
Protein, total serum		
Sodium		
Urea nitrogen (BUN)		
Uric Acid		

[1] Pregnancy test for women of childbearing potential. Serum pregnancy test will be conducted at visits where Chemistry and Hematology are performed. Urine pregnancy test will be conducted at Visit 1 and visits where no other central laboratory testing is being conducted.

[2]COVID-19 test (optional) may be performed locally.

Abbreviations: CYP=cytochrome P450; CYP2C9=CYP isoenzyme 2C9; CYP2D6=CYP isoenzyme 2D6; HBsAg= hepatitis B surface antigen; anti-HBs= hepatitis B surface antibody; anti-HBc=total hepatitis B core antibody; IL=interleukin.

Additional Instructions:

- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF.
- If additional tests (Except COVID-19 test) are required to be completed urgently by a local lab to assess an adverse event or for any other reason, these labs should also be

completed by the central laboratory for this study using the unscheduled laboratory forms and procedures provided in the laboratory manual. The values obtained by the central laboratory will override the values obtained by the local laboratory.

- COVID-19 test may be performed locally.
- The laboratory reports must be signed by the investigator who reviewed the report and filed with the source documents.
- Clinically significant abnormal laboratory findings are those that are not associated with the patient's healthy status and judged by the Investigator to be more severe than expected.
- All laboratory tests with values considered clinically significantly abnormal after randomization should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.
    - All protocol-required laboratory assessments must be conducted in accordance with the laboratory manual that will be developed by the central laboratory vendor and per the timelines outlined in the SoA (Section 1.3).
    - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in patient management or are considered clinically significant by the Investigator (e.g. SAE or AE), then the results must be recorded in the eCRF.

11.4 Appendix 4: ECG Exclusion Criteria

A 12-lead ECG recording at Screening showing any of the following abnormalities:

- Sinus tachycardia ≥110 bpm (Sinus tachycardia ≥110 bpm should be confirmed by 2 additional readings at least 5 minutes apart.).
- Sinus bradycardia < 45 bpm (Sinus bradycardia < 45 bpm should be confirmed by 2 additional readings at least 5 minutes apart).
- Multifocal atrial tachycardia
- Junctional (heart rate >100 bpm)
- Supraventricular tachycardia (>100 bpm)
- Ventricular tachycardia
- Atrial fibrillation with rapid ventricular response (rate >100 bpm).
- Atrial flutter
- Frequent VPCs (>2 on a 10 sec ECG)
- Ventricular flutter
- Ventricular fibrillation
- Torsades de Pointes
- Wide QRS tachycardia (diagnosis unknown)
- Electrical alternans
- Pacemaker or ICD
- Idioventricular rhythm – heart rate <100 bpm
- Mobitz type II second degree or third degree atrioventricular (AV) block.
- AV dissociation
- Bifascicular Block (RBBB plus LAHB or RBBB plus LPHB)
- Left bundle branch block
- Wolff Parkinson White Syndrome
- Brugada Syndrome pattern
- QTcF ≥ 480 msec when RBBB is present
- Patients without complete right bundle branch block: QTc(F) ≥ 450 msec or an ECG that is unsuitable for QT measurements (e.g. poorly defined termination of the T wave).

11.5 Appendix 5: ECG Withdrawal Criteria

All ECGs conducted or overread after a patient has been randomized will be subject to ECG Withdrawal Criteria (including the pre-dose ECGs at Visit 1 and subsequent visits). A patient may be withdrawn from study medication if the 12-lead ECG recording during the study shows any of the following abnormalities:

The Investigator may withdraw patients from study treatment for any other clinically significant finding (Section 7.0). Triplicate ECGs (over a brief period of time) should be performed on patients experiencing any of the following or a clinically significant abnormality on their ECG per the Investigator's discretion, in order to confirm the abnormality in 2 of 3 measurements. The decision to withdraw a patient should also take into consideration the patient's medical history and prior/baseline ECGs.

- Sinus tachycardia ≥120 bpm (Sinus tachycardia ≥120 bpm should be confirmed by 2 additional readings at least 5 minutes apart.).
- Sinus bradycardia < 37 bpm (Sinus bradycardia < 37 bpm should be confirmed by 2 additional readings at least 5 minutes apart).
- Increase in heart rate ≥40 bpm relative to baseline.
- Multifocal atrial tachycardia
- Supraventricular tachycardia (>100 bpm)
- Atrial fibrillation with rapid ventricular response (rate >120 bpm).
- Atrial flutter with rapid ventricular response (rate >120 bpm).
- Ventricular tachycardia (non-sustained, sustained, polymorphic or monomorphic)
- Ventricular flutter
- Ventricular fibrillation
- Torsades de Pointes
- Evidence of Mobitz type II second degree or third degree atrioventricular (AV) block.
- AV dissociation
- 2:1 AV block
- Bifascicular Block (RBBB plus LAHB or RBBB plus LPHB)
- An increase in QTcF >60 msec from baseline ECG
- Uncorrected QT >600 msec
- For patients with QRS duration <120 msec: QTc(F) ≥500 msec or an ECG that is unsuitable for QT measurements (e.g. poor defined termination of the T wave).
- For patients with QRS duration ≥120 msec: QTc(F) ≥530 msec or an ECG that is unsuitable for QT measurements (e.g. poor defined termination of the T wave).
- Myocardial infarction (acute or recent) Note: Evidence of an old resolved Myocardial infarction is not exclusionary.

11.6 Appendix 6: Guidelines for Identifying COPD Exacerbation

11.6.1 COPD Exacerbation Signs and Symptoms

The following are signs and symptoms of an exacerbation of COPD (Anthonisen, 1987):

Worsening of two or more of the following major symptoms for at least two consecutive days:

- Dyspnea
- Sputum volume
- Sputum purulence (color)

OR

Worsening of any one major symptom together with any one of the following minor symptoms for at least two consecutive days:

- Sore throat
- Colds (nasal discharge and/or nasal congestion)
- Fever (oral temperature >37.5 °C) without other cause
- Increased cough
- Increased wheeze

Patients experiencing worsening COPD symptoms for greater than 24 hours should:

- Contact the Investigator/study site immediately if they feel they need medical assistance.
- If the patient is unable to contact the Investigator/ study site, they should contact their primary care physician (or other health care practitioner as required) and contact the study site as soon as possible.
- Continue to record their symptoms and rescue albuterol/salbutamol use in their eDiary.
- If the patient seeks emergency/acute care for worsening respiratory symptoms, he/she should request the Health Care Provider (HCP) to contact the Investigator as soon as possible.

11.6.2 COPD Symptom Verification

Each exacerbation event will be verified with symptoms as defined in Section 11.6.1 and these symptoms will be documented in the case report form as part of the exacerbation assessment.

11.6.3 COPD Exacerbation Severity:

The definition of COPD exacerbation severity is as follows:

11.6.3.1 Moderate

A moderate exacerbation is defined as worsening symptoms of COPD *requiring a minimum of three days of treatment* with oral/systemic corticosteroids and/or antibiotics.

11.6.3.2 Severe

A severe exacerbation is defined as worsening symptoms of COPD requiring in-patient hospitalization.

11.6.3.3 Guideline for assessing exacerbations that increase in severity

If an exacerbation begins as moderate but becomes severe, the exacerbation should be captured as severe.

11.6.4 Onset and Resolution of COPD Exacerbations:

The date of onset is the first day of the worsening of signs and symptoms of COPD exacerbation.

The date of resolution is when the Investigator and/or patient ascertain the signs and symptoms have returned to pre-exacerbation levels or to a new baseline.

The date of onset and the date of resolution will be recorded in the eCRF.

11.6.5 Treatment of COPD Exacerbations

11.6.5.1 Guidelines for Treatment with Corticosteroids

- The duration of treatment with oral/systemic corticosteroids should be less than or equal to 14 days (dose and type according to local practice).
- The duration of treatment with oral/systemic corticosteroids greater than 14 days should be discussed with the Medical Monitor and Sponsor to determine if the patient should remain in the study.
- Any course of oral/systemic corticosteroids started within 7 days of finishing a previous course will be considered as treatment for a single exacerbation.

11.6.5.2 Guidelines for Treatment with Antibiotics

If there is evidence of respiratory infection that warrants treatment with antibiotics in the opinion of the Investigator or treating physician, the following guidelines should be used:

- The duration of treatment with antibiotics should be 7 to 14 days (dose and type according to local practice). If first antibiotic treatment fails and additional antibiotics are warranted, the total duration of antibiotic treatment should not exceed 30 days. If the duration of treatment with antibiotics needs to be greater than 30 days, the Investigator or treating physician should discuss the patient with the Medical Monitor and Sponsor to determine if the patient should remain in the study.
- Any course of antibiotics started within 7 days of finishing a previous course will be considered as treatment for a single exacerbation.

Use of antibiotics for the treatment of upper or lower respiratory tract infections is not considered a COPD exacerbation unless the patient experiences worsening of signs and symptoms associated with exacerbations as given above.

11.6.6 Recording COPD Exacerbations

Exacerbation details will be recorded in the exacerbation form of the eCRF. COPD exacerbations will not be recorded as adverse events (AE), unless they meet the definition of a serious adverse event (SAE). Pneumonia details will be recorded in the Pneumonia form of the eCRF and will also be recorded as an AE or SAE. Pneumonia should be confirmed by chest-x-ray. Every effort should be made to obtain a chest x-ray within 48 hours suspected pneumonia.

11.6.7 Study Continuation or Withdrawal Due to COPD Exacerbation

- Patients who experience a single COPD exacerbation during the treatment period may remain in the study and should continue to take their blinded study medication if possible and record their symptoms and rescue albuterol/salbutamol usage in their eDiary.
- Patients who experience a second COPD exacerbation and/or a severe COPD exacerbation that requires in-patient hospitalization will be discontinued from study treatment (Section 7.0).

11.7 Appendix 7: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

Definition of AE

- An AE is any untoward medical occurrence in a patient or subject, temporally associated with the use of blinded study medication, whether or not considered related to the blinded 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 blinded study medication.

Events Meeting the AE Definition

- Any abnormal laboratory test results (eg, hematology, clinical chemistry) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, 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 blinded 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 blinded 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 patient'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 patient's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- 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 (eg, 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 patient 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 patient 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 (eg, 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 patient 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 (eg, 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 patient'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 patient 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 patient, 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 blinded study medication and each occurrence of each AE/SAE. The AE must be characterized as unrelated, unlikely to be related, possibly related, probably related, or unknown (unable to judge).
  - "Probably related" conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
  - "Possibly related" suggests that the association of the AE with the blinded study medication is unknown; however, the AE is not reasonably supported by other conditions.
  - "Unlikely to be related" suggests that only a remote connection exists between the blinded study medication and the AE. Other conditions, including chronic illness, progression or expression of the disease state or reaction to concomitant therapy, appear to explain the reported AE.
  - "Unrelated" is used if there is not a reasonable possibility that the blinded study medication caused the AE.
  - All efforts should be made to classify the AE according to the above categories. The category "unknown" (unable to judge) may be used only if the causality is not assessable (eg, because of insufficient evidence, conflicting evidence, conflicting data, or poor documentation).
- 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 blinded 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 in light of 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 blinded study medication (none, blinded study medication stopped, blinded 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)
  - Recovered or resolving (patient 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 patient 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 patient 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.
- 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 the Sponsor/Sponsor's designee via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the Sponsor/Sponsor's designee will be the electronic data collection tool.
- If the electronic system is unavailable, then the study center will use the paper SAE data collection tool (see next section).
- The study center will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given study center, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a study center receives a report of a new SAE from a patient or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the study center can report this information on a paper SAE form (see next section) or to the Medical Monitor/SAE coordinator by telephone.
- Contacts for SAE reporting can be found in Section 11.2 on the Medical Monitor Contact Information page.

SAE Reporting to Sponsor/ Sponsor's Designee via Paper CRF if eCRF is not available

- 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 equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- 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 Section 11.2 on the Medical Monitor Contact Information page.

11.8 Appendix 8: 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. Premenarchal: Note premenarchal females ***ARE NOT ELIGIBLE TO PARTICIPATE*** in this study.

2. 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 patient's medical records, medical examination, or medical history interview.

3. Postmenopausal female:

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

Contraception Guidance

Male Patients

- Male patients 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 14 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
- In addition, male patients must refrain from donating sperm for the duration of the study and for 30 days after the last dose of study medication.
- Male patients 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 patients

Female patients 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 14: 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 patient.*
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 patients participating in clinical studies.

Table 14: Highly Effective Contraceptive Methods

[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 highly sensitive pregnancy test.
- 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 patients with partners who become pregnant

The Investigator will attempt to collect pregnancy information on any male patient's female partner who becomes pregnant while the male patient is in the study. This applies only to male patients who receive ensifentrine.

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 Patients who become pregnant

- The Investigator will collect pregnancy information on any female patient who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a patient's pregnancy.
- The patient will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the patient and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for 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.

- Any post-study pregnancy related SAE considered reasonably related to the blinded study medication by the Investigator will be reported to the Sponsor as described in Section 8.7.5. While the Investigator is not obligated to actively seek this information in former patients, he or she may learn of an SAE through spontaneous reporting.
- Any female patient who becomes pregnant while participating in the study will discontinue blinded study medication and be withdrawn from the study.

11.9 Appendix 9: Liver Safety

Phase III-IV liver chemistry stopping and follow-up criteria have been designed to assure patient safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance). Phase III-IV liver chemistry stopping criteria 1-5 are defined below. Investigators may at their discretion refer patients meeting liver safety criteria below to a specialist who may determine the appropriate or medically necessary additional or confirmatory laboratory tests or procedures as required by the protocol or otherwise deemed necessary (e.g. liver imaging).

1. ALT ≥ 3xULN and bilirubin ≥ 2xULN (35% direct bilirubin) (or ALT ≥ 3xULN and INR > 1.5, if INR measured.

   Note: if serum bilirubin fractionation is not immediately available, withdraw study drug for that patient if ALT ≥ 3xULN and bilirubin ≥ 2xULN. 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.

2. ALT ≥ 8xULN.

3. ALT ≥ 5xULN but < < 8 xULN persists for ≥ 2 weeks.

4. ALT ≥ 3xULN 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 ≥ 5xULN but < 8 xULN and cannot be monitored weekly for ≥ 2 weeks.

When any of the liver stopping criteria 1-5 is met do the following:

- **Immediately** discontinue blinded study medication/investigational product for that patient.
- Report the event to IQVIA within 24 hours of learning its occurrence.
- Complete the liver event CRF and SAE data collection tool if the event also meets the criteria for an SAE. All events of ALT ≥ 3xULN and bilirubin ≥ 2xULN (35% direct bilirubin) (or ALT ≥ 3xULN and INR > 1.5, if INR measured); INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants), termed ‘Hy’s Law’ must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

Note: if serum bilirubin fractionation is not immediately available, discontinue blinded study medication/investigational product for that patient if ALT ≥ 3xULN and bilirubin ≥ 2xULN. 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.

- Complete the liver imaging and/or liver biopsy CRFs if these tests are performed.
- Perform liver event follow-up assessments and monitor the patient until liver chemistries resolve, stabilize, or return to baseline values as described below.
- Discontinue blinded study medication/investigational product after completion of the liver chemistry monitoring as described below.
- Do not restart investigational product.

In addition, for criterion 1:

- Make every reasonable attempt to have patients return to clinic within 24 hours for repeat liver chemistries, liver event follow-up assessments (see below), and close monitoring.
- A specialist or hepatology consultation is recommended.
- Monitor patients twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

For criteria 2, 3, 4, and 5:

- Make every reasonable attempt to have patients return to clinic within 24-72 hours for repeat liver chemistries and liver event follow-up assessments (see below).
- Monitor patients weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize, or return to within baseline values; criterion 5 patients should be monitored as frequently as possible.

Patients with ALT ≥ 5xULN and < 8xULN which exhibit a decrease to ALT ≥3xULN, but <5xULN and bilirubin <2xULN without hepatitis symptoms or rash, and who can be monitored for 4 weeks:

- Notify the IQVIA Medical Monitor within 24 hours or learning of the abnormality to discuss patient safety.
- Can continue investigational product
- Must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize or return to within baseline.
- If at any time these patients meet the liver chemistry stopping criteria, proceed as described above.
- If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor patients twice monthly until live chemistries normalize or return to within baseline values.

For criteria 1-5, make every attempt to carry out the liver event follow up assessments described below:

- Viral hepatitis serology including
  - Hepatitis A IgM antibody
  - Hepatitis B surface antigen and Hepatitis B Core antibody (IgM)
  - Hepatitis C RNA
  - Cytomegalovirus IgM antibody
  - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing).
  - Hepatitis E IgM antibody
- Blood sample for PK analysis, obtained within 72 hours of the last dose. Record the date/time of the PK blood sample draw and the date/time of the last dose of blinded study medication/investigational product prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the patient's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SPM.
- Serum creatinine phosphokinase (CPK) and lactate dehydrogenase (LDH)
- Fractionate bilirubin, if total bilirubin ≥ 2xULN
- Obtain complete blood count with differential to assess eosinophilia.
- Record the appearance or worsening of clinical symptoms of hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia as relevant on the AE report form.
- Record use of concomitant medications, acetaminophen, herbal remedies, or over the counter medications, or putative hepatotoxins, on the concomitant medications report form.
- Record alcohol use on the liver event alcohol intake case report form.

The following are required for patients with ALT ≥ 3xULN and bilirubin ≥ 2xULN (35% direct) but are optional for the other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies and quantitative total immunoglobulin G (IgG or gamma globulins).

- Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in patients with definite or likely acetaminophen use in the preceding week [James, 2009]. NOTE: not required in China.

- 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 (Le Gal, 2005).

11.10 Appendix 10: Medical Device Information

Definitions of a Medical Device Incident

The detection and documentation procedures described in this protocol apply to all Sponsor medical devices provided for use in the study (see Section 6.2.2) for the list of Sponsor medical devices).

Medical Device Incident Definition

- A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient/user/other person or to a serious deterioration in his/her state of health.
- Not all incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

- An incident associated with a device happened.

  AND

- The incident was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include any of the following:

- Life-threatening illness.
- Permanent impairment of body function or permanent damage to body structure.
- Condition necessitating medical or surgical intervention to prevent 1 of the above.
- Fetal distress, fetal death, or any congenital abnormality or birth defects.

Examples of Incidents

- A patient, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse.
- A patient's blinded study medication is interrupted or compromised by a medical device failure.
- A misdiagnosis due to medical device failure leads to inappropriate treatment.
- A patient's health deteriorates due to medical device failure.

Documenting Medical Device Incidents

Medical Device Incident Documenting

- Any medical device incident occurring during the study will be documented in the patient's medical records, in accordance with the Investigator's normal clinical practice, and on the appropriate form of the CRF.
- For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE CRF page will be completed as described in Section 11.7.
- The CRF will be completed as thoroughly as possible and signed by the Investigator before transmittal to the Sponsor or designee.
- It is very important that the Investigator provides his/her assessment of causality (relationship to the medical device provided by the Sponsor) at the time of the initial AE or SAE report and describes any corrective or remedial actions taken to prevent recurrence of the incident.
- A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the device design to prevent recurrence.

11.11 Appendix 11: Country Specific Requirements

Germany: a CXR or CT scan must be available in the 12 months prior to Screening for eligibility.

11.12 Appendix 12: Signature of Investigator

PROTOCOL TITLE: A Phase III Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Ensifentrine over 24 Weeks in Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease.

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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 in which 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:

[redacted] _____ [redacted]

[redacted]

[redacted] _____

[redacted] _____

[redacted] _____

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