Statistical Analysis Plan

Study ID: 212655

Official Title of Study: Phase IV, 12-week, Single Arm, Open Label Study Evaluating the Safety and Efficacy of Fixed Dose Triple Combination FF/UMEC/VI Administered Once Daily in the Morning Via a Dry Powder Inhaler in Participants With Chronic Obstructive Pulmonary Disease in India

NCT ID: NCT04923347

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STATISTICAL ANALYSIS PLAN

Protocol title: Phase IV, 12-week, single arm, open label study evaluating the safety and efficacy of fixed dose triple combination FF/UMEC/VI administered once daily in the morning via a dry powder inhaler in participants with chronic obstructive pulmonary disease in India.	
Protocol number: 212655	**Applicable protocol version:** Amendment 04
Author: PPD Biostatistician	**Internal reviewer(s):** PPD Associate Principal Biostatistician **Sponsor representative(s):** PPD
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The layout of this document is based on the Guideline on the International Conference on Harmonization (ICH E9).

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Glossary of abbreviations

ABBREVIATION	DESCRIPTION
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
CI	Confidence interval
CV	Coefficient of variation
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease 2019
DBL	Database lock
eCRF	Electronic case report form
ECG	Electrocardiogram
ENRL	Enrolled Population Set
FEV1	Forced expiratory volume in 1 second
ICH	International Conference on Harmonisation
ITT	Intended-to-Treat population
MedDRA	Medical dictionary for regulatory activities
MMRM	Mixed Model Repeated Measure
N	Sample size
ODS	Output delivery system
PT	Preferred term
RTF	Rich text format
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SOC	System organ class
TEAEs	Treatment-emergent adverse events
TLFs	Tables, data listings and figures
WHO	World Health Organization
WHO-DD	WHO Drug Dictionary

1. Overview

1.1 Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the Protocol Amendment No. 4 for 212655 dated 03 May 2023. The scope of this plan includes the final analysis, which will be executed by the Biostatistics department unless otherwise specified. Any post-hoc or unplanned analyses performed but not described in this SAP will be clearly described in the CSR.

2. Trial objectives

The following objectives are those stated in the protocol.

Objectives	Estimands/ Endpoints
Primary	
• To evaluate the safety profile of FF/UMEC/VI over 12 weeks in patients from India	The primary Estimand is defined by the following:
	• Endpoint: incidence of adverse events (AE), serious adverse events (SAE) and adverse events of special interest (AESIs). • Summary number and percentage of participants experiencing an AEs, SAEs and number and percentage of participants experiencing AESIs by system organ class and by preferred term. • Population of interest: COPD patients in India. • Key intercurrent events: discontinuation of treatment • Strategy for intercurrent events: a While on Treatment strategy will be used for treatment discontinuation. This estimates the percentage of participants experiencing an AE or SAE while taking treatment. • Participants that test positive for COVID-19 will immediately discontinue study treatment. Therefore COVID-19 will be included as the intercurrent event of study treatment discontinuation and will be handled with While on Treatment strategy for the primary estimand. • A supplementary estimand will be defined using identical properties as for the primary estimand (summary measure, population of interest and key intercurrent events), however this supplementary estimand will report all AEs regardless of the discontinuation of study treatment.

	• Endpoints:
	  • Incidence of AEs, SAEs and AESIs
	
	• Strategy for intercurrent events:
	  • Treatment policy strategy will be used for treatment discontinuation. This summary will therefore be inclusive of all on-treatment and post-treatment AEs.

Secondary	

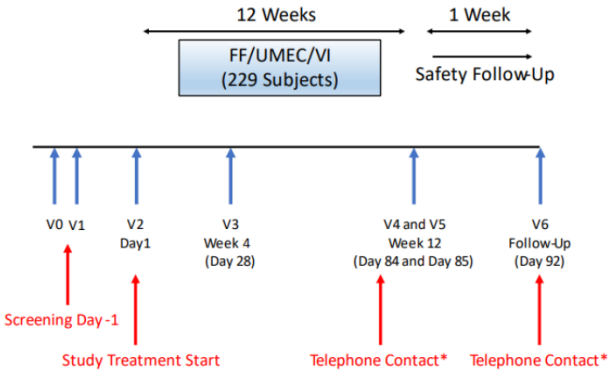
• To evaluate the effect of FF/UMEC/VI on lung function	The secondary Estimands are defined by the following:
	• Endpoints:
	  • change from baseline in trough FEV1 on Day 85 (trough FEV1 on Day 85 is defined as the mean of the FEV1 values obtained 24 hours after morning dosing on Day 84)
	  • change from baseline in trough FEV1 on Day 28 (trough FEV1 on Day 28 is defined as the mean of the FEV1 values obtained prior to dosing on Day 28)
	• Summary measure:
	  • mean change from baseline in trough FEV1 on Day 85
	  • mean change from baseline in trough FEV1 on Day 28
	
	• Population of interest: COPD patients in India.
	
	• Key intercurrent events:
	discontinuation of treatment
	
	• Strategy for intercurrent events: a hypothetical strategy will be used for treatment discontinuation. This estimates the effect under the hypothetical scenario that participants had not discontinued treatment.
	
	• Participants that test positive for COVID-19 will immediately discontinue study treatment. Therefore COVID-19 will be included as the intercurrent event of study treatment discontinuation and will be handled with hypothetical strategy for the secondary estimands.

3. Trial design

3.1 Design overview

This is a phase IV, 12-week, single arm, multi-centre study evaluating single inhaler triple therapy (FF/UMEC/VI) once daily via the ELLIPTA inhaler.

Figure 4.1.1 Study Design Schema



*At day 84 (telephonic visit), participant will be instructed by the investigator telephonically to take the morning dose of study treatment/COPD medication, between 8am and 11am.

Approximately 306 participants will be screened to enrolled 229 (assuming 25% screen failure) to the study treatment phase for achieving 220 evaluable participants at the end of the study (assuming 4% withdrawal from study treatment).

At the start of the treatment period, participants will discontinue all existing COPD medications but may continue their study-supplied rescue salbutamol on an as-needed basis (rescue medication) throughout the study.

Clinic Visits will occur at Pre-Screening (Visit 0), Screening (Visit 1), Start of Treatment (Day 1, Visit 2), Day 28 (Visit 3), and Day 85 (Visit 5). Day 84 (Telephonic Visit 4) and Safety follow-up (Visit 6) conducted 1 week after completing the 12-week treatment period will be a telephone contact. Participants will sign an informed consent form (ICF) at a Pre-Screen or Screening Visit and will be assigned a participant identifier. Note: Visit 0 and Screening (Visit 1) may occur on the same day based on discretion of the study participant and discretion of Investigator.

3.2 Schedule of events

Refer to section 1.3 schedule of activities of the protocol.

4. Changes/deviations from the planned analysis

The statistical analysis/methods as described in the protocol were adopted. For secondary endpoint analysis, as mentioned in the protocol, treatment policy shall be used as supplementary estimand for secondary endpoints if >5% of the ITT participants discontinued study treatment. However as per the discussion of study team analysis will be done using treatment policy (as supplementary estimands) even if 5% do not discontinue the study treatment. That is the condition of 5% will not be applicable.

Any deviation from original statistical analysis plan will be described and justified in the SAP or final clinical study report.

5. Analysis populations

The following sets will be used for the statistical analyses:

5.1 Screened population

This population will include all participants for whom a record exists in the study database, including screen failures and any participant who was not screened but experienced an SAE between the date of informed consent and the planned date of the screening visit.

5.2 Enrolled population (ENRL)

This population will include all participants who signed the informed consent form (ICF), and screen passed and who received study intervention or underwent a post-screening procedure.

NOTE: Participants screened but never enrolled into the study (Met eligibility but not needed) are excluded from the Enrolled Analysis set as they did not enter the study.

5.3 Intended-to-Treat population (ITT)

This analysis population will include all participants who received at least one dose of study treatment.

6. General considerations

6.1 Baseline

Baseline is defined as the last non-missing observation made prior to the first administration of study treatment including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline. Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

Participants who prematurely withdrew from study will not be replaced. For ECG, if the latest, non-missing pre-dose values is from triplicate, the subject level baseline is defined as the mean of triplicate baseline assessments.

6.2 Stratification

This is single arm trial; hence, stratification is not required.

6.3 Statistical tests

There will be no formal hypothesis testing for this study. Mixed model repeated measure model (MMRM) will be used for secondary efficacy analysis.

6.4 Common calculations

For quantitative measurements, change from baseline will be calculated as: (Test value at Visit Day X – Baseline value), where the baseline value is defined as the last non-missing observation taken prior to first exposure to study treatment.

6.5 Software

All analyses will be conducted using SAS® Version 9.4 or higher.

7. Statistical considerations

7.1 Multicentre studies

This study will be conducted over multiple centres.

7.2 Missing data

For efficacy data, missing values will be assumed to be missing at random (MAR) & no imputation will be performed.

For adverse event, prior and concomitant medication data, partial date imputations will be performed where at least the year is provided.

8. Output presentations

The templates provided in the separate output templates document describe the format and content for presentation of tables, listings, and figures (TLFs).

For continuous measures, summary statistics will include number of participants (n), mean, standard deviation (SD), median, minimum, and maximum for both the actual and the change from baseline measurements. For categorical measures, summary statistics will include number of participants (n), frequency, and percentages.

All percentages (%) for a specific summary are calculated using the total number of participants included in the relevant analysis population as the denominator, unless otherwise specified.

9. Participant disposition and withdrawal

9.1 Variables and derivations

End of trial classifications are defined as follows:

- Screening failure:

  Participants who consent to participate in the clinical study but are not subsequently entered in the study & do not meet the criteria for participation in the study.

- Completed trial:

  All participants who completed the trial, as indicated in the end of study: Trial Disposition page of eCRF form, will be assumed to have completed trial.

- Lost to follow-up:

  A participant 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 site. Site personnel or designee are expected to make diligent attempts to contact participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

The following parameters will be summarized for the Participant's disposition table as per eCRF:

- Number of screened participants
- Screening status
  - Entered into trial
  - Failed
- Screen failure reasons
- Number of participants in screened population
- Number of participants in enrolled population
- Number of participants in Intent-to-Treat population
- Number of treatment completed participants
- Number of study ongoing participants
- Number of treatment discontinued participants
- Reason of treatment discontinued participants
- Number of study completed participants
- Number of study withdrawn participants
- Reason of study withdrawn

Note- Subjects may have only one primary reason.

Participants who completed the study, as indicated on the “End of Study: Trial Disposition” form of the (eCRF), will be assumed to have completed the study. And participants who completed the treatment, as indicated on the “Study Treatment Discontinuation: Treatment Discontinuation” form of the (eCRF), will be assumed to have completed the treatment. (i.e., participants who completed the trial will be counted under both the “completed treatment” and “completed trial” category).

The following parameters will be summarized for the study discontinuation table as per eCRF Participant’s primary reason for discontinuation (reasons mentioned in eCRF end of study form) which is as follows:

- Adverse event
- Death
- Lost to follow-up
- Pregnancy
- Protocol violation
- Screen failure
- Consent withdrawal not due to an adverse event
- Study terminated by sponsor
- Migration from the study site such that follow up visits are not possible
- Other

9.2 Analysis

Population: SCREENED and ITT

Statistics: All above mentioned participant’s disposition parameters, will be summarised (frequency & percentage) and participants listing for all participants in the study population by participant number will be provided. Screening status table will be present on screened population.

The percentage calculation of End of study/treatment classification is based on ITT population. Protocol deviation data will be summarized and listed for ITT population.

10. Participant demographics and other baseline characteristics

10.1 Variables and derivations

The following demographic and other baseline characteristics will be summarized:

- Age
    - Number of subjects by age continuous
    - Number of subjects enrolled by age categories:
        - 18-64 Years
        - 65-84 Years
        - ≥ 85 Years
        - Missing
- Gender
- Height (cm)
- Weight (kg)

10.2 Analysis

Population:	Table: ITT Listing: ITT
Statistics:	Baseline and Demographic variables will be summarized and listed by participant number. Overall summaries will include descriptive statistics for continuous measures (number of participants, mean, SD, median, minimum & maximum) and for categorical measures (frequency, percentages, and number of missing values).

11. Exposure and Compliance to study treatment

11.1 Variables and derivations

The date of first study treatment administration will be derived as the first date of dosing from the treatment administration eCRF page. The date of last study treatment administration will be derived as the date of last dose of study treatment from the treatment administration eCRF page. If this date is not available, then the date of last administration will be derived as the last date of dosing from the treatment administration eCRF page.

Interruptions, compliance, and dose changes will not be considered for calculating the duration of exposure, which will be derived as follows:

- $Duration\ of\ exposure\ (days) = (Date\ of\ last\ study\ treatment\ administration - Date\ of\ first\ study\ treatment\ administration) + 1$

Treatment compliance:

Treatment compliance will be assessed for the entire treatment period, as well as at visits 3 and 5.

If a dose counter start count is missing, then it will be assumed to be 30 for the ELLIPTA DPI. If any dose counter stop is missing, then the number of doses taken will be set to missing for that inhaler.

Number of doses of study drug taken by each participant from each inhaler = Dose counter start value – dose counter stop value.

The derivation for treatment compliance during the treatment period is defined as the sum of (dose counter start value – dose counter stop value) over all inhalers dispensed to the participant and returned during the treatment period (i.e., from study Treatment administration to EOS/EW visit) and percentage compliance will be calculated as follows:

- $Treatment\ compliance\ (\%) = \frac{Total\ number\ of\ doses\ received}{Duration\ of\ exposure\ (days)}\ X\ 100$

Overall compliance will be categorized as follows:

- < 50 %
- ≥50 % to < 80%
- ≥80 % to < 95 %
- ≥95 % to ≤105 %
- >105 % to ≤120 %
- >120 %

If a participant receives a treatment other than the scheduled treatment during the study, the compliance will still be calculated using data from all containers received and overall exposure start and stop dates.

11.2 Analysis

Population: Table: ITT
Listing: ITT

Statistics: Overall treatment exposure and compliance to study medication will be summarized by using continuous measures (number of participants, mean, SD, median, minimum & maximum) and Overall compliance categorized by count and percentage.

The visit wise compliance counts will be presented for Visit 3, Visit 5 and End of Treatment.

The listing will be presented by participant number.

12. Medical and treatment history

12.1 Variables and derivations

Medical history will be coded using the MedDRA central coding dictionary Version 26.0 or higher.

The following parameters will be summarised for the participant's medical history:

- Number of participants with at least one medical history
- Number of participants for each medical history by SOC and PT

12.2 Analysis

Population:	Table: ITT Listing: ITT
Statistics:	Medical history will be summarised by SOC and PT (frequency and percentages) for table and listing also be presented.

13. Prior, concomitant, and other medications

13.1 Variables and derivations

All medications will be coded using the WHO-DD, dated March, 1, 2023 or higher.

Prior medications are defined as any medication taken prior to first administration of the study treatment.

'Concomitant medications' are defined as any medication taken after or on the day of first administration of the study treatment.

In section 22 Appendix 2 the algorithm is given for calculation of partial date imputation for prior and concomitant medications, and it will be used for partially missing prior and concomitant medications, start and end date imputation.

The following parameters will be summarised as prior and concomitant medications separately:

- Number of participants with at least one prior and concomitant medication
- Number of participants for each prior and concomitant medication by ATC and PT.

13.2 Analysis

Population:	Table: ITT Listing: ITT
Statistics:	Prior and concomitant medication will be summarised by ATC and PT (frequency and percentages) for table and listing also be presented.

14. Adverse events

14.1 Variables and derivations

Adverse Events (AEs) will be coded using standard GSK dictionary, MedDRA central coding dictionary, version 26.0 or higher.

For the definition of Adverse events (AE) and Serious adverse event (SAE) refer to the protocol section 10.6.

The following parameters will be summarised for the participant's adverse events as mentioned in eCRF:

- Number of participants with at least one AEs pre treatment
- Number of participants with at least one AE during treatment
- Number of participants with at least one AE post treatment
- Number of participants with at least one Drug related AE.
- Number of participants with at least one serious AEs
- Number of participants with at least one Drug related serious AEs
- Number of participants with at least one AESI
- All Adverse Events
- Ongoing AEs
- AEs by Severity
- AEs by Outcome
- AEs by Action Taken with Study treatment
- AEs leading to Death

Derivations:

- The question "Adverse event related to study treatment" is answered "Yes," then respective AEs will be considered as treatment related AE.
- The question "Is the adverse event serious" is answered as "Yes" then respective AE will be considered as serious AEs.
- The question "Is the adverse event serious" is answered as "Yes" and the question "Adverse event related to study treatment" is answered "Yes," then respective AEs will be considered as treatment related SAEs.
- If seriousness criteria are "DEATH" and outcome of adverse event is "FATAL" then we will consider it as AE leading to death.
- Participant's primary reason for discontinuation captured in the eCRF page, study treatment discontinuation is "ADVERSE EVENT" then we will consider it as AE leading to early withdrawal from study.
- Pre- Treatment AEs: AE Start Date < Study Treatment Start Date
- Post- Treatment AE's: AE Start Date > Study Treatment Stop Date

- During Treatment AE's: Treatment Start Date ≤ AE Start Date ≥ Treatment Stop Date

In section 22 Appendix 2 the algorithm is given for calculation of partial date imputation for Adverse Events, and it will be used for partially missing AE, start and end date imputation.

14.2 Analysis

Population: Table: ITT
Listing: ITT

Statistics: An overall summary will be presented as the number of participants within each of the event type categories described in the above section, including the incidence of AEs by preferred term (PT) and System organ class (SOC) sorted by decreasing frequency within the SOC & PT. Number and proportion of participants with AEs will be presented. Both number of participants, number of event (One participant may be counted more than once) and percentage will be provided.

The summary of drug related adverse events, serious adverse events, serious drug related adverse events, Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study and Adverse events of Special interest will be presented by SOC and PT also summary of drug-related AEs by SOC, PT and maximum intensity will be provided.

The most common reported (≥ 3%) AEs and SAEs will be summarized by overall frequency. The Adverse Event will be summarized and presented in data listings using ITT population with all AEs (including coding details SOC and PT only) and participants with SAEs, AESIs, Fatal AEs and events resulting in study discontinuation will be listed separately by participant's number.

Note: If there are uncoded adverse events, then the uncoded category will be added in the AEs by SOC/PT summary tables.

15. Vital Signs

15.1 Variables and derivations

The following vital signs parameters will be reported for this study:

- Temperature (c)
- Weight (Kgs)
- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Pulse (beats per minute)

15.2 Analysis

Population:	Table: ITT Listing: ITT
Statistics:	Summaries of vital parameters will include descriptive statistics at each assessment for the actual and change from baseline (number of participants, mean, SD, median, minimum & maximum) (for quantitative measurements). Listing will be presented by participant, timepoint and parameter.

16. Physical and Oropharyngeal Examination

16.1 Variables and derivations

The following physical examination parameters will be reported for this study:

- Skin
- Cardiovascular
- Respiratory
- Gastrointestinal
- Neurology

16.2 Analysis

Population:	Table: ITT Listing: ITT
Statistics:	The physical examination & oropharyngeal assessment will be presented in data listings and summarised as number and percentage (n and %) at all assessment timepoints. Physical & oropharyngeal examination data will be classified as normal & abnormal.

17. Primary Estimand

17.1 Incidence of adverse events (AE), serious adverse events (SAE) and adverse events of special interest (AESIs) during 12 weeks.

As per the protocol, estimand will be defined as follows:

- **Summary measure:** Number and percentage of participants experiencing an AEs, SAEs and number and percentage of participants experiencing AESIs by system organ class and by preferred term.
- **Population of interest:** COPD patients in India.
- **Key intercurrent events (ICEs):** Discontinuation of treatment (for any reason).
- **Strategy for intercurrent events:** A while on treatment strategy will be used for treatment discontinuation. This estimates the percentage of participants experiencing an AE or SAE while taking treatment. Participants that test positive for COVID-19 will immediately discontinue study treatment. Therefore COVID-19 will be included as the intercurrent event of study treatment discontinuation and will be handled with while on treatment strategy for the primary estimand.
- **Supplementary Estimand:** Incidence of adverse events (AE), serious adverse events (SAE) and adverse events of special interest (AESIs).
- A supplementary estimand will be defined using identical properties as for the primary estimand (summary measure, population of interest and key intercurrent events), however this supplementary estimand will report all AEs regardless of the discontinuation of study treatment.
- **Strategy for intercurrent events:** Treatment policy strategy will be used for treatment discontinuation. This summary will therefore be inclusive of all on-treatment and post-treatment AEs.

17.1.1 Variables and derivations

For the definition of Adverse events (AE) and Serious adverse event (SAE) refer to the protocol section 10.6.

Derivations:

- The question “Is the adverse event serious” is answered as “Yes” then respective AE will be considered as serious AEs.
- The question “Is this event an adverse event of special interest (AESI)” is answered as “Yes” then respective AE will be considered as AESI.

17.1.2 Primary estimand analyses

Population: Table: ITT

Listing: NA

Statistics:

While on-treatment Policy: Values of the variable up to the time of the intercurrent event.

This strategy summarises the variable while the patient actually receives their randomised treatment. An example of use of this strategy is the standard approach to safety data. Adverse events in efficacy trials are usually summarised over the period while a subject is receiving the randomised treatment.

The primary estimand analysis will be performed for participants experiencing an AE, AESI & SAE while taking treatment. It will follow while on treatment policy. But if a subject discontinues treatment during this period of Visit 2-Visit 4 then values only before discontinuation point will be considered.

Treatment Policy: Actual values of the variable regardless of whether the intercurrent event has occurred.

This approach requires collection of data after the intercurrent event of interest (e.g. continued collection if a patient discontinues treatment) and corresponds to a full ITT approach. If the patient also withdraws from the study, then this becomes a missing data problem. The supplementary estimand analysis will be performed for participants experiencing AE, AESI & SAE while taking treatment and post treatment. It will follow treatment policy.

Summary will be presented as the number of participants experiencing AE, AESI & SAE including the incidence of AEs by alphabetically preferred term (PT) sorted by decreasing frequency within the system organ class (SOC). Number and proportion of participants with AEs will be presented. Both number of participants, number of event (One participant may be counted more than once) and percentage will be provided.

Note: If there are uncoded adverse events, then the uncoded category will be added in the AEs by SOC/PT summary tables.

For the supplementary analysis refer to the SAP section 14.

18. Secondary efficacy estimands

18.1 Change from baseline in trough FEV1 on Day 85 and Day 28

As per the protocol, estimand will be defined as follows:

- **Summary measure:** Mean change from baseline in trough FEV1 on Day 85.
  Mean change from baseline in trough FEV1 on Day 28.
- **Population of interest:** COPD patients in India.
- **Key intercurrent events (ICEs):** Discontinuation of treatment.
- **Strategy for intercurrent events:** A hypothetical strategy will be used for treatment discontinuation. This estimates the effect under the hypothetical scenario that participants had not discontinued treatment. Participants that test positive for COVID-19 will immediately discontinue study treatment. Therefore COVID-19 will be included as the intercurrent event of study treatment discontinuation and will be handled with hypothetical strategy for the secondary estimands.
- **Supplementary Estimands:**
  Mean change from baseline in trough FEV1 on Day 85.
  Mean change from baseline in trough FEV1 on Day 28.
  A supplementary estimand will be defined using identical properties (summary measure, population of interest and key intercurrent events), however this supplementary estimand will report the actual values recorded regardless of the discontinuation of study treatment.
- **Strategy For ICE under Supplementary Estimands:** A supplementary estimand will be estimated using treatment policy strategy for the intercurrent event of treatment discontinuation unrelated to the COVID-19 pandemic and using hypothetical strategy for the intercurrent event of treatment discontinuation related to the COVID-19 pandemic.
- **Treatment Policy:** Actual values of the variable regardless of whether the intercurrent event has occurred. This approach requires collection of data after the intercurrent event of interest (e.g. continued collection if a patient discontinues treatment) and corresponds to a full ITT approach. If the patient also withdraws from the study, then this becomes a missing data problem.

18.1.1 Variables and derivations

- Trough FEV1 on Day 85 is defined as the mean of the FEV1 values obtained 24 hours after morning dosing on Day 84.
- Trough FEV1 on Day 28 is defined as the mean of the FEV1 values obtained prior to dosing on Day 28

18.1.2 Secondary estimand analyses

Population:	Table: ITT Listing: ITT
Statistics:	The mean change in FEV1 values from baseline to Day 28 and Day 85 will be summarized using descriptive statistics (mean, median, SD, minimum, maximum, and number with missing values). Only scheduled spirometry observations will be used for the analysis and unscheduled spirometry observations will be presented in data listing.

The MMRM model will be used for analysis of the change in FEV1 values from baseline to Day 28 and Day 85. Least-square means, standard error, 95% CI derived from the analysis model will be displayed by day for two models within the MMRM output. The first model will include change from baseline in FEV1 values as response variable, FEV1 values at baseline and day as covariates and an interaction between FEV1 values at baseline and day. Day will be specified as the repeated effect, and with SUBJECT option to account for the repeated measures within subjects. OM will be used in lsmeans statement. An unstructured covariance structure will be used to model the within-participant variability. If this analysis fails to converge, the following covariance structures will be tested in order:

1. Toeplitz with heterogeneity
2. Autoregressive with heterogeneity, by day
3. Compound symmetry with heterogeneous variances, by day
4. Toeplitz
5. Autoregressive
6. Compound symmetry without heterogeneous variances, by day

The first covariance structure that converges will be used. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Significance tests will be based on least-squares mean using Type III sum of squares.

The second model will use absolute FEV1 values as response variable, whilst all other components remain the same as described above.

Trough FEV1 data collected up to the time of treatment discontinuation will be used in the analysis. This estimates effect under the hypothetical scenario that participants do not discontinue treatment. Trough FEV1 collected after treatment discontinuation will be set to missing. Missing data will be assumed to be missing at random (MAR).

A supplementary estimand will be estimated using treatment policy strategy for the intercurrent event of treatment discontinuation unrelated to the COVID-19 pandemic and using hypothetical strategy for the intercurrent event of treatment discontinuation related to the COVID-19 pandemic.

19. Other assessments

The following assessments will only be presented in data listings for the ITT population:

- Chest X-ray
- Urine Pregnancy test
- Inclusion/Exclusion criteria
- ECG
- COPD assessment test
- COVID-19 test
- Exacerbation assessment

20. Revision history

Version	Date	Change
1.0	06-Jun-2023	Initial Version
2.0	18-Aug-2023	Listings' population has been changed ENRL to ITT for section 10.2, 11.2, 12.2, 13.2, 14.2, 15.2, 16.2, 18.1.2 and 19.
3.0	29-Feb-2024	As per updated eCRF and sponsor requirement, drug compliance summary analysis added in section 11. In section 18.1.2. clarify about the unscheduled visit observations for spirometry test.
4.0	25-Apr-2024	Updated section 18.1.2 to provide clarification on inputs to the MMRM model.

21. Appendix 1: Programming Conventions for Tables, Data Listings and Figures (TLFs)

21.1 Paper Size, Orientation and Margins

The margin, page size and line size specifications as stipulated in Table 23.1 will be used for the presentation of all TLFs.

Table 23.1: Output margin, page size and line size specifications

	Landscape	Portrait
Margins (Inches):		
Top	1.25	1
Bottom	1.25	1
Left	0.87	1.25
Right	0.87	1
Header (Inches)	0.5	0.5
Footer (Inches)	0.5	0.5
SAS® specifications:		
PAGESIZE	46	67
LINE SIZE	134	93

21.2 Fonts

The font type “Courier New” should be used as default for tables and data listings, with a font size of 10 The font color should be black. No bolding, underlining and italics are permitted.

Figures should have a default font of “Times Roman,” “Helvetica” or “Courier New.”

21.3 Header Information

Headers should be defined as follows:

- The header should be placed at the top of the page (same place on each page).
- The sponsor’s name should appear in row 1, left-aligned.
- The word “CONFIDENTIAL” should appear in row 1, right aligned.
- The protocol number should appear in row 2, left-aligned.
- The page identification in the format Page X of Y (where Y is the total number of pages for the TLF) should appear in row 2, right aligned.
- The TLF identification number should appear in row 3, centered.
- The TLF title should start in row 4, centered.

- The TLF population should appear in row 5, centered. The population should be spelled out in full, e.g., *Safety analysis population* in preference to *Safety analysis population*.
- Row 6 should be a continuous row of underscores ('_') (the number of underscores should equal the line size).
- Row 7 should be a blank line.
- Mixed case should be used for titles.
- Titles should not contain quotation marks or footnote references.
- The column headings should be underlined with a row of underscores ('_').
- Column headings spanning more than one column should be underlined and have underscores on either side of the title and should be centered.
- Column headings containing numbers should be centered.
- Column headings should be in mixed case.
- In general, the analysis population count should appear in the column header in the form "(N=XX)."

21.4 Table and Data Listing Table, Listing and Figure (TLF) Conventions

21.4.1 General

- The first row in the body of the table or data listing should be blank.
- The left-hand column should start in Column 1. No indenting or centering of the TLF should occur.
- Rounding should be done with the SAS® function ROUND.
- Numerical values in tables should be rounded, not truncated.
- Numerical values should be decimal point aligned.
- Text values should be left aligned.
- The first letter of a text entry should be capitalized.
- The study drug should appear first in tables with treatment group as columns.
- All variables contained on the eCRF (which have data present) should appear in the data listings, along with all derived data appearing in the corresponding tables.
- The width of the TLF should match the line size.

21.4.2 Univariate statistics

- Statistics should be presented in the same order across tables (i.e., n, mean, SD, minimum, median and maximum).

- If the original data has N decimal places, then the summary statistics should have the following decimal places:
  - Minimum and maximum = N
  - Mean and Percentiles (e.g., median, Q1 and Q3) =N + 1.
  - SD = N + 2.

21.4.3 Frequencies and percentages [n, (m) and %]

Percent values should be reported inside parentheses with percent symbol, no blank spaces are included within the parentheses, e.g., "(25%)." percentages greater than 0 and less than 1 as "<1%" and those greater than 99 and less than 100 as ">99%". Percentages exactly equal to 0% will be shown as blanks in the table. So, counts of 0 will be presented as 0 and not as 0 (0%).

21.4.4 Confidence intervals (CIs)

- CIs should be presented with one additional decimal place as that of the raw data, and SDs and standard errors (SEs) with two additional decimal places as that of the raw data.
- Confidence intervals are displayed within round brackets and separated by a comma. The lower limit is presented first, and the upper limit is presented second. The confidence interval is placed either beside or below the corresponding estimate. The estimate and the confidence limits are presented using the same degree of precision.

21.4.5 P-values

The precision of calculated p-values is expressed to one more decimal place than the precision of the significance criteria. For example, if the significance threshold is 0.05, the calculated p-values are expressed to three decimal places; if the significance threshold is 0.025, the calculated p-values are expressed to four decimal places. If the p-value is smaller than can be represented in this number of decimal places, use a "<" with the smallest printable value (e.g. when presenting p-values to three decimal places and a calculated p-value is less than 0.001, it is reported as "<0.001," rather than "0.000"). Avoid rounding p-values to the nearest decimal place. Instead use the most conservative value (e.g. ceiling) based on the test being performed.

21.4.6 Ratios

- Ratios should be reported with one additional decimal place as that of the raw data.

21.4.7 Spacing

- There should be a minimum of 1 blank space between columns (preferably 2).

21.4.8 Missing values

- A “0” should be used to indicate a zero frequency.

- A blank will be used to indicate missing data in data listings.

21.5 Figure output conventions

Figures should be provided in RTF files using the SAS® Output Delivery System (ODS).

21.6 Dates and times

Depending on data available, dates and times will take the form ddMMMyyyy and hh: mm.

21.7 Spelling format

The spelling format to be used is English US.

21.8 Presentation of treatment group

FF/UMEC/VI

21.9 Presentation of visits

- Pre-screen (Visit 0)
- Screen (Visit 1)
- Visit 2
- Visit 3
- Telephonic (Visit 4)
- Visit 5
- Safety follow-up (Visit 6)

22. Appendix 2: Partial date conventions and Concomitant medication guidelines

The whole missing date will not be imputed for this study; only partial date imputation will be performed. Conventions pertaining to partial dates are presented.

Table: Algorithm for partial date imputation

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td>General</td><td>• Partial dates will be displayed as captured in participant listing displays.
• However, where necessary, display macros may impute dates as temporary variables for sorting data in listings only. In addition, partial dates may be imputed for ‘slotting’ data to study phases or for specific analysis purposes as outlined below.
• Imputed partial dates will not be used to derive study day, time to onset or duration (e.g., time to onset or duration of adverse events), or elapsed time variables (e.g., time since diagnosis). In addition, imputed dates are not used for deriving the last contact date in overall survival analysis dataset.</td></tr>
<tr><td>Adverse Events</td><td>• Partial dates for AE recorded in the CRF will be imputed using the following conventions:
<table>
<tr><td>Missing start day</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = 1st of month.
Else if study intervention start date is not missing:
• If month and year of start date = month and year of study intervention start date, then
– If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month.
– Else set start date = study intervention start date.
Else set start date = 1st of month.</td></tr>
<tr><td>Missing start day and month</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = January 1.
Else if study intervention start date is not missing:
• If year of start date = year of study intervention start date, then</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>– If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1.
– Else set start date = study intervention start date.
Else set start date = January 1.</td></tr>
<tr><td>Missing end day</td><td>A '28/29/30/31' will be used for the day (dependent on the month and year).</td></tr>
<tr><td>Missing end day and month</td><td>No Imputation</td></tr>
<tr><td>Completely missing start/end date</td><td>No imputation</td></tr>
</table>
</td></tr>
<tr><td>Concomitant Medications</td><td>
• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:
<table>
<tr><td>Missing start day</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = 1st of month.
Else if study intervention start date is not missing:
• If month and year of start date = month and year of study intervention start date, then
– If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month.
– Else set start date = study intervention start date.
Else set start date = 1st of month.</td></tr>
<tr><td>Missing start day and month</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = January 1.
Else if study intervention start date is not missing:
• If year of start date = year of study intervention start date, then
– If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1.</td></tr>
</table>
</td></tr>
</table>

Element	Reporting Detail	
		– Else set start date = study. intervention start date. Else set start date = January 1.
	Missing end day	A '28/29/30/31' will be used for the day (dependent on the month and year).
	Missing end day and month	A '31' will be used for the day and 'Dec' will be used for the month.
	Completely missing start/end date	No imputation
Age	• Age will be calculated based on the Pre-Screening Visit date (or Screening if pre-screening not performed). • Only year of birth is collected on eCRF. Day and Month of birth are imputed as 30 June. Age is derived using the date of the screening visit. • All participants with imputed age of 39 or 40 years will be source data verified, and presence/ absence of protocol deviation on the inclusion criteria #1 will be taken into consideration in the derivation for the analysis variable age. Birth date will be presented in listings as 'YYYY'.	