VERTEX PHARMACEUTICALS INCORPORATED

Final Analysis

Statistical Analysis Plan (Methods)

Protocol Number VX15-809-114

A Phase 4, Open-label Treatment, Randomized, Multicenter, 2-arm, Parallel-group, Pilot Study of Adherence to Lumacaftor/Ivacaftor in CF Subjects Homozygous for the *F508del-CFTR* Mutation

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3 INTRODUCTION

This statistical analysis plan (SAP) Methods describes the final analysis for Study VX15-809-114 and is based on the following:

- approved clinical study protocol (Version 2.0, dated 19 October 2016)
- approved electronic case report form (eCRF) (Version 2.0, dated 22 December 2016)

Study VX15-809-114 is a Phase 4, open-label treatment, randomized, multicenter, 2-arm, parallel-group, pilot study of adherence to lumacaftor/ivacaftor (LUM/IVA) in cystic fibrosis (CF) subjects homozygous for *F508del*.

This study was terminated early by a business decision. The collected data at the time of termination are limited and therefore, the planned statistical analyses in the protocol will not be performed. Descriptive summary of statistics will be performed. Please refer to Section 8 for details.

4 STUDY OBJECTIVES

4.1 Primary Objective

To evaluate the impact of smart adherence technology for monitoring of LUM/IVA adherence rates among subjects 16 years of age and older with CF who are homozygous for the *F508del-CFTR* mutation

4.2 Secondary Objectives

To collect subject and physician feedback on the use of smart adherence technology to monitor LUM/IVA adherence

4.3 Other Objectives

Not applicable

5 STUDY ENDPOINTS

5.1 Adherence Endpoint

This study was terminated early by a business decision. The data collected at the time of termination are limited and premature due to early termination. Therefore, the planned adherence endpoints listed in Sections 2 and 7 of the protocol will not be performed. Based on the expected available data, a list of applicable adherence endpoints below will be analyzed as follows:

- Mean percentage adherence to LUM/IVA treatment over any treatment duration for all subjects.
- Mean percentage adherence to LUM/IVA treatment over 0 through 12 weeks for subjects who have at least 12 weeks of eligible smart pill bottle data.

- Proportion of subjects with ≥80% adherence over 0 through 12 weeks for subjects who have at least 12 weeks of eligible smart pill bottle data
- Proportion of subjects with ≥90% adherence over 0 through 12 weeks for subjects who have at least 12 weeks of eligible smart pill bottle data

[redacted]

6 STUDY DESIGN

This is a Phase 4, open-label, randomized, multicenter, 2-arm, parallel-group pilot study evaluating LUM/IVA adherence. Each study arm will use a smart technology with either active or inactive dosing alert features.

This study includes:

- Screening Period (Day −28 through Day −1)
- Treatment Period (Day 1 through Week 48)
- Safety Follow-Up Visit (28 [± 7] days after the final dose of study drug). Subjects who begin commercially available LUM/IVA combination therapy within 28 (± 7) days of the last dose of LUM/IVA do not have to complete the Safety Follow-up Visit.

Figure6-1 depicts a schematic of the study design. Approximately 75 subjects will be enrolled in this study. All subjects will receive LUM 400 mg/IVA 250 mg every 12 hours (q12h) through Week 48.

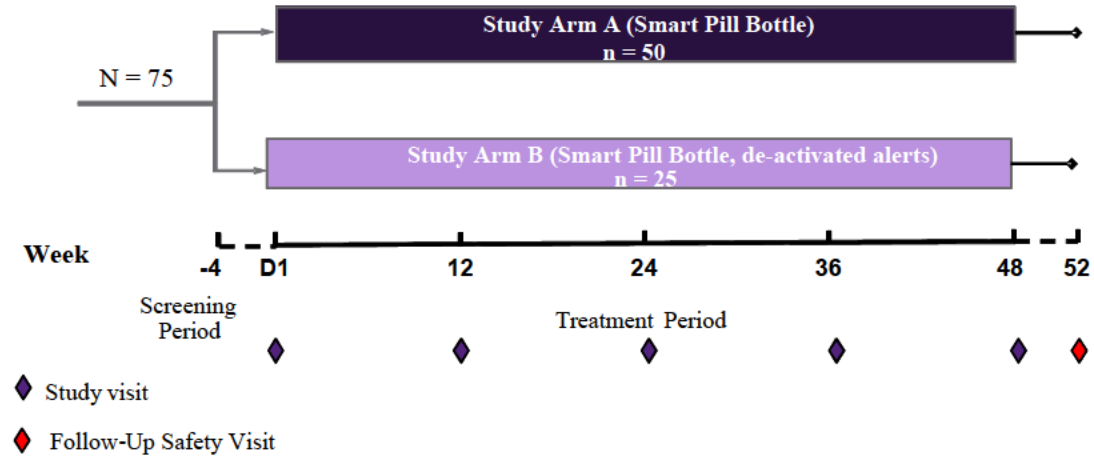
Randomization of subjects to the 2 study arms will be stratified by age (<23 versus ≥23 years of age) and forced expiratory volume in 1 second (FEV_1) severity (<70% versus ≥70% predicted) at the Screening Visit. All subjects will be randomized at 2:1 ratio to 1 of the following 2 smart adherence technology study arms:

- **Study Arm A:** Smart Pill Bottle, activated
- **Study Arm B:** Smart Pill Bottle (control), de-activated alerts and feedback features

Subjects will receive standardized education on the benefit of medication adherence and training on the use of the assigned smart adherence technology. During applicable study visits, subjects will complete adherence and technology satisfaction assessments; and physicians will complete technology satisfaction assessments at Week 48. Tables 11-1 and 11-2 in Appendix A provide a list of assessments by study visit.

All subjects will be required to complete study assessments for all scheduled visits. Subjects who prematurely discontinue study drug treatment will complete a Safety Follow-up Visit.

Figure6-1 Study Design



- All subjects start treatment with lumacaftor/ivacaftor on Day 1.
- Safety Follow-up visit is required only for subjects who do not begin commercially available LUM/IVA within 28 (± 7) days of last dose of study drug.

6.1 Sample Size and Power

A total of approximately 75 subjects were to be enrolled and randomized at 2:1 ratio to 1 of 2 study arms: Smart Pill Bottle (Study Arm A) and Smart Pill Bottle (control) de-activated alerts and feedback features (Study Arm B, control arm), resulting in approximately 50 subjects in the intervention arm and approximately 25 subjects in the control arm.

The primary endpoint is the mean percentage adherence to LUM/IVA treatment over 48 weeks. Assuming a standard deviation (SD) of 8, a sample size of 50 in the intervention arm and 25 in the control arm will have 80% power to detect a difference of 5.6% between the means for the 2 arms using a 2-sided, 2-sample *t*-test at the 5% significant level.

Data from studies VX09-809-102, VX12-809-103, and VX12-809-104 were used for this sample size calculation. Sample sizes based on a range of SDs [redacted].

[redacted]

6.2 Randomization

Randomization of subjects to the 2 study arms will be stratified by age (<23 versus ≥23 years of age) and forced expiratory volume in 1 second (FEV_1) severity (<70% versus ≥70% predicted) determined at the Screening Visit. All subjects will be randomized at 2:1 ratio to 1 of the following 2 smart adherence technology study arms:

- **Study Arm A:** Smart Pill Bottle, activated
- **Study Arm B:** Smart Pill Bottle (control), de-activated alerts and feedback features

An interactive web response system (IWRS) will be used to assign subjects to study arms using a list of randomization codes generated by a designated vendor.

6.3 Blinding and Unblinding

This is a study of adherence with a deactivated smart adherence technology as the control arm. LUM/IVA treatment is given open-label to all subjects.

7 ANALYSIS SETS

The following analysis sets are defined: Full Analysis Set (FAS), and Safety Set.

The **All Subjects Set** is defined as all subjects who have been randomized or have received at least one dose of study drug. This analysis set will be used for all individual subject data listings and the disposition summary table, unless specified otherwise.

The **Full Analysis Set** (FAS) will include all randomized subjects who received at least 1 dose of LUM/IVA. The FAS will be used for all analyses except the safety analyses in this study. Given the nature and objective of this study, the subjects will be grouped and analyzed according to the smart technology arm that they actually received and not according to the arm that they were randomized to.

The **Safety Set** will include all subjects who received at least 1 dose of LUM/IVA. The Safety Set will be used for all safety analyses.

8 STATISTICAL ANALYSIS

8.1 General Considerations

The Schedule of Assessments is provided in Appendix A.

Continuous variables will be summarized using the following descriptive summary statistics: the number of subjects (n), mean, standard deviation (SD), standard error (SE), median, minimum value (min), and maximum value (max).

Categorical variables will be summarized using counts and percentages.

Baseline value, unless specified otherwise, will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug.

Change (absolute change) from baseline will be calculated as postbaseline value minus baseline value

Treatment-emergent (TE) Period will be from the first dose date of the study drug to the Safety Follow-up Visit or 28 days after the last dose, whichever is latest. The TE period will be used for safety analyses.

Unscheduled visits: Unscheduled visit measurements will be included in analysis as follows:

- In scheduled visit windows per specified visit windowing rules.
- In the derivation of baseline/last on-treatment measurements.
- In the derivation of maximum/minimum on-treatment values and maximum/minimum change from baseline values for safety analyses.
- In individual subject data listings as appropriate.

Visit windowing rules: Day 1 is defined as the day of first dose of study treatment. Relative days after Day 1 are calculated as (assessment date – Day 1 date) + 1. Relative days prior to Day 1 are calculated as (assessment date – Day 1 date). The day prior to Day 1 is Day -1. The analysis visit windows for protocol-defined visits are provided in Appendix B. Visit window rules will not apply to the smart technology-reported adherence, which will be collected and stored daily and will be summarized at actual date. Visit window rules will apply to other visit-dependent assessments, including liver function tests, and patient-reported, as well as, physician-reported outcomes.

Incomplete/missing data will not be imputed, unless specified otherwise.

Outliers: No formal statistical analyses will be performed to detect or remedy the presence of statistical outliers, unless specified otherwise.

Multiplicity: No multiplicity adjustment will be performed for hypothesis testing.

Malfunction of smart bottle: any subject who got a smart bottle with a malfunction signal and never received the alerts who was subsequently switched to the control (Arm B) will be considered as a control subject (Arm B).

8.2 Background Characteristics

8.2.1 Subject Disposition

The number of subjects in the following categories will be summarized overall and by study arm:

- Randomized
- Safety Set
- Full Analysis Set (FAS)

The number and percentage (based on FAS) of subjects in each of the following disposition categories will be summarized overall and by study arm:

- Completed study drug
- Prematurely discontinued study drug and the reason for discontinuation
- Completed study (defined as completed the planned study treatment and Safety Follow-up Visit)
- Prematurely discontinued the study and the reason for discontinuation

A listing will be provided for subjects who discontinued treatment or who discontinued study, along with reasons for discontinuations.

8.2.2 Demographics and Baseline Characteristics

Demographics, medical history and baseline characteristics will be summarized overall and by study arm based on the FAS.

Demographic data will include the following:

- Age at screening (in years)
- Age group at screening (≥16 to <23, and ≥23 years)
- Sex (female and male)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, and not collected per local regulations)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian, Other Pacific Islander, and Other)

Baseline characteristics will include the following:

- Weight (kg) at study baseline
- Height (cm) at study baseline
- BMI (kg/m^2) at study baseline

Other baseline characteristics will include the following:

- Percent predicted FEV_1 at screening
- Percent predicted FEV_1 severity (<70% versus ≥70% predicted) at screening

No statistical tests will be carried out to evaluate any imbalance at enrollment between study arms.

Medical history will be summarized by MedDRA system organ class (SOC) and preferred term (PT).

8.2.3 Medical History

Medical history will be coded by using the Medical Dictionary for Regulatory Activities (MedDRA). Medical history will be summarized descriptively by system organ class (SOC) and preferred term (PT) overall and by study arm based on the FAS. It will also be listed.

8.2.4 Prior and Concomitant Medications

Medications used in this study will be coded by using the World Health Organization Drug Dictionary Enhanced (WHODDE) and categorized as the following:

Prior medication: any medication that started before the first dose date of study drug, regardless of when the medication ended.

Concomitant medication: medication continued or newly received during the TE period.

Post-treatment medication: medication continued or newly received after the TE period.

A given medication may be classified as follows: prior, concomitant, post-treatment, both prior and concomitant, both concomitant and post-treatment, or prior, concomitant, and post-treatment.

For medications with partial start dates, missing month will be imputed with January and missing day will be imputed with 1. For medications with partial stop dates, missing month will be imputed with December and missing day will be imputed with the last day of the month. Details for imputing missing or partial start and/or stop dates of medication are described in Appendix C.

If a medication has a completely missing or partially missing start/stop date and it cannot be determined whether it was taken before the first dose date, concomitantly, or after the TE period, it will be classified as prior, concomitant, and post-treatment.

The logic to decide the category of a medication is presented in Table 8-1:

Table 8-1 Logic for Determining the Category of a Medication

	Medication end date		
Medication start date	< first dose date of study drug	≥ first dose date and ≤ End date of TE period	> End date of TE period
< first dose date of study drug	P	PC	PCA
≥ first dose date and ≤ End date of TE period	-	C	CA
> End date of TE period	-	-	A

P: Prior; C: Concomitant; A: Post-treatment

Summaries of prior and concomitant medications will be based on the FAS. They will also be listed by subject.

8.2.5 Study Drug Exposure

Exposure summaries will be based on the FAS and presented by treatment group.

Duration of study drug exposure is defined as follows: last dose date – first dose date + 1 day within the treatment period, regardless of any interruption in dosing between the first and the last dose.

If the last dose date of study drug is missing, the subject's discontinuation or completion date will be used for analysis purposes.

Exposure will be summarized as a continuous variable in weeks, and also in the following categories: ≤6 weeks, >6 and ≤12 weeks; >12 and ≤24 weeks; >24 and ≤36 weeks; >36 and ≤48 weeks; and >48 weeks, for each treatment group.

8.2.6 Study Drug Compliance

Study drug compliance based on number of tablets will be assessed by calculating the percentage of tablets consumed relative to the expected number of tablets administered during the subject's actual time on-study. The expected number of tablets administered during the subject's actual time on-study will be 4 tablets per day multiply the number of days in the study. The number of tablets consumed is the difference between the expected number of tablets dispensed and the total number of tablets returned.

These pharmacy and subject reported compliance data will be summarized during the overall treatment duration (from first dose to last dose), based on the medication interruption days.

Compliance rate based on the interruption days will be calculated as follow:

$100 \times [1 - (\text{total number of days of any study drug interruption}) / (\text{duration of study drug exposure})]$

The total number of days study drug interrupted is defined as the total of number of days the study drug was interrupted in each interruption interval, where number of days study drug interrupted in each interval is defined as the interruption end date - the corresponding interruption start date + 1.

Study drug compliance will be summarized descriptively by the number of subjects (n), mean, SD, median, min, and max. They will also be summarized in categories: <80% and ≥80% using frequency tables.

Study drug compliance summaries will be based on the FAS.

8.2.7 Important Protocol Deviations

An important protocol deviation (IPD) is a protocol deviation that has the potential to affect the interpretation of study results. IPDs will be identified from the clinical database and/or site deviation log.

The protocol deviations that may be considered as potential IPDs include, but are not limited to:

- Violation of subjects rights, safety or well-being
- Subject entered the study despite violation of any inclusion or exclusion criteria
- Subject received prohibited concomitant medications
- Subject received the wrong treatment or incorrect doses
- Subject remained in study despite meeting withdrawal criteria

All IPDs will be presented in an individual subject data listing.

8.3 Adherence Analysis

All analyses described in this section will be based on the FAS, unless specified otherwise. The analysis will include all available measurements through the last scheduled on-treatment visit (Week 48), including measurements after treatment discontinuation, per the visit windowing rules described in Appendix B.

8.3.1 List of Analyzed Adherence Endpoints

This study was terminated early by a business decision. The data collected at the time of termination are limited and premature due to early termination. Therefore, we will perform the descriptive summary for the following applicable endpoints as described in Section 5.3.1:

- Mean percentage adherence to LUM/IVA treatment over any treatment duration for all subjects.
- Mean percentage adherence to LUM/IVA treatment over 0 through 12 weeks for subjects who have at least 12 weeks of eligible smart pill bottle data.
- Proportion of subjects with ≥80% adherence over 0 through 12 weeks for subjects who have at least 12 weeks of eligible smart pill bottle data
- Proportion of subjects with ≥90% adherence over 0 through 12 weeks for subjects who have at least 12 weeks of eligible smart pill bottle data

[redacted]

8.3.2 Analysis of Adherence Endpoints

Mean percentage adherence to LUM/IVA treatment over treatment duration for all subjects

The percentage adherence over treatment duration for each subject is defined as:

> 100 × (total number of smart bottle openings over the eligible treatment duration excluding the physician-directed interruption periods of the eligible treatment duration) / [2 × (eligible duration of treatment - the number of physician-directed interruption days of the eligible treatment duration)

Note: (1) the physician-directed interruption is defined as the reported interruptions due to reasons not being "Non-compliance"; (2) if there are more than 2 smart bottle openings at any day, they will be counted as 2 in calculation of the adherence endpoints. (3) the eligible treatment duration = eligible date of last dose – date of first dose + 1, where the eligible date of last dose is defined to be either the CRF collected date of last dose or the last activity date of smart bottle data, whichever is earlier.

Descriptive statistics will be provided by the number of subjects (n), mean, SD, SE, median, min, and max by treatment arm based on FAS. [redacted]

The percentage adherence will also be listed.

Mean percentage adherence to LUM/IVA treatment over 0 through 12 weeks for subjects who have at least 12 weeks of eligible smart pill bottle data

Subjects who have at least 12 weeks of eligible smart pill bottle data are defined as those who have at least 12 weeks of eligible treatment duration = eligible date of last dose – date of first dose + 1, where the eligible date of last dose is defined to be either the CRF collected date of last dose or the last activity date of smart bottle data, whichever is earlier.

The percentage adherence over 12 weeks for each eligible subject is defined as:

> 100 × (total number of smart bottle openings over the first 12 weeks excluding the physician-directed interruption periods of the first 12 weeks) / [2 × (12 weeks (ie, 84 days)- the number of physician-directed interruption days of the first 12 weeks)

Note: (1) the physician-directed interruption is defined as the reported interruptions due to reasons not being "Non-compliance"; (2) if there are more than 2 smart bottle openings at any day, they will be counted as 2 in calculation of the adherence endpoints.

Descriptive statistics will be provided by the number of subjects (n), mean, SD, SE, median, min, and max by treatment arm based on FAS. [redacted]

The percentage adherence will also be listed.

In addition, the number of smart bottle openings during the physician-directed interruption periods will be presented in a by-subject listing. Please note that if there are more than 2 smart bottle openings at any day, they will be counted as the actual number in this listing.

Further exploratory analyses may be performed if deemed necessary and sufficient data is available.

Proportion of subjects with ≥80% (or 90%) adherence 0 through 12 weeks for subjects who have at least 12 weeks of eligible smart pill bottle data

For each eligible subject, the percentage of adherence over 12 weeks will be calculated as described above. The proportion of subjects with ≥80% adherence rate over 12 weeks and the proportion of subjects with ≥90% adherence rate over 12 weeks will be presented in a summary table. [redacted]

8.4 Safety Analysis

The overall safety profile of study drug will be assessed in terms of the following safety and tolerability endpoints:

- Treatment-emergent adverse events (TEAEs)
- Clinical laboratory values (i.e., liver function tests)
- Vital signs
- Ophthalmological examinations

Safety endpoints will be analyzed based on the Safety Set. Only a descriptive analysis of safety will be performed.

8.4.1 Adverse Events

AEs will be classified as pretreatment AEs, TEAEs, or post-treatment AEs, defined as follows:

Pretreatment AE: any AE that started before the first dose date of study drug

TEAE: any AE that worsened (either in severity or seriousness) or that was newly developed at or after the first dose date of study drug through the end of the TE period

Post-treatment AE: any AE that worsened (either in severity or seriousness) or that was newly developed beyond the TE period

For AEs with completely missing or partially missing start dates, if there is no clear evidence that the AEs started before or after study treatment, the AEs will be classified as TEAEs.

Details for imputing missing or partial start dates of adverse events are described in Appendix D.

AE overall summary table, TEAEs by SOC and PTs summary table, TEAEs by PTs summary table, related TEAEs by SOC and PTs summary table will be presented by study arms and overall. In addition, SAEs, AEs, TEAEs leading to treatment discontinuation, TEAEs leading to drug interruption will be listed.

8.4.2 Clinical Laboratory

For the on-treatment laboratory measurements, the raw values and change from baseline values of the liver function test results will be summarized in SI units by study arms at each visit.

The abnormal (high) LFT test results will be listed.

The abnormal (high or low) chemistry and hematology test results will be listed.

The abnormal urine or serum pregnancy test for female subjects of childbearing potential will be listed.

8.4.3 Vital Signs

The vital sign results will be listed.

8.4.4 Ophthalmological Examinations

Listings for subjects with abnormal ophthalmological examinations for subjects <18 years old at screening will be provided.

Listings for ophthalmological history data for all subjects will be provided.

8.4.5 Physical Examination

Listings for abnormal physical examination results will be provided.

9 INTERIM ANALYSES

Not applicable.

10 REFERENCES

1. Siracusa, C. M., Ryan, J., Burns, L., Wang, Y., Zhang, N., Clancy, J. P., & Drotar, D. (2015). Electronic monitoring reveals highly variable adherence patterns in patients prescribed ivacaftor. Journal of Cystic Fibrosis, 14(5), 621-626.

2. Jonas V. Bilenas. Scatter Plot smoothing using PROC LOESS and Restricted Cubic Splines. Available at: http://support.sas.com/resources/papers/proceedings14/1503-2014.pdf Accessed 25 January 2016.

11 LIST OF APPENDICES

Appendix A: Schedule of Assessments

Schedules of Assessments are shown in Table 11-1 and Table 11-2. These tables provide the schedule of assessments during the study from the Screening Period through the Safety Follow-up Visits.

All visits are to be scheduled relative to the Day 1 Visit.

Table 11-1 Screening Period Assessments – Study VX15-809-114

Assessment	Screening Period Day -28 to Day -1
Informed consent and assent (where applicable)	X
Inclusion and exclusion criteria review	X
Demographics	X
Height, weight, and BMI	X
Review of medical history (includes *CFTR* genotype)[a]	X
Ophthalmologic examination[b]	X
Prior and concomitant medications	X
Vital signs[c]	X
Physical examination[d]	X
Spirometry[e]	X
Serum pregnancy test (all female subjects of childbearing potential)[f]	X
Serum FSH[g]	X
Hematology[h]	X
Liver Function Testing[i]	X
[redacted]	
AEs and SAEs	Continuous from signing of ICF or assent (where applicable) through Safety Follow-up Visit

[a] Genotype testing will be performed if this is not documented in medical history. CF genotyping can be waived with documented CFTR genotype (Protocol Section **Error! Reference source not found.**).

[b] An ophthalmologic examination will be conducted by either a licensed ophthalmologist or an optometrist for all subjects <18 years of age. The exam may be waived if there is documentation of an exam within 3 months of the date of informed consent (or assent, when applicable). Subjects with documentation of bilateral lens removal do not need the ophthalmologic examination (Protocol Section 11.5.6.).

[c] Vital signs will be assessed following a 5-minute rest in the seated or supine position.

[d] Physical examination of all body systems (Protocol Section **Error! Reference source not found.**).

[e] Spirometry may be performed pre- or postbronchodilator (Protocol Section 11.5.5)

[f] Any female subject initiating LUM/IVA combination therapy who is considered to be of childbearing potential should have a serum pregnancy test. Women of childbearing potential are defined as: female subjects after puberty unless they are postmenopausal for at least 1 year and have documented FSH levels within the postmenopausal reference range of the performing laboratory, or are surgically sterile.

[g] Serum FSH levels will be measured for any suspected postmenopausal female subjects with at least 12 months of continuous spontaneous amenorrhea.

[h] Blood samples will be collected for clinical laboratory assessments (Protocol Section 11.5.2).

[i] Liver function testing (alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma-glutamyl transpeptidase [GGT], alkaline phosphatase [ALP], and total bilirubin) must be performed at the scheduled visits (Protocol Section 11.5.2).

Table 11-2 Treatment Period and Safety Follow-up Visit Assessments – Study VX15-809-114

Event/Assessment	Day 1	Week 12	Week 24	Week 36	Week 48	Safety Follow-up Week 52[a]
Clinic visit	X	X	X	X	X	X
Vital signs[b]	X	X	X	X	X	X
Physical examination[c]					X	X[d]
Liver Function Testing[e]	X	X	X	X	X	X
Urine pregnancy test (all female subjects of childbearing potential)	X	X	X	X	X	X
Randomization[f]	X					
Standardized education on adherence	X					
Concomitant medications, treatments, and procedures	X	X	X	X	X	X
Smart Adherence Technology-Reported Adherence[g]		X	X	X	X	
[redacted]						
LUM/IVA drug count[i]		X	X	X	X	
Ophthalmologic examination[j]					X	
AEs and SAEs	Continuous from signing of ICF or assent (where applicable)					
LUM/IVA resupply	Every 3 months throughout study					

[a] The Safety Follow-up Visit is 28 (± 7) days after the last dose of LUM/IVA (Protocol Section 8.1.3).
[b] Vital signs will be assessed following a 5-minute rest in the seated or supine position.
[c] Symptom-targeted PEs will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator.
[d] Required for subjects who do not begin commercial LUM/IVA after Week 48 only.
[e] Day 1 only blood draws will be collected before the first dose of LUM/IVA. Liver function testing (alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma-glutamyl transpeptidase [GGT], alkaline phosphatase [ALP], and total bilirubin) must be performed at the scheduled visits (Protocol Section 11.5.2).
[f] Randomization must occur after all inclusion and exclusion criteria are met and before the first dose of LUM/IVA. Randomization will be done through IWRS.
[g] Data will be collected for all subjects throughout the study in real-time. Subjects in Study Arm A will review data with physicians at study visits.
[redacted].
[i] LUM/IVA drug count will be collected at the end of specified study visits.
[j] See Protocol Section 11.5.6.

Appendix B: Analysis Visit Windows for Safety and Adherence/PROs Assessments

Table 11-3 Analysis Visit Windows for Study Assessments

Assessment	Analysis Visit[a]	Target Study Day[b]	Analysis Visit Window (in study days)
Safety Assessment			
LFTs; Vital Signs;	Baseline	Day 1	≤1
	Week 12	Day 85	[2, 127]
	Week 24	Day 169	[128, 211]
	Week 36	Day 253	[212, 295]
	Week 48	Day 337	[296, 379]
	Safety Follow-up (Week 52)	Day 364	Use nominal visit
Adherence [redacted]			
[redacted] Subject Satisfaction with Smart Adherence Technology	Baseline	Day 1	≤1
	Week 12	Day 85	[2, 127]
	Week 24	Day 169	[128, 211]
	Week 36	Day 253	[212, 295]
	Week 48	Day 337	[296, 379]

[redacted]

Notes:
The analysis visit windows will be applied using the following rules for both scheduled and unscheduled visits:

1. If no numerical measurement is available within a visit window, the measurement will be considered missing for the visit.
2. If there is more than 1 numerical measurement available within the same visit window, use the following rules:
   a. For **Adherence** [redacted]: if there are multiple measurements within a visit window, the measurement at the scheduled visit will be used. Otherwise,
      i. If there are no measurements at the scheduled visit, then the measurement closest to the target day will be used; or
      ii. If there are multiple measurements with the same distance to the target day, the latest measurement will be used.
   b. For **safety** parameters: if there are multiple measurements within a visit window,
      i. The measurement closest to the target day will be used; or
      ii. If there are multiple measurements within the same distance from the target day, the latest measurement will be used.

[a] Analysis Visit is used to report data in tables and figures, but not listings.
[b] Target day time point per protocol is predose.

Appendix C: Imputation Rules for Missing Prior/Concomitant Medication Dates

Imputation rules for missing or partial medication start/stop dates are defined below:

1. Missing or partial medication start date:
    a. If only DAY is missing, use the first day of the month.
    b. If DAY and Month are both missing, use the first day of the year.
    c. If DAY, Month and Year are all missing, use a date before the first dose date (in practical, use Jan. 01, 2000 to impute or other equivalent method).
2. Missing or partial medication stop date:
    a. If only DAY is missing, use the last day of the month.
    b. If DAY and Month are both missing, use the last day of the year.
    c. If DAY, Month and year are all missing, assign 'continuing' status to stop date (in practical, use Dec. 31, 2050 to impute or other equivalent method).

In summary, the prior, concomitant or post categorization of a medication is described below.

Table 11-4 Prior, Concomitant, and Post Categorization of a Medication

	Medication Stop Date		
Medication Start Date	**< First Dose Date of Study Drug**	**≥ First Dose Date and ≤ End Date of TE Period**	**> End Date of TE Period**
< First dose date of study drug	P	PC	PCA
≥ First dose date and ≤ End date of TE period	-	C	CA
> End date of TE period	-	-	A

A: Post; C: Concomitant; P: Prior

Appendix D: Imputation Rules for Missing AE dates

Imputation rules for missing or partial AE start date are defined below:

If only Day of AE start date is missing:

If the AE start year and month are the same as that for the first dose date, then:

- If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then impute the AE start day as the day of first dose date; otherwise, impute the AE start day as 1.
- Otherwise, impute the AE start day as 1.

Compare the imputed AE start date with TE period to determine whether the AE is pretreatment AE, TEAE or post-treatment AE.

If Day and Month of AE start date are missing:

If AE start year = first dose year, then:

- If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then impute the AE start Month and Day as the Month and Day of first dose date; otherwise, impute the AE start Month as January and the Day as 1.
- Otherwise, impute the AE start MONTH as January and the DAY as 1.

Compare the imputed AE start date with TE period to determine whether the AE is pretreatment AE, TEAE or post-treatment AE.

If Year of AE start date is missing:

If the year of AE start is missing or AE start date is completely missing then query site with no imputation. Also compare the full (or partial) AE end date to the first dose date. If the AE end date is before the first dose date then the AE should be considered as a pretreatment AE. Otherwise, the AE will be considered as TEAE.

Appendix E: Coefficients for Hankinson and Wang Methods for Calculating Predicted Spirometry Parameters

Percent predicted FEV_1 is the ratio of FEV_1 (L) to the predicted FEV_1 (L), expressed as a percentage. The predicted FEV_1 (L) will be calculated using the Hankinson and Wang standards.

The Hankinson standard will be applied to male patients 18 years and older and female patients 16 years and older; the Wang standard will be applied to male patients 6 to 17 years and female patients 6 to 15 years of age. During the study, the patients who have a birthday that would move them from Wang to Hankinson will use the Wang standard before that birthday and the Hankinson standard at or after that birthday.

Hankinson Normal Values (HNVs) will be calculated for FEV_1, forced vital capacity (FVC), forced expiratory flow mid expiratory phase ($FEF_{25-75\%}$), and FEV_1/FVC% using the Hankinson equation:

$$\text{Predicted lung function parameter} = b0+b1 \times age+b2 \times age^2+ b3 \times height^2$$

In the equation, height is given in centimeters, age is given in years, and the coefficients b_0, b_1, b_2, and b_3 are determined based on patient's sex, race, and age group as shown in Table 4.

Wang Normal Values (WNVs) will be calculated for FEV_1, FVC, $FEF_{25-75\%}$, and FEV_1/FVC using the Wang equation:

$$\ln(\text{Predicted lung function parameter}) = \alpha + \beta \ln(\text{height})$$

Wang Normal Values (WNVs) will be calculated for FEV_1, FVC, $FEF_{25-75\%}$, and FEV_1/FVC using the Wang equation. In the equation, height is given in meters, and the coefficients α and β are determined based on patient's sex, race, and age as shown in Table 11-8 and Table 11-9.

If either height or age is missing, and the spirometry measurement is non-missing, the last non-missing value of height and age will be used in the calculation of predicted values.

Table 11-7 HNVs Equation Coefficients by Sex, Race, and Age

Parameter	Sex	Race	Age (years)	b_0	b_1	b_2	b_3
HNV_{FEV1}	Male	Caucasian	<20	-0.7453	-0.04106	0.004477	0.00014098
			≥20	0.5536	-0.01303	-0.000172	0.00014098
		African American	<20	-0.7048	-0.05711	0.004316	0.00013194
			≥20	0.3411	-0.02309		0.00013194
		Mexican American	<20	-0.8218	-0.04248	0.004291	0.00015104
			≥20	0.6306	-0.02928		0.00015104
	Female	Caucasian	<18	-0.8710	0.06537		0.00011496
			≥18	0.4333	-0.00361	-0.000194	0.00011496
		African American	<18	-0.9630	0.05799		0.00010846
			≥18	0.3433	-0.01283	-0.000097	0.00010846
		Mexican American	<18	-0.9641	0.06490		0.00012154
			≥18	0.4529	-0.01178	-0.000113	0.00012154
HNV_{FVC}	Male	Caucasian	<20	-0.2584	-0.20415	0.010133	0.00018642
			≥20	-0.1933	0.00064	-0.000269	0.00018642
		African American	<20	-0.4971	-0.15497	0.007701	0.00016643
			≥20	-0.1517	-0.01821		0.00016643
		Mexican American	<20	-0.7571	-0.09520	0.006619	0.00017823
			≥20	0.2376	-0.00891	-0.000182	0.00017823
	Female	Caucasian	<18	-1.2082	0.05916		0.00014815
			≥18	-0.3560	0.01870	-0.000382	0.00014815
		African American	<18	-0.6166	-0.04687	0.003602	0.00013606
			≥18	-0.3039	0.00536	-0.000265	0.00013606
		Mexican American	<18	-1.2507	0.07501		0.00014246
			≥18	0.1210	0.00307	-0.000237	0.00014246
$HNV_{FEF25-75\%}$	Male	Caucasian	<20	-1.0863	0.13939		0.00010345
			≥20	2.7006	-0.04995		0.00010345
		African American	<20	-1.1627	0.12314		0.00010461
			≥20	2.1477	-0.04238		0.00010461
		Mexican American	<20	-1.3592	0.10529		0.00014473
			≥20	1.7503	-0.05018		0.00014473
	Female	Caucasian	<18	-2.5284	0.52490	-0.015309	0.00006982
			≥18	2.3670	-0.01904	-0.000200	0.00006982
		African American	<18	-2.5379	0.43755	-0.012154	0.00008572
			≥18	2.0828	-0.03793		0.00008572
		Mexican American	<18	-2.1825	0.42451	-0.012415	0.00009610
			≥18	1.7456	-0.01195	-0.000291	0.00009610
$HNV_{FEV1/FVC\%}$	Male	Caucasian		88.066	-0.2066		
		African American		89.239	-0.1828		
		Mexican American		90.024	-0.2186		
	Female	Caucasian		90.809	-0.2125		
		African American		91.655	-0.2039		
		Mexican American		92.360	-0.2248		

Table 11-8 WNVs Equation Coefficients by Sex and Age in White Boys and Girls

		FEV_1		FVC		$FEF_{25-75\%}$		FEV_1/FVC	
Sex	**Age**	**α**	**β**	**α**	**β**	**α**	**β**	**α**	**β**
Male	6	-0.109	2.252	-0.024	2.470			-0.078	-0.248
	7	-0.104	2.270	-0.018	2.489			-0.086	-0.220
	8	-0.089	2.257	0.005	2.443	0.264	1.505	-0.091	-0.199
	9	-0.063	2.197	0.017	2.426	0.308	1.443	-0.086	-0.206
	10	-0.057	2.212	0.030	2.407	0.290	1.557	-0.081	-0.209
	11	-0.093	2.324	0.009	2.468	0.242	1.738	-0.101	-0.147
	12	-0.161	2.512	-0.061	2.649	0.165	1.982	-0.101	-0.133
	13	-0.292	2.843	-0.175	2.924	0.007	2.396	-0.116	-0.085
	14	-0.329	2.983	-0.219	3.060	0.014	2.483	-0.106	-0.087
	15	-0.141	2.709	-0.079	2.859	0.241	2.163	-0.060	-0.155
	16	0.062	2.409	0.104	2.591	0.503	1.764	-0.045	-0.178
	17	0.262	2.099	0.253	2.374	0.762	1.368	0.008	-0.272
Female	6	-0.109	1.949	-0.013	2.007			-0.097	-0.055
	7	-0.144	2.243	-0.062	2.385			-0.084	-0.132
	8	-0.137	2.239	-0.055	2.381	0.247	1.668	-0.079	-0.152
	9	-0.123	2.222	-0.039	2.351	0.254	1.710	-0.084	-0.128
	10	-0.161	2.364	-0.068	2.458	0.195	1.933	-0.092	-0.097
	11	-0.223	2.558	-0.120	2.617	0.161	2.091	-0.102	-0.061
	12	-0.264	2.709	-0.174	2.776	0.185	2.120	-0.090	-0.067
	13	-0.153	2.535	-0.061	2.576	0.294	1.976	-0.093	-0.040
	14	0.046	2.178	0.139	2.208	0.450	1.711	-0.096	-0.026
	15	0.148	2.008	0.210	2.099	0.581	1.486	-0.062	-0.093

Table 11-9 WNVs Equation Coefficients by Sex and Age in Black Boys and Girls

		FEV_1		FVC		$FEF_{25-75\%}$		FEV_1/FVC	
Sex	**Age**	**α**	**β**	**α**	**β**	**α**	**β**	**α**	**β**
Male	6	-0.166	1.723	-0.088	1.961			-0.091	-0.152
	7	-0.122	1.846	-0.040	2.040			-0.091	-0.153
	8	-0.225	2.271	-0.094	2.323	0.097	1.544	-0.118	-0.104
	9	-0.142	2.059	-0.074	2.308	0.255	1.248	-0.079	-0.218
	10	-0.157	2.117	-0.110	2.417	0.230	1.428	-0.047	-0.303
	11	-0.176	2.166	-0.138	2.453	0.256	1.438	-0.048	-0.263
	12	-0.307	2.548	-0.224	2.710	0.085	1.936	-0.084	-0.162
	13	-0.486	2.962	-0.342	2.975	-0.121	2.476	-0.141	-0.018
	14	-0.472	3.010	-0.337	3.035	-0.115	2.536	-0.123	-0.050
	15	-0.318	2.789	-0.226	2.889	0.170	2.120	-0.070	-0.140
	16	0.074	2.140	0.058	2.425	0.663	1.299	0.018	-0.289
	17	0.053	2.223	0.148	2.310	0.505	1.618	-0.095	-0.087
Female	6	-0.288	2.182	-0.172	2.117			-0.109	0.059
	7	-0.250	2.158	-0.135	2.132			-0.104	-0.030
	8	-0.276	2.295	-0.176	2.362	-0.283	2.990	-0.103	-0.066
	9	-0.294	2.330	-0.200	2.452	0.025	2.062	-0.097	-0.104
	10	-0.344	2.507	-0.230	2.571	0.051	2.028	-0.120	-0.043
	11	-0.308	2.460	-0.204	2.526	0.078	2.006	-0.089	-0.105
	12	-0.219	2.312	-0.107	2.342	0.225	1.804	-0.115	-0.021
	13	-0.117	2.196	-0.042	2.294	0.418	1.504	-0.051	-0.148
	14	0.041	1.920	0.105	2.021	0.574	1.257	-0.063	-0.103
	15	0.203	1.662	0.253	1.787	0.599	1.281	-0.043	-0.139