VERTEX

VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)

Protocol Number VX15-809-110

A Phase 3, Rollover Study to Evaluate the Safety and Efficacy of Long-term Treatment With Lumacaftor in Combination With Ivacaftor in Subjects Aged 6 Years and Older With Cystic Fibrosis, Homozygous for the *F508del-CFTR* Mutation

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[redacted]

2 LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline aminotransferase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index (kg/m^2)
bpm	beats per minute
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire – Revised
CFTR	cystic fibrosis transmembrane conductance regulator
CI	confidence interval
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
FAS	full analysis set
[redacted]	[redacted]
$FEF_{25-75\%}$	forced expiratory flow, midexpiratory phase
FEV_1	forced expiratory volume in 1 second
FET	Forced expiratory time
FRC	functional residual capacities
FVC	forced vital capacity
F508del	*CFTR* gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein
IA	Interim analysis
ICF	Informed consent form
[redacted]	[redacted]
IVA	ivacaftor
KM analysis	Kaplan-Meier analysis
LCI	lung clearance index
$LCI_{2.5}$	lung clearance $index_{2.5}$, the number of lung turnovers (for functional residual capacity, FRC) required to reduce the end tidal inert gas concentration to $1/40^{th}$ of its starting value
$LCI_{5.0}$	lung clearance $index_{5.0}$, the number of lung turnovers (for functional residual capacity, FRC) required to reduce the end tidal inert gas concentration to $1/20^{th}$ of its starting value
LFT	liver function test
LLN	lower limit of normal
LMM	linear mixed effect model
LUM	lumacaftor
Max	maximum value
Min	minimum value
MBW	N2-multiple-breath washout
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measure
n	number of subjects

Abbreviation	Term
PEF	Peak expiratory flow
PT	preferred term
$ppFEV_1$	percent predicted forced expiratory volume in 1 second
$ppFEF_{25-75\%}$	percent predicted forced expiratory flow, midexpiratory phase
ppFVC	percent predicted forced vital capacity
q12h	every 12 hours
QRS	Q, R, and S-wave define the QRS-complex in an ECG
QT	QT interval: The duration of ventricular depolarization and subsequent repolarization; it is measured from the beginning of the QRS complex to the end of the T wave
QTc	QT interval corrected
ROS	Rollover Set
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SE	standard error of mean
SI	System International
SOC	system organ class
TEAE	treatment-emergent adverse event
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	upper limit of normal
WNV_{FEV}	Wang predicted value of FEV_1 (L)
$WNV_{FEF25-75\%}$	Wang predicted value of $FEF_{25-75\%}$ (L/sec)
WNV_{FVC}	Wang predicted value of FVC (L)
WHODD	World Health Organization Drug Dictionary

4 INTRODUCTION

This SAP describes the planned final analyses for the Study VX15-809-110 (Study 110) data and is based on the following:

- Approved clinical study protocol for Study 110 (SAP is based on the study design in Protocol Version 2.1)
  - Version 2.1 FR, dated 30 November 2017 (For France Only).
  - Version 2.0, dated 15 September 2015 (For the Other Countries)
- Approved electronic case report form (eCRF) for Study 110 (Version 3.0, dated 29 January 2016).

Study 110 is a Phase 3, multicenter study in subjects aged 6 years and older with cystic fibrosis (CF) who are homozygous for the *F508del-CFTR* mutation and who participated in Study VX14-809-109 (Study 109) or Study VX13-809-011B (Study 011B). Study 110 is designed to evaluate the safety and efficacy of long-term treatment of lumacaftor in combination with ivacaftor.

This study consists of Treatment Cohorts (Treatment Cohort Period 1 and optional Treatment Cohort Period 2) and an Observational Cohort. Treatment Cohort Period 1 and the Observational Cohort will be enrolled in parallel for Study 109 and Study 011B subjects who meet the inclusion criteria. French subjects 6 through 11 years of age who complete Treatment Cohort Period 1 may enroll in the optional Treatment Cohort Period 2.

This SAP (Methods) documents the planned final statistical analyses and data presentations of final analysis for subjects who previously participated in Studies 109 or Study 011B and those enrolled in Study 110. It also documents additional efficacy and safety analyses not prespecified in the protocol, but necessary for the scientific understanding of the drug entity.

[redacted] has been contracted by Vertex to perform the statistical analysis of the efficacy and safety data; SAS (Version 9.2 or higher) will be used to generate all statistical outputs (tables, figures, listings, and datasets). The SAP will be finalized and approved prior to the final clinical data lock for the study.

5 STUDY OBJECTIVES

5.1 Primary Objective

To evaluate the long-term safety and tolerability of lumacaftor in combination with ivacaftor in subjects aged 6 years and older with CF, homozygous for the *F508del-CFTR* mutation, who are in the Treatment Cohort Period 1.

5.2 Secondary Objectives

- To evaluate the long-term efficacy and durability of lumacaftor in combination with ivacaftor for subjects in Treatment Cohort Period 1
- To evaluate the long-term safety of lumacaftor in combination with ivacaftor for subjects in Treatment Cohort Period 2

- To evaluate the post-treatment safety of lumacaftor in combination with ivacaftor for subjects in the Observational Cohort

6 STUDY ENDPOINTS

6.1 Primary Endpoint

Treatment Cohort Period 1

Safety and tolerability assessments of long-term treatment of lumacaftor in combination with ivacaftor based on adverse events (AEs), clinical laboratory values (serum chemistry, hematology, coagulation studies, and urinalysis), standard 12-lead electrocardiograms (ECGs), vital signs, pulse oximetry, ophthalmological examinations, and spirometry.

Treatment Cohort Period 2 and Observational Cohort

Not applicable

6.2 Secondary Endpoints

Treatment Cohort Period 1

The following efficacy endpoints are defined using baseline values in the previous study (i.e., Study 109 or Study 011B):

- Absolute change from baseline in $LCI_{2.5}$ (subjects from Study 109 and Study 011B LCI Substudy only)
- Absolute change from baseline in sweat chloride
- Absolute change from baseline in body mass index (BMI)
- Absolute change from baseline in Cystic Fibrosis Questionnaire – Revised (CFQ-R) respiratory domain score

The following efficacy endpoints are defined using baseline values in the current study (i.e., Study 110):

- Absolute change from baseline in $LCI_{2.5}$ (subjects from Study 109 and Study 011B LCI Substudy only)
- Absolute change from baseline in sweat chloride
- Absolute change from baseline in BMI
- Absolute change from baseline in CFQ-R respiratory domain score

Treatment Cohort Period 2

- Safety, as determined by AEs and serious adverse events (SAEs), liver function tests (LFTs), and ophthalmologic examinations

Observational Cohort

Safety, as determined by SAEs

6.3 Other Secondary Endpoints

Treatment Cohort Period 1

The following efficacy endpoints are defined using baseline values in the previous study (i.e., Study 109 or Study 011B):

- Absolute change from baseline in $LCI_{5.0}$ (subjects from Study 109 and Study 011B LCI Substudy only)
- Absolute change from baseline in $ppFEV_1$
- Relative change from baseline in $ppFEV_1$
- Absolute change from baseline in BMI-for-age z-score
- Absolute change from baseline in weight
- Absolute change from baseline in weight-for-age z-score
- Absolute change from baseline in height
- Absolute change from baseline in height-for-age z-score
- Absolute change from baseline in Treatment Satisfaction Questionnaire for Medication (TSQM) domains

The following efficacy endpoints are defined using baseline values in the current study (i.e., Study 110):

- Absolute change from baseline in $LCI_{5.0}$ (subjects from Study 109 and Study 011B LCI Substudy only)
- Absolute change from baseline in $ppFEV_1$
- Relative change from baseline in $ppFEV_1$
- Absolute change from baseline in BMI-for-age z-score
- Absolute change from baseline in weight
- Absolute change from baseline in weight-for-age z-score
- Absolute change from baseline in height
- Absolute change from baseline in height-for-age z-score
- Absolute change from baseline in TSQM domains

The following pulmonary exacerbation-related endpoints are defined for subjects from Study 109 only:

- Time-to-first pulmonary exacerbation, including pulmonary exacerbations in the previous study and the current study
- Event of having at least 1 pulmonary exacerbation, including pulmonary exacerbations in the previous study and the current study
- Number of pulmonary exacerbations, including pulmonary exacerbations in the previous study and the current study

The following efficacy endpoints are also defined:

- Rate of change in $LCI_{2.5}$ (subjects from Study 109 and the Study 011B LCI Substudy only)
- Rate of change in $LCI_{5.0}$ (subjects from Study 109 and the Study 011B LCI Substudy only)
- Rate of change in $ppFEV_1$

Treatment Cohort Period 2 and Observational Cohort

Not applicable

[redacted]

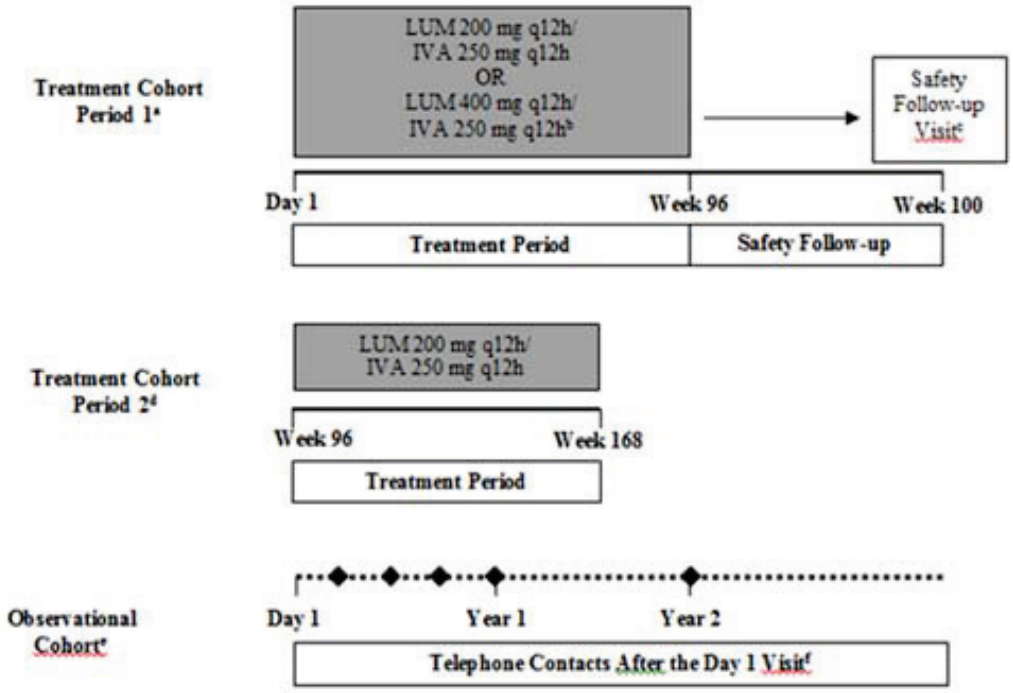
7 STUDY DESIGN

7.1 Overall Design

This is a Phase 3, multicenter study in subjects aged 6 years and older with CF who are homozygous for the *F508del-CFTR* mutation and who participated in Study 109 or Study 011B. Study 110 is designed to evaluate the safety and efficacy of long-term treatment of lumacaftor in combination with ivacaftor.

This study consists of Treatment Cohorts (Treatment Cohort Period 1 and Treatment Cohort Period 2) and an Observational Cohort. Treatment Cohort Period 1 and the Observational Cohort will be enrolled in parallel as shown in Figure 7-1.

Figure 7-1 Schematic of Study Design



IVA: ivacaftor; LUM: lumacaftor; q12h: every 12 hours.

[a] The following subjects may be eligible for enrollment in the Treatment Cohort: (1) subjects who completed 24 weeks of study drug treatment (i.e., lumacaftor in combination with ivacaftor or placebo) in Study 109 or completed 24 weeks of study drug treatment and the Week 26 Safety Follow-up in Study 011B (NOTE: the last dose of study drug is the evening dose administered the day before the Week 24 Visit or the dose at the Week 24 Visit [based on the applicable protocol version for which a subject screens (provides consent/assent) under] in Study 109 or the evening dose administered the day before the Week 24 Visit in Study 011B) and (2) subjects who are not receiving study drug treatment at the end of the Treatment Period in Study 109 or Study 011B (NOTE: subjects from Study 011B have a planned Washout Period from Week 24 to Week 26 and must still complete the Week 26 Safety Follow-up), including subjects that require study drug interruption to be either continued or initiated at Day 1 in Study 110, and who have received Vertex approval for entry. Subjects who prematurely discontinued study drug treatment are not eligible for enrollment in the Treatment Cohort.

[b] Subjects who turn 12 years of age in the previous study or Day 1 of this rollover study will begin receiving LUM 400 mg q12h/IVA 250 mg q12h on Day 1. Subjects who turn 12 years of age after the Day 1 Visit of this rollover study will begin receiving LUM 400 mg q12h/IVA 250 mg q12h at their next scheduled visit.

[c] The Safety Follow-up Visit is scheduled to occur 4 weeks (± 7 days) after the last dose of study drug.

[d] Subjects 6 through 11 years of age who complete Treatment Cohort Period 1 may enter Treatment Cohort Period 2. Week 96 of Treatment Cohort Period 1 will be the start of Treatment Cohort Period 2.

[e] The following subjects from Study 109 or Study 011B may be eligible for enrollment in the Observational Cohort: (1) subjects who received at least 4 weeks of study drug in Study 109 or Study 011B and completed visits up to Week 24 of Study 109 or Week 26 of Study 011B but who are not eligible for the Treatment Cohort with lumacaftor in combination with ivacaftor and (2) subjects who received at least 4 weeks of study drug in Study 109 or Study 011B (and did not prematurely discontinue study drug treatment) and completed visits up to Week 24 of Study 109 or Week 26 of Study 011B but who elect not to continue treatment with lumacaftor in combination with ivacaftor .

[f] A telephone contact will be made every 3 to 4 months during the first year and at approximately 2 years (± 4 weeks).

Treatment Cohorts

The following subjects from Study 109 or Study 011B who meet the study eligibility criteria (Protocol Sections 9.1 and 9.2) and elect to enroll in Study 110 are eligible for enrollment in the Treatment Cohort Period 1:

- Subjects from Study 109: Subjects who completed 24 weeks of study drug treatment (i.e., lumacaftor in combination with ivacaftor or placebo) in Study 109 (NOTE: the last dose of study drug is the evening dose administered the day before the Week 24 Visit or the dose at the Week 24 Visit [based on the applicable protocol version for which a subject screens (provides consent/assent) under] in Study 109).
- Subjects from Study 011B: Subjects who completed the Week 26 Safety Follow-up in Study 011B (NOTE: the last dose of study drug is the evening dose administered the day before the Week 24 Visit in Study 011B).
- Subjects who are not receiving study drug treatment at the end of the Treatment Period in Study 109 or Study 011B (NOTE: subjects from Study 011B have a planned Washout Period from Week 24 to Week 26 and must still complete the Week 26 Safety Follow-up), including subjects who require study drug interruption to be either continued or initiated at Day 1 in Study 110, and who have received Vertex approval for entry.

Subjects who prematurely discontinued Study 109 or Study 011B drug treatment are not eligible for enrollment in the Treatment Cohort Period 1.

French subjects 6 through 11 years of age who complete Treatment Cohort Period 1 may enroll in the optional Treatment Cohort Period 2.

Treatment Cohort Period 1

Treatment Cohort Period 1 will be open-label and will consist of the following dose regimens:

- LUM 200 mg q12h/IVA 250 mg q12h (subjects aged 6 through 11 years)
- LUM 400 mg q12h/IVA 250 mg q12h (subjects aged 12 years and older)

Subjects who turn 12 years of age before or on Day 1 of Study 110 will begin receiving LUM 400 mg q12h/IVA 250 mg q12h on Day 1. Subjects who turn 12 years of age after the Day 1 Visit of this rollover study will begin receiving LUM 400 mg q12h/IVA 250 mg q12h at their next scheduled visit.

Treatment Cohort Period 2 (France only)

Treatment Cohort Period 2 will be open-label and will consist of the following dose regimen:

- LUM 200 mg q12h/IVA 250 mg q12h (subjects aged 6 through 11 years)

French subjects who turn 12 years of age during Treatment Cohort Period 2 will be discontinued from the study because there is sufficient long-term safety data in this age population. It is recommended that these subjects discuss available treatment options with their treating physicians.

Observational Cohort

The following subjects from Study 109 or Study 011B who meet the study criteria (Protocol Section 9.1) and elect to enroll in Study 110 are eligible for enrollment in the Observational Cohort:

- Subjects who received at least 4 weeks of study drug in Study 109 or Study 011B and completed visits up to Week 24 of Study 109 or Week 26 of Study 011B but who are not eligible (Protocol Sections 9.1 and 9.2) for the Treatment Cohort with lumacaftor in combination with ivacaftor.
- Subjects who received at least 4 weeks of study drug in Study 109 or Study 011B (and did not prematurely discontinue study drug treatment) and completed visits up to Week 24 of Study 109 or Week 26 of Study 011B but who elect not to continue treatment with lumacaftor in combination with ivacaftor.

Subjects in the Observational Cohort will not receive study drug and will have regularly scheduled telephone calls for approximately 2 years after their last dose of study drug in Study 109 or Study 011B to assess the post-treatment safety of lumacaftor and ivacaftor combination therapy.

7.2 Sample Size and Power

This is a rollover study that plans to enroll subjects from qualifying previous studies (Study 109 and Study 011B) who meet the inclusion and exclusion criteria for this study. Approximately 256 subjects are potentially eligible to be enrolled into Study 110: approximately 200 subjects from Study 109 and approximately 56 subjects from Study 011B. Table 7-1 provides the 95% Confidence Intervals (CIs) for observing the CF lung events assuming different incidence of CF lung (i.e., pulmonary exacerbation) in CF subjects.

Table 7-1 95% CIs Assuming Different Observed Incidences of CF lung

Observed CF lung incidence	95% CI (n=256)
0.1	(0.063, 0.137)
0.2	(0.151, 0.249)
0.3	(0.244, 0.356)
0.4	(0.340, 0.460)

7.3 Randomization

This is an open-label study. No randomization is planned.

7.4 Blinding and Unblinding

This is an open-label study; however, subjects and their parent/caregiver should not be informed of their study-related LCI, spirometry, sweat chloride, [redacted] results until all Treatment Cohort Period 1 subjects complete Treatment Cohort Period 1, regardless if the subject has prematurely discontinued from Study 110 Treatment Cohort Period 1 or not.

8 ANALYSIS SETS

Enrolled subjects are those who signed informed consent/assent form and had an enrollment date on the CRF. For Treatment Cohort Period 2 and Observational Cohort, all summaries will be based on all enrolled subjects from the corresponding cohort.

All Subjects Set includes all subjects randomized or dosed in Study 109 and all subjects enrolled or dosed in Study 011B.

110 All Subjects Set includes all subjects enrolled or dosed in Study 110 Treatment Cohort Period 1.

8.1 Efficacy Set

Full Analysis Set (FAS) includes all subjects who are randomized and dosed in Study 109, or subjects enrolled and dosed in Study 011B. The FAS treatment group assignment is shown in Table 8-1; the treatment group will be as randomized/enrolled in the previous studies.

Table 8-1 FAS Treatment Group Assignment in Study 110

Treatment Groups	Description
L200/I-L/I	Subjects randomized/enrolled to L200/I in the previous studies (Study 109 or Study 011B)[a]
P-L/I	Subjects randomized to placebo in Study 109[a]

I: ivacaftor; L: lumacaftor; P: placebo.
[a] Subjects who turn 12 years of age in the previous studies or Day 1 of this rollover study will begin receiving L400/I on Day 1. Subjects who turn 12 years of age after the Day 1 Visit of this rollover study will begin receiving L400/I at their next scheduled visit.

110 Full Analysis Set (110 FAS): The 110 FAS will include all subjects who rolled over from Study 109 and Study 011B, and who are enrolled and exposed to any amount of study drug in Study 110. The 110 FAS treatment group assignment is shown in Table 8-2; the treatment group will be as randomized/enrolled in the previous studies.

Table 8-2 110 FAS Treatment Group Assignment in Study 110

Treatment Groups	Description
L200/I-L/I	Subjects randomized/enrolled to L200/I in the previous studies (Study 109 or Study 011B) and enrolled and dosed in Study 110[a]
P-L/I	Subjects randomized to placebo in Study 109 and enrolled and dosed in Study 110[a]

I: ivacaftor; L: lumacaftor; P: placebo.
[a] Subjects who turn 12 years of age in the previous studies or Day 1 of this rollover study will begin receiving L400/I on Day 1. Subjects who turn 12 years of age after the Day 1 Visit of this rollover study will begin receiving L400/I at their next scheduled visit.

109 Full Analysis Set (109 FAS): The 109 FAS will include all subjects who are randomized and exposed to any amount of study drug in Study 109.

109 Rollover Set (109 ROS): The 109 Rollover Set will include subjects who rolled over from Study 109 (enrolled in Study 110) and were exposed to any amount of study drug in Study 110.

8.2 Safety Set

Safety Set includes all subjects who are exposed to any amount of study drug in the previous studies. The treatment group will be as treated in the previous studies. The Safety Set treatment group assignment is shown in Table 8-3. For subjects who received study drug from both of the placebo and active treatment groups in Study 109, the treatment group allocation for as-treated analysis will be the L200/I-L/I group.

Table 8-3 Safety Set Treatment Group Assignment in Study 110

Treatment Groups	Description
L200/I-L/I	Subjects dosed with any L200/I in the previous studies (Study 109 or Study 011B)
P-L/I	Subjects dosed with placebo only in Study 109

I: ivacaftor; L: lumacaftor; P: placebo.
[a]: Subjects who turn 12 years of age in the previous studies or Day 1 of this rollover study will begin receiving L400/I on Day 1. Subjects who turn 12 years of age after the Day 1 Visit of this rollover study will begin receiving L400/I at their next scheduled visit.

110 Safety Set: The 110 Safety Set will include all subjects dosed in previous studies who are exposed to any amount of study drug in Study 110. The 110 Safety Set treatment group assignment is shown in Table 8-4. For subjects who received study drug from both of the placebo and active treatment groups in Study 109, the treatment group allocation for as-treated analysis will be the L200/I-L/I group.

Table 8-4 110 Safety Treatment Group Assignment in Study 110

Treatment Groups	Description
L200/I-L/I	Subjects dosed with any L200/I in the previous studies (Study 109 or Study 011B) and dosed in Study 110[a]
P-L/I	Subjects dosed with placebo only in Study 109 and enrolled and dosed in Study 110[a]

I: ivacaftor; L: lumacaftor; P: placebo.
[a] Subjects who turn 12 years of age in the previous studies or Day 1 of this rollover study will begin receiving L400/I on Day 1. Subjects who turn 12 years of age after the Day 1 Visit of this rollover study will begin receiving L400/I at their next scheduled visit.

8.3 Other Analysis Set

All subjects from Study 109 and subjects from Study 011B LCI substudy will undergo LCI assessments in Study 110, the following analysis sets are defined to provide related summaries:

LCI Set is a subset of the FAS including the 109 FAS subjects and the FAS subjects from Study 011B who consent to the Study 011B LCI Substudy.

110 LCI Set is a subset of the LCI Set including subjects in the LCI Set who enrolled and exposed to any amount of study drug in Study 110.

[redacted]

[redacted]

9 ANALYSIS PERIODS

9.1 Treatment Cohort Period 1

Three different Study Periods, as detailed below, will be defined and analyzed for Treatment Cohort Period 1 subjects. The safety analysis for the corresponding Study Period will be based on its treatment-emergent period.

9.1.1 Previous Study Period

Previous Study Period starts from the first dose date of study drug in the parent studies (109 and 011B) to up to the first dose date of study drug in Study 110, including 1) the planned 2-week washout period per Study 011B design; or 2) the Roll-Over Gap between the previous studies (Study 109 and Study 011B) and Study 110.

For the majority of the subjects, the first dose of study drug and assessments in Study 110 will happen on the same day as the Week 24 Visit in Study 109 or the Week 26 Visit in Study 011B.

For assessment performed on the first dose day in Study 110:

- If information regarding the assessment timing is available, then the assessment time will be compared to the first dose time in Study 110 to decide whether the assessment is before the first dose, concurrent with the first dose, or after the first dose.
- If information regarding assessment timing is not available, then the record will be included in the Previous Study Period if it comes from the Previous Study database, and the record will be included in the Current Study Period if it comes from the Current Study database.

Treatment-Emergent Period for the Previous Study Period

The treatment-emergent period for the Previous Study Period is the period on or after the first dose of study drug in the previous studies to 28 days after the last dose of the previous studies, or the last day of the Previous Study Period, or up to the first dose date in Study 110 (not including the first dose date in Study 110), whichever occurs first, for subjects dosed in Study 110.

For subjects not dosed in Study 110, the treatment-emergent period will be the period on or after the first dose of study drug in the previous studies to 28 days (inclusive) after the last dose of study drug in the previous studies or to the last day in the previous studies (inclusive), whichever occurs first.

9.1.2 Current Study Period

Current Study Period starts from the first dose date of study drug in Study 110 to the last day in Study 110.

Treatment-Emergent Period for the Current Study Period

The treatment-emergent period for the Current Study Period is the period on or after the first dose of study drug in Study 110 to 28 days (inclusive) after the last dose of study drug in Study 110 or up to the last day in Study 110, whichever occurs first.

9.1.3 Cumulative Study Period

Cumulative Study Period starts from the first dose of study drug in the parent studies (109 and 011B) to the last day in Study 110, regardless of whether there is 1) the planned 2-week washout period per Study 011B design; or 2) a Roll-Over Gap between the previous studies (Study 109 and Study 011B) and Study 110. For subjects not enrolled in Study 110, the Cumulative Study Period will be the same as the Previous Study Period.

Treatment-Emergent Period for the Cumulative Study Period

The treatment-emergent period for the Cumulative Study Period is the period on or after the first dose of study drug in the previous studies to 28 days (inclusive) after the last dose of study drug in Study 110, or up to the last day in Study 110, whichever occurs first. For subjects not enrolled in Study 110, the treatment-emergent period for the Cumulative Study Period will be the same as that of the Previous Study Period.

Handling of the data during the gap between previous studies (Study 109 and Study 011B) and the rollover study (Study 110)

There may be a Roll-Over Gap between the previous studies and the rollover study, defined as the time period between the Week 24 Visit of Study 109 or the Week 26 Visit of Study 011B and the date prior to the Day 1 Visit of Study 110. All analyses will be performed regardless of whether there is a Roll-Over Gap between the previous studies (Study 109 and Study 011B) and Study 110.

- This affects summary of the following possibly continuing events: 1) AEs; 2) CMs; and 3) Pulmonary Exacerbation related endpoints: Pulmonary Exacerbations, Pulmonary Exacerbations requiring hospitalizations (planned and unplanned), and Pulmonary Exacerbations requiring IV antibiotics.

  Events that happen during the Roll-Over Gap will be included in the Cumulative Study Period related analysis, but not necessarily in the analysis of the previous studies or the Current Study Period for Study 110. There are possible differences between results from Cumulative Study Period and combining results from previous studies and the Study 110.

- The Roll-Over Gap will not be considered in the derivation of the analysis window. The assessments will be selected per windowing rules specified for visits in Study 110 as described in Appendix D. The same set of selected records will be associated with different visit labels for different dosing periods.

9.2 Treatment Cohort Period 2

Treatment-Emergent Period for the Treatment Cohort Period 2

For Treatment Cohort Period 2 subjects, safety analysis will be based on the treatment-emergent period, which starts from the Study 110 Week 96 dose date +1, or Week 96 visit date +1,

whichever occurs later; up to 28 days (inclusive) after the last dose of this dosing period, or the last available date in Study 110 Treatment Cohort Period 2, whichever occurs first.

10 STATISTICAL ANALYSIS

10.1 General Considerations

In later sections, for analysis related to FAS, Safety Set, LCI Set [redacted] in Treatment Cohort Period 1, the population will not be limited to subjects in Treatment Cohort Period 1, regardless of the subtitle "Treatment Cohort Period 1". The analysis will strictly follow their definitions in Section 8 of the SAP.

For subjects in the Observational Cohort, summaries will only be provided for the disposition, demographic and baseline characteristics, and SAEs. Summaries will be provided based on all enrolled subjects in the Observational Cohort.

For subjects in the Treatment Cohort Period 2, summaries will only be provided for the disposition, demographics, AEs, SAEs, LFTs, and ophthalmologic examinations analyses.

The Schedule of Assessments is provided in Appendix A.

Treatment Cohort Period 1

For Treatment Cohort Period 1, all analyses will be provided using all available data, regardless of whether subjects turned 12 years of age and subsequently switched to the higher dose with LUM 400 mg q12h/IVA 250 mg q12h.

The efficacy and safety analysis for different Study Periods will be based on different analysis set as summarized in Table 10-1.

Table 10-1 Analysis of Efficacy and Safety Based on Different Analysis Set in Different Study Periods

Period	Efficacy				Safety
Previous/Cumulative Study Period	FAS	109 FAS	LCI Set	[redacted]	Safety Set
Current Study Period	110 FAS	109 ROS	110 LCI Set	[redacted]	110 Safety Set

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). Precisions of the summary for continuous variables are detailed in Table 13-4, Appendix B.

Categorical variables will be summarized using counts and percentages. Percentages will be presented to 1 decimal place.

Baseline: The baseline value of each Study Period for the Treatment Cohort Period 1 is defined as the most recent measurement (scheduled or unscheduled) before intake of the first dose of the corresponding Study Period, except if specified otherwise. These baselines are referred to as previous study baseline, current study baseline and cumulative study baseline.

- For LCI-related parameters, the values at each visit will be calculated based on the multiple replicates per the algorithm provided by the LCI central reader as detailed in Appendix C.

The baseline of LCI will be the most recent visit with non-missing value before the initial administration of study drug in the corresponding Study Period.

- For ECG, the baseline will be defined as the average of the 3 pretreatment measurements on the start of each Study Period.
- For sweat chloride, the values at each visit will be based on the averaged measurements from left and right arms.
  - The current study baseline will be the value at the most recent visit before the first dose of Study 110.
  - The previous study baseline and cumulative study baseline will be the baseline from the previous study, i.e., average of the values at screening and the pretreatment measurement on Day 1 from the previous studies. If only 1 sweat chloride measurement before the first dose is available, that measurement will be considered the baseline.

Absolute Change from baseline: will be calculated as Post baseline value - Baseline value.

Relative change from baseline: will be calculated and expressed in percentages as 100×(Post baseline value - Baseline value)/Baseline value.

Unscheduled Visits: Unscheduled visit measurements will be included in listings, for derivation of visit windows and computation of baseline/last on-treatment visit, and for the analysis of maximum/minimum values and maximum/minimum changes from baseline values.

Visit Windows: Table 13-5 defines the visit window mapping rules to derive the actual visits for the scheduled post-baseline measurements.

Repeated observations within the same visit window

- For all efficacy parameters, if there are multiple measurements within a visit window, the record at the scheduled visit will be used. If there are no measurements at the scheduled visit, then 1) the record closest to the target day will be used; or 2) if there are multiple records with the same distance to the target day, the latest record will be used.
- For all safety parameters, if there are multiple measurements within a visit window, then 1) the record closest to the target day will be used; or 2) if there are multiple records with the same distance to the target day, the latest record will be used.

BMI, weight, and height will follow safety and efficacy windowing rules. For predose spirometry, efficacy windowing rules will be applied. For postdose serial spirometry, analyses will be based on nominal assessment.

Incomplete/Missing data will not be imputed, unless otherwise specified; i.e., all missing values will remain as missing in all statistical analyses and listings, unless otherwise specified.

Outliers: No formal statistical analyses will be performed to detect and/or remedy the presence of statistical outliers.

Repeated Observations: Measurements recorded at different time points are defined as repeated observations. If an assessment has planned repeated measurements, then statistical summaries will present all planned time points, as appropriate.

10.1.1 Efficacy Analysis Presentation Rules and Format

Treatment Cohort Period 1

For all continuous efficacy variables, change from previous study baseline with two treatment groups: L200/I-L/I and P-L/I, will be summarized descriptively and using a mixed model repeated measure (MMRM) model. The presentation format is provided in Table 10-2. Descriptive summary of raw values and change from current study baseline for P-L/I will also be summarized in separate tables with one column.

Table 10-2 Continuous Efficacy Variable Summary Presentation Format

Summary statistics	109/011B and 110	
	L200/I-L/I	P-L/I
109/011B Baseline	xx	xx
109/011B Day 15	xx	xx
Change at 109/011B Day 15	xx	xx
…	…	…
109/011B Week 24	xx	xx
Change at 109/011B Week 24	xx	xx
110 Day 15	xx	xx
Change at 110 Day 15	xx	xx
…	…	…

10.1.2 Safety Analysis Presentation Rules and Format

10.1.2.1 Event Data

Treatment Cohort Period 1

Unless otherwise specified, incidence tables summarizing n and percentages for categorical safety data will be provided for:

- Previous Study Period (Studies 109/011B) based on the Safety Set with two treatment groups (L200/I, Placebo);
- Current Study Period (Study 110) based on the 110 Safety Set with two treatment groups (L200/I-L/I, P-L/I) and Overall;
- Cumulative Study Period based on Safety Set with L200/I-L/I, and Current Study Period based on 110 Safety Set with P-L/I, pooled together. The pooled treatment group is presented as L/I Overall.

Exposure-adjusted number of events will summarize number of events per 100 patient-year (100PY) for AE related safety data. Note: 1 patient with 48 weeks of exposure duration is defined as 1 patient-year (1PY). The exposure-adjusted number of events will be provided for the Study Periods with the analyses sets and treatment groups as defined above.

The categorical safety summary tables with incidence only will be presented in the table format as shown in Table 10-3. The categorical safety summary tables with both incidence and

exposure-adjusted number of events summaries will be presented in the table format as shown in Table 10-4.

Table 10-3 Presentation Format for Summary Tables of Categorical Safety Endpoints with Incidence Summary Only

109/011B		110			109/011B and 110
L200/I	Placebo	L200/I-L/I	P-L/I	Overall	L/I Overall

Table 10-4 Presentation Format for Summary Tables of Categorical Safety Endpoints with Both Incidence and Exposure-Adjusted Number of Events Summaries

109/011B				110						109/011B and 110	
L200/I		Placebo		L200/I-L/I		P-L/I		Overall		L/I Overall	
n (%)	Events/100PY	n (%)	Events/100PY	n (%)	Events/100PY	n (%)	Events/100PY	n (%)	Events/100PY	n (%)	Events/100PY

10.1.2.2 Continuous Variable

Treatment Cohort Period 1

For continuous variables, the raw values and change from previous study baseline will be summarized by treatment group (L200/I-L/I and P-L/I) based on Safety Set at each scheduled time point in the Cumulative Study Period. The presentation format is similar as the continuous efficacy variable summary in Table 10-2.

10.2 Background Characteristics

10.2.1 Subject Disposition

Treatment Cohort Period 1

Number of subjects in the following categories will be summarized and tabulated:

- 110 All Subjects Set
- 110 FAS
- 109 ROS
- Subjects enrolled in Treatment Cohort Period 1 but never dosed

The number and percentage of subjects in each of the following disposition categories in Study 110 Treatment Cohort Period 1 for the Current Study Period will be summarized with the number in 110 FAS as the denominator:

- Completed treatment in Treatment Cohort Period 1
- Prematurely discontinued the treatment and the reasons for discontinuations
    - Last completed scheduled on-treatment assessment

- Completed Study 110 Treatment Cohort Period 1
- Prematurely discontinued the study in Treatment Cohort Period 1 and the reasons for discontinuations

Subject disposition will be summarized similarly with the number of subjects in 110 Safety Set as denominator for the Current Study Period.

Disposition table will also be provided based on 110 LCI Set and 110 [redacted]. A separate table summarizing the following analysis population will also be provided:

- All Subjects Set
- Safety Set
- FAS
- 109 FAS
- LCI Set

[redacted]

- All Enrolled Subjects for Treatment Cohort Period 1

Subject enrollment by region, country and by site will be summarized in a separate table based on all subjects enrolled into Study 110 Treatment Cohort Period 1.

A listing will be provided for subjects who discontinued treatment or who discontinued Study 110 in Treatment Cohort Period 1 with reasons for discontinuation.

Observational Cohort

Number and percentage of subjects in the following categories will be summarized:

- Enrolled in Study 110 Observational Cohort (overall, by region, country and by site)
- Completed Long-term Follow-up Visits (telephone contacts)
- Prematurely discontinued the study during the Long-term Follow-up and the reasons for discontinuations

Treatment Cohort Period 2

The number and percentage of subjects in each of the following disposition categories in Study 110 Treatment Cohort Period 2 will be summarized with the number of subjects enrolled in Treatment Cohort Period 2 as the denominator.

- Enrolled in Study 110 Treatment Cohort Period 2 (overall and by site)
- Enrolled and dosed in Study 110 Treatment Cohort Period 2
- Enrolled in Study 110 Treatment Cohort Period 2 but never dosed
- Completed treatment in Treatment Cohort Period 2
- Prematurely discontinued the treatment in Treatment Cohort Period 2 and the reasons for discontinuations

- Completed Study 110 Treatment Cohort Period 2
- Prematurely discontinued the study in Treatment Cohort Period 2 and the reasons for discontinuations

A listing will be provided for subjects who discontinued treatment or who discontinued study in Treatment Cohort Period 2 with reasons for discontinuation.

10.2.2 Demographics and Baseline Characteristics

Treatment Cohort Period 1 and Observational Cohort

Demographic, baseline characteristics and medical history with respect to the previous studies will be summarized by treatment groups of the Current Study Period based on 110 FAS for Treatment Cohort Period 1, 110 Safety Set for Treatment Cohort Period 1, and based on Observational Cohort separately.

Demographics:

- Age (years)
- Age (< 9 years and ≥ 9 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 or Other Pacific Islander, Not collected per Local Regulation, and Other)
- Geographic region (North America, Europe, and Australia)

Characteristics of previous studies baseline (the summary below is the baseline summary unless otherwise specified):

- Weight (<25 kg and ≥25 kg)
- Weight (kg)
- Weight z-score
- Height (cm)
- Height z-score
- BMI (kg/m^2)
- BMI z-score
- Sweat Chloride
- $ppFEV_1$
- $ppFEV_1$ (<90, and ≥90)
- FEV_1 (L)
- Forced vital capacity (FVC, L)

- ppFVC (L)
- Forced expiratory flow, midexpiratory phase ($FEF_{25-75\%}$, L/sec)
- $ppFEF_{25-75\%}$
- FEV_1/FVC
- Percent predicted FEV_1/FVC
- Forced expiratory time (FET , sec)

[redacted]

- Received dornase alfa before first dose of study drug (Yes, No)
- Received any inhaled antibiotic before first dose of study drug (Yes, No)
- Received any inhaled bronchodilator before first dose of study drug
  - Yes [Short-Acting Only, Short-Acting and Long-Acting or Long-Acting only]
  - No
- Received any inhaled hypertonic saline before first dose of study drug (Yes, No)
- Received any inhaled corticosteroids before first dose of study drug (Yes, No)
- *Pseudomonas aeruginosa* status at baseline
  - Positive
    - Non-mucoid only
    - Mucoid only
    - Non-specific only
    - Non-mucoid and Mucoid
    - Non-mucoid and Non-specific
    - Mucoid and Non-specific
    - Non-mucoid and Mucoid and Non-specific
  - Negative

For Treatment Cohort Period 1, similar demographic and baseline characteristics tables will be provided based on the previous studies baseline for 110 LCI Set and 110 [redacted], with the following additional LCI related baseline summaries:

- $LCI_{2.5}$
- $LCI_{2.5}$ (<7.5 and ≥7.5)

- $LCI_{5.0}$
- Functional Residual Capacities (FRC)

Treatment Cohort Period 2

Demographic information of subjects enrolled into Treatment Cohort Period 2 will be summarized with respect to the previous studies with the following:

- Age (years)
- Age (< 9 years and ≥ 9 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 or Other Pacific Islander, Not collected per Local Regulation, and Other)

The important protocol deviation programming rules (based on the clinical database) are provided in Appendix I. Important protocol violations/deviations (based on the clinical database or from the site deviation log) will be summarized descriptively based on the 110 FAS. Important protocol deviations/violations will be provided as a subject data listing, indicating the source (clinical database versus site deviation log).

10.2.3 Prior and Concomitant Medications

Treatment Cohort Period 1

Medications used in this study will be coded by using the World Health Organization Drug Dictionary which is the Global dictionary that includes Enhanced and Herbal dictionaries (WHODD). Number and percentage of subjects with prior medication and concomitant medications will be summarized for the Previous Study Period based on the Safety Set, the Current Study Period based on 110 Safety Set, and the Cumulative Study Period based on the Safety Set, for the following:

- **Prior medication**: medication continued or newly received before the first dose of study drug in the previous study. The prior medication will be the same for Current Study Period and Cumulative Study Period.

Previous Study Period

- **Concomitant medication**: medication continued or newly received during the treatment-emergent period of the Previous Study Period.
- **Post-treatment medication**: any medication continued or newly received after the end of treatment-emergent period of the Previous Study Period. This is only defined for those subjects not dosed in Study 110.

Current Study Period

- **Concomitant medication**: medication continued or newly received during the treatment-emergent period of the Current Study Period.

- **Post-treatment medication**: any medication continued or newly received after the end of treatment-emergent period of the Current Study Period.

Cumulative Study Period

- **Concomitant medication**: medication continued or newly received during the treatment-emergent period of the Cumulative Study Period.
- **Post-treatment medication**: any medication continued or newly received after the end of treatment-emergent period of the Cumulative Study Period.

A given medication can be classified as a prior medication, a concomitant medication, or a post-treatment medication; both prior and concomitant; both concomitant and post-treatment; or prior, concomitant, and post-treatment. If a medication has a missing or partially missing start/end date or time and it cannot be determined whether it was taken before initial dosing, concomitantly, or more than 28 days after the last dose of study drug, it will be considered as prior, concomitant, and post-treatment.

Prior medications and concomitant medications will be summarized descriptively by preferred names. Concomitant medications with a frequency of ≥5% at the preferred name level in any treatment group will be summarized descriptively by preferred names. Post-treatment medications will be listed for each subject.

Details for imputing missing or partial start and/or stop dates of medication are described in Appendix E.

In addition, to evaluate whether the medications have stable use after receiving study drug, shifts from use prior to the first dose (Yes, No) in previous studies to use during the treatment-emergent period (chronic versus intermittent, intermittent will be further categorized as “no use” versus “Intermittent (Excluding No Use)”) will be summarized using number of subjects and percentages for the three Study Periods following Table 10-3 for the following medication categories:

- Inhaled antibiotics
- Inhaled bronchodilator
- Inhaled hypertonic saline
- Inhaled corticosteroids
- Dornase alfa

A medication is considered to be used chronically during the treatment-emergent period if it is used on ≥ 25% days during the treatment-emergent period; and is considered to be used intermittently (including no use) during the treatment-emergent period if it is used on <25% days during the treatment-emergent period.

10.2.4 Study Drug Exposure

Treatment Cohort Period 1

Study drug exposure will be summarized for the Previous Study Period based on Safety Set, for the Current Study Period based on 110 Safety Set, and for the Cumulative Study Period based on Safety Set.

Duration of exposure is defined as: last available dose date of the Study Period− first dose date of the same Study Period + 1 day, regardless of 1) unplanned interruptions, 2) the Roll-Over Gap between Previous Study and Study 110 and 3) the 2-week planned wash-out period for subjects from Study 011B for the summary of study drug exposure for the Cumulative Study Period. Duration/cumulative duration of study drug exposure will be summarized descriptively as a quantitative variable (number, mean, SD, SE, median, min, and max) for:

- Previous Study Period (Studies 109/011B) based on Safety Set with two treatment groups (L200/I, Placebo);
- Current Study Period (Study 110) based on 110 Safety Set with two treatment groups (L200/I-L/I, P-L/I) and Overall;
- Cumulative Study Period based on Safety Set with L200/I-L/I, and Current Study Period based on 110 Safety Set with P-L/I, pooled together. The pooled treatment group is presented as L/I Overall.

Additionally, the total duration of study drug exposure, defined as the sum of the subject's duration of treatment exposure and expressed in patient years, will be provided. Duration/cumulative duration of exposure will also be summarized as a categorical variable: ≥1 dose of study drug to <24 weeks, ≥24 to <48 weeks, ≥48 to <72 weeks, ≥72 to <96 weeks, ≥96 weeks to 120 weeks, and ≥120 weeks.

10.2.5 Study Drug Compliance

Treatment Cohort Period 1

Study drug compliance for each Study Period (the Previous Study Period, Current Study Period and Cumulative Study Period) in Treatment Cohort Period 1 will be calculated as follows respectively:

100 × [1 - (Total number of days study drug interrupted in a Study Period in Treatment Cohort Period 1) / (Duration of study drug exposure in the Study Period in Treatment Cohort Period 1+ Total number of days study drug interrupted after last dose in the Study Period in Treatment Cohort Period 1, if any)].

Note: A subject may have treatment interruption first, followed by permanent treatment discontinuation. In such cases, drug interruption would be after the last dose date of the corresponding Study Period.

The total number of days of study drug interrupted in a Study Period is defined as the sum of (number of days of study drug interrupted in each interval in the Study Period), where number of days of study drug interrupted in each interval in the Study Period is defined as the interruption end date - the corresponding interruption start date + 1.

Percent of tablets taken in Treatment Cohort Period 1 will be calculated as follows:

100 × (Total number of tablets administered in a Study Period in Treatment Cohort Period 1) / [4× (Duration of study drug exposure in days in the Study Period in Treatment Cohort Period

1+ Total number of days study drug interrupted after last dose in the Study Period in Treatment Cohort Period 1, if any)].

Subjects having calculated percent of tablets taken >100% will be considered as 100% in percent of tablets taken.

In calculating the total number of days study drug being interrupted, only the interruptions with duration of ≥3 days will be considered. An interruption with duration of < 3 days will not be considered in the calculation.

Treatment compliance and percent of tablets taken will be summarized descriptively (n; mean, SD, SE, median, min, and max in days) and will be tabulated for:

1) Previous Study Period based on Safety Set by treatment groups (L200/I and Placebo);

2) Current Study Period based on 110 Safety Set by treatment groups (L200/I-L/I and P-L/I) and Overall;

3) Cumulative Study Period based on Safety Set with L200/I-L/I, and Current Study Period based on 110 Safety Set with P-L/I, pooled together. The pooled treatment group is presented as L/I Overall.

A list of subjects with <80% compliance in Treatment Cohort Period 1 will be provided. The number and percentage of subjects whose compliance is <80% or ≥80% and the number and percentage of subjects whose percent of tablets taken is <80% or ≥80% in Treatment Cohort Period 1 will be summarized.

Treatment Cohort Period 2

Study drug compliance for Treatment Cohort Period 2 will be calculated as follows:

100 × [1 - (Total number of days study drug interrupted in Treatment Cohort Period 2) / (Duration of study drug exposure in Treatment Cohort Period 2 + Total number of days study drug interrupted after last dose in the Treatment Cohort Period 2, if any)].

Note: A subject may have treatment interruption first in Treatment Cohort Period 2, followed by permanent treatment discontinuation in Treatment Cohort Period 2. In such cases, drug interruption would be after the last dose date of the Treatment Cohort Period 2.

The total number of days of study drug interrupted in the Treatment Cohort Period 2 is defined as the sum of (number of days of study drug interrupted in each interval in the Treatment Cohort Period 2), where number of days of study drug interrupted in Treatment Cohort Period 2 is defined as the interruption end date - the interruption start date + 1.

In calculating the total number of days study drug being interrupted, only the interruptions with duration of ≥3 days will be considered. An interruption with duration of < 3 days will not be considered in the calculation.

Study drug compliance during the Treatment Cohort Period 2 will be listed.

10.3 Efficacy Analysis

10.3.1 Analysis of Primary Efficacy Endpoint

Not applicable.

10.3.2 Analysis of Secondary Efficacy Endpoints

The analysis of Secondary efficacy endpoints will be conducted for Treatment Cohort Period 1 only.

10.3.2.1 Definition of Secondary Efficacy Endpoints

10.3.2.1.1 Definition of Secondary Efficacy Endpoints

Absolute change from baseline in $LCI_{2.5}$

$LCI_{2.5}$ represents the number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value.

The LCI assessments are derived from N_2-multiple-breath washout (MBW) testing. Each MBW will be performed in multiple replicates at each visit and the final LCI value will be calculated from all the technically acceptable washout replicates, as determined by a central reader. The final LCI value at each visit will be the value calculated based on the multiple replicates per the algorithm provided by the LCI central reader as detailed in Appendix C.

Absolute change from baseline in sweat chloride

For each subject and at each time point, 2 sweat chloride measurements will be collected: 1 from the right arm, and 1 from left arm. Of the 2 measurements, only the sweat chloride value obtained from a sample volume ≥15 μL will be included in any analysis (i.e., values from samples with volumes <15 μL will be considered missing for analysis purposes). If a subject has replicated measurements at a post-baseline time point, then the median of the values will be used in data analyses. The sweat chloride results for the left and right arms will be averaged and used in the analysis if the sweat chloride values for the left and right arms are both ≥15 μL; if only 1 arm is ≥15 μL, then only that value will be used.

Note: Any sweat chloride values reported as <10 mmol/L or >160 mmol/L will be considered missing for analysis purposes.

Absolute change from baseline in BMI

BMI will be calculated as the following:

$$\text{BMI} = \text{Weight (kg)}/(\text{height (m)}^2)$$

Absolute change from baseline in CFQ-R respiratory domain

The CFQ-R[3,4,5] is a validated CF-specific instrument that measures quality-of-life domains. There are two different versions of CFQ-R forms in this study:

- CFQ-R Child Version has a total of 35 questions to form 8 domains. All questions are scored 1, 2, 3, or 4.
  - Interviewer Format for Children Ages 6 to 11
  - Self-completion for Children >=12 years of age after the Day 1 Visit of Study 110
- CFQ-R for Parents/Caregivers (subjects 13 years and younger) has a total of 44 questions to form 11 domains. Question 37 is scored 1, 2, 3, 4, or 5 and is not used in calculating any domains; all the other 43 questions are scored 1, 2, 3, or 4.

Note that subjects will complete the same version of the CFQ-R that was completed in the previous studies (Study 109 or Study 011B), regardless of whether the subject subsequently turns 14 years of age during the study.

For both CFQ-R versions, to calculate the score for each domain, the response scores on the negatively phrased questions are reversed (reversed scores = 5 – response scores). Therefore, 1 always represents the worst condition and 4 always represent the best condition. In each domain, in cases where individual questions were skipped, the missing scores are imputed with the mean score of the non-missing questions for that domain rounded to the nearest integer.

The scaled score for each domain ranges from 0 (worst condition) to 100 (best condition) and is calculated as follows:

$$\text{Scaled score for a domain} = 100 \times (\text{mean (scores of all questions in that domain)} - 1)/3$$

The scaled score for a specific domain will not be calculated if more than half of the questions in the domain have missing scores.

Table 10-5 and Table 10-6 provide the questions included in each domain, the questions with the reversed scores, as well as the maximum number of missing questions for the CFQ-R Child version and the CFQ-R Parents/Caregivers Version respectively.

Table 10-5 CFQ-R Child Version (Interview Format for Children Ages 6 to 11, and Self-completion for Children ≥ 12)

Domain	Questions		Reversed questions	Maximum number of missing questions
	Total	Individual		
Physical	6	1, 2, 3, 4, 5, 6	1, 2, 3, 4, 5	3
Emotion	8	7, 8, 9, 10, 11, 12, 13, 14	14	4
Social	7	20, 21, 22, 23, 24, 25, 26	20, 22, 24, 26	3
Body	3	27, 28, 29	-	1
Eat	3	15, 17, 19	19	1
Treatment burden	3	16, 18, 30	18	1
Respiration	4	31, 32, 33, 34	-	2
Digestion	1	35	-	0

Table 10-6 CFQ-R for Parents/Caregivers (Subjects 13 Years and Younger)

Domain	Questions		Reversed questions	Maximum number of missing questions
	Total	Individual		
Physical	9	1, 2, 3, 4, 5, 13, 14, 15, 16	15	4
Vitality	5	8, 9, 10, 11, 12	10, 12	2
Emotion	5	6, 7, 23, 25, 26	6	2
School	3	27, 28, 29	28	1
Body	3	19, 20, 21	-	1
Eat	2	17, 44	-	0
Treatment burden	3	18, 30, 31	31	1

Table 10-6 CFQ-R for Parents/Caregivers (Subjects 13 Years and Younger)

Domain	Questions		Reversed questions	Maximum number of missing questions
	Total	Individual		
Health perceptions	3	22, 24, 32	22, 24, 32	1
Weight	1	33	-	0
Respiration*	6	34, 35, 36, 38, 39, 40	37	3
Digestion	3	41, 42, 43	-	1

*: Question 37 not used to calculate a domain.

10.3.2.1.2 Definition of Other Secondary Efficacy Endpoints

Absolute change from baseline in $LCI_{5.0}$

$LCI_{5.0}$ represents the number of lung turnovers required to reduce the end tidal inert gas concentration to $1/20^{th}$ of its starting value.

As clarified with regard to $LCI_{2.5}$, each MBW will be performed in multiple replicates for each visit and the final LCI value will be calculated from the technically acceptable washout replicates by a central reader. The final LCI value at each visit will be the value provided by the LCI vendor based on the triplicates.

Absolute and relative change from baseline in $ppFEV_1$

$ppFEV_1$ is the ratio of FEV_1 (L) to the predicted FEV_1 (L), expressed as a percentage. The predicted FEV_1 will be calculated using the Wang[1] standards with details in Appendix F.

Relative change in $ppFEV_1$ is the ratio of absolute change in $ppFEV_1$ to baseline $ppFEV_1$.

Absolute change from baseline in BMI-for-age z-score

BMI, adjusted for age and sex, will be referred to as BMI-for-age z-score (BMI z-score). BMI z-score will be calculated by using Centers for Disease Control and Prevention (CDC) growth charts[6]. The BMI z-score will be calculated as follows:

$$z = \begin{cases} \dfrac{\left(\dfrac{X}{M}\right)^{L} - 1}{LS}, & L \neq 0 \\ \dfrac{\ln\left(\dfrac{X}{M}\right)}{S}, & L = 0 \end{cases}$$

Where X is the derived BMI value in kg/m^2 based on the raw weight and raw height and L, M, and S are selected from the CDC BMI-for-age chart by subject sex and age. The BMIAGE file contains these parameters by sex (1=male, 2=female) and age; it is available at: http://www.cdc.gov/growthcharts/percentile_data_files.htm. Additionally, SAS code for calculating percentiles and z-scores is available at: http://www.cdc.gov/growthcharts/computer_programs.htm.

NOTE: The CDC BMI-for-age charts are designed for use in pediatric populations (2 to 20 years of age).

Absolute change from baseline in weight and weight-for-age z-score

Weight, adjusted for age and sex, will be referred to as weight-for-age z-score (weight z-score). The calculation of weight z-score is similar to that of BMI z-score (using the CDC growth charts and the derivation described above). Using the same equation above, *X* in the equation is the collected weight and *L*, *M*, and *S* parameters are selected from the CDC weight-for-age chart. The WTAGE file contains these parameters by sex and age; it is available at the website http://www.cdc.gov/growthcharts/percentile_data_files.htm.

NOTE: The CDC growth charts are designed for use in pediatric populations (2 to 20 years of age).

Absolute change from baseline in height and height-for-age z-score

Height, adjusted for age and sex, will be referred to as height-for-age z-score (height z-score). The calculation of height z-score is similar to that of BMI z-score (using the CDC growth charts and the derivation described above). Using the same equation above, *X* in the equation is the collected height and *L*, *M*, and *S* parameters are selected from the CDC height-for-age chart. The STATAGE file contains these parameters by sex and age; it is available at the website http://www.cdc.gov/growthcharts/percentile_data_files.htm.

NOTE: The CDC growth charts are designed for use in pediatric populations (2 to 20 years of age).

Absolute change from baseline in TSQM domains

TSQM is a widely used generic measure of satisfaction with medication. It was developed from a published literature review of treatment satisfaction and qualitative research with patients with chronic illnesses. It was originally validated in a sample of patients with a variety of chronic conditions, but has been demonstrated to be a valid and reliable measure of treatment satisfaction in patients with CF. It consists of 14 items to form 4 domains: effectiveness (items 1, 2, 3), side effects (items 4, 5, 6, 7, 8), convenience (items 9, 10, 11), and global satisfaction (items 12, 13, 14).

The score of each domain is a scaled score ranges from 0 (least satisfied) to 100 (best satisfied) calculated as follows:

Score of a domain=100 × (mean (non-missing scores in the domain) - 1) / (mean (the greatest possible score of the non-missing items) - 1).

When the score of each domain is calculated, only one item may be missing from the domain for the domain to be considered valid.

For the side effect domain, if question 4 (As a result of taking this medication, do you experience any side effects at all?) is answered ‘No’, then the score of the side effect domain = 100. If question 4 is answered ‘Yes’, then the score of the side effect domain is calculated based on items 5, 6, 7, and 8 using the formula described above. The TSQM scoring manual is attached in Appendix G.

Pulmonary Exacerbation-related Endpoints

As specified in protocol Section 11.6.7.1, new or changed antibiotic therapy (IV, inhaled, or oral) for the following sinopulmonary signs/symptoms will be determined and documented at visits as indicated in Appendix A:

- Change in sputum
- New or increased hemoptysis
- Increased cough
- Increased dyspnea
- Malaise, fatigue, or lethargy
- Temperature above 38°C (equivalent to approximately 100.4°F)
- Anorexia or weight loss
- Sinus pain or tenderness
- Change in sinus discharge
- Change in physical examination of the chest
- Decrease in pulmonary function by 10%
- Radiographic changes indicative of pulmonary infection

For this study, pulmonary exacerbation is defined as a new or change in antibiotic therapy (IV, inhaled, or oral) for any 4 or more of the above signs/symptoms. This definition is based on the definition of a pulmonary exacerbation used in previous clinical studies, including ivacaftor clinical studies.

Pulmonary exacerbation related endpoints include:

- Number of pulmonary exacerbations
- Event of having at least 1 pulmonary exacerbation
- Time-to-first pulmonary exacerbation

Time-to-first pulmonary exacerbation is defined as days from the reference study drug initiation to the date of first pulmonary exacerbation. Subjects who do not experience any protocol-defined pulmonary exacerbation will be censored.

10.3.2.2 Analysis of Secondary Endpoints

10.3.2.2.1 Analysis of Secondary Endpoints

The analysis of secondary efficacy endpoints will be conducted for the Treatment Cohort Period 1 only.

Absolute change from baseline in $LCI_{2.5}$

The analysis for efficacy endpoints will be focused on within-group comparison and summaries. No between-groups comparisons will be performed.

For Treatment Cohort Period 1, the mixed model repeated measures (MMRM) analysis will be used for the Cumulative Study Period based on the FAS. It will include two treatment groups (L200/I-L/I and P-L/I) using baseline of the Previous Study Period.

The absolute change from previous study baseline (including all measurements at each visit, both on-treatment measurements and measurements after treatment discontinuation), will be included as the dependent variable; treatment group, visit, and treatment-by-visit interaction as fixed effects; and subject as a random effect with adjustment for previous studies (Study 109 versus Study 011B), weight (<25 kg versus ≥25 kg), and ppFEV$_1$ severity (<90 versus ≥90), both as determined at screening in the previous studies, and previous study baseline LCI$_{2.5}$ as a continuous variable.

In the model, visit will be treated as a class variable, and an unstructured covariance matrix will be assumed to model the within-subject variability. This model imposes no assumptions on the correlational structure and is considered robust. If there is a convergence problem due to the unstructured covariance matrix, the unstructured covariance matrix will be replaced by compound symmetry in the primary analysis. Denominator degrees of freedom for the *F*-test for fixed effects will be estimated using the Kenward-Roger approximation.[1] With a mixed-effects model as the primary analysis model based on restricted maximum likelihood estimation and assuming that conditional on fixed and random effects data are missing at random, no imputation of missing data will be done.

The result obtained from the model will be the treatment effect at each post baseline visit. The estimated mean within-group treatment effect, i.e., Least Square (LS) Means, SE, 95% CI, and a 2-sided within treatment group *P* value, will be provided. The LS means of absolute change from previous study baseline with 95% CI at each visit during the Cumulative Study Period will be plotted by treatment groups (L200/I-L/I and P-L/I).

Raw values and absolute change from previous study baseline, at each visit during the Cumulative Study Period, will be summarized in a separate table. Descriptive statistics, including number of subjects (n), mean, SD, SE, median, minimum, and maximum, will be provided.

In addition, descriptive summary statistics will be provided in a separate table for raw values and absolute change from current study baseline for P-L/I for visits in the Current Study Period using 110 FAS, including number of subjects (n), mean, SD, SE, median, minimum, and maximum along with the 95% CI based on Normal approximation.

Absolute change from baseline in sweat chloride

The analysis of sweat chloride will be similar to the MMRM analysis described above for LCI$_{2.5}$, with the absolute change from previous study baseline in sweat chloride at each visit as the dependent variable; and replacing the baseline LCI$_{2.5}$ with baseline sweat chloride of the previous studies as a continuous covariate. Figure for sweat chloride endpoints will be plotted similar to absolute change in LCI$_{2.5}$ above. Descriptive summary based on the current study baseline for P-L/I, similar to the summary of LCI$_{2.5}$, will be provided separately.

Absolute change from baseline in BMI and BMI-for-age Z-score

The analysis of BMI and BMI-for-age Z-score will be similar to the MMRM analysis described above for LCI$_{2.5}$, with the absolute change from previous study baseline in BMI or BMI-for-age z-score, respectively, at each visit as the dependent variable; and removing the continuous

covariate baseline $LCI_{2.5}$. Figure for BMI and BMI-for-age z-score will be plotted similar to absolute change in $LCI_{2.5}$ above. Descriptive summary based on the current study baseline for P-L/I, similar to the summary of $LCI_{2.5}$, will be provided separately.

Absolute change from baseline in CFQ-R respiratory domain

The analysis of CFQ-R respiratory domain will be similar to those specified for the MMRM analysis of $LCI_{2.5}$, with the absolute change from previous study baseline in CFQ-R respiratory domain score at each visit as the dependent variable; and replacing the baseline $LCI_{2.5}$ with baseline CFQ-R respiratory domain score of the previous studies as a continuous covariate. Figure for CFQ-R respiratory domain score will be plotted similar to absolute change in $LCI_{2.5}$ above. Descriptive summary based on the current study baseline for P-L/I, similar to the summary of $LCI_{2.5}$, will be provided separately.

10.3.2.2.2 Analysis of Other Secondary Endpoints

The analysis of other secondary endpoints will be conducted for Treatment Cohort Period 1 only.

Absolute change from baseline in $LCI_{5.0}$

The analysis of $LCI_{5.0}$ will be similar to those specified for the MMRM analysis of $LCI_{2.5}$, with the absolute change from previous study baseline in $LCI_{5.0}$ at each visit as the dependent variable; and replacing the baseline $LCI_{2.5}$ with baseline $LCI_{5.0}$ of the previous studies as a continuous covariate. Figure for absolute change from previous study baseline in $LCI_{5.0}$ will be plotted similar to absolute change in $LCI_{2.5}$ above. Descriptive summary based on the current study baseline for P-L/I, similar to the summary of $LCI_{2.5}$, will be provided separately.

Absolute/relative change from baseline in $ppFEV_1$

The analysis of $ppFEV_1$ will be similar to those specified for the MMRM analysis of $LCI_{2.5}$, with the absolute or relative change from previous study baseline in $ppFEV_1$ at each visit as the dependent variable, respectively; and removing the continuous covariate baseline $LCI_{2.5}$. Figure for absolute change from previous study baseline in $ppFEV_1$ will be plotted similar to absolute change in $LCI_{2.5}$ above. Descriptive summary based on the current study baseline for P-L/I, similar to the summary of $LCI_{2.5}$, will be provided separately.

Absolute change from baseline in body weight and weight-for-age-z-score

The analysis of body weight and weight-for-age z-score will be similar to the MMRM analysis described above for $LCI_{2.5}$, with the absolute change from previous study baseline in weight or weight-for-age z-score, respectively, at each visit as the dependent variable; and removing the continuous covariate baseline $LCI_{2.5}$. Figure for weight and weight-for-age Z-score will be plotted similar to absolute change in $LCI_{2.5}$ above. Descriptive summary based on the current study baseline for P-L/I, similar to the summary of $LCI_{2.5}$, will be provided separately.

Absolute change from baseline in height and height-for-age-z-score

The analysis of height and height-for-age Z-score will be similar to those specified for the MMRM analysis of $LCI_{2.5}$, with the absolute change from previous study baseline in height or height-for-age z-score, respectively, at each visit as the dependent variable; and replacing the baseline $LCI_{2.5}$ with baseline height or height-for-age z-score of the previous studies, respectively, as a continuous covariate. Figure for height and height-for-age Z-score will be

plotted similar to absolute change in $LCI_{2.5}$ above. Descriptive summary based on the current study baseline for P-L/I, similar to the summary of $LCI_{2.5}$, will be provided separately.

Absolute change from baseline in TSQM domains

For TSQM domains, the analysis will be similar to those specified for the MMRM analysis of $LCI_{2.5}$, with the absolute change from previous study baseline in each domain at each visit as the dependent variable; and replacing the baseline $LCI_{2.5}$ with domain baseline of the previous studies as a continuous covariate. Descriptive summary based on the current study baseline for P-L/I, similar to the summary of $LCI_{2.5}$, will be provided separately.

Number of pulmonary exacerbations (109 Subjects Only)

The number of pulmonary exacerbations will be analyzed using negative binomial regression model (PROC GENMOD) with two treatment groups: L200/I-L/I based on 109 FAS including events in the Cumulative Study Period, and P-L/I based on 109 ROS including events in the Current Study Period. All pulmonary exacerbation events in each corresponding Study Period will be included.

The model will include treatment (L200/I-L/I and P-L/I), weight (<25 kg and ≥25 kg) and $ppFEV_1$ severity at screening of the previous study (<90 versus ≥90). The log of time spent for each Study Period (end date of the Study Period – first dose date of the corresponding Study Period +1) in patient-years will be treated as the offset in this model.

The data during the placebo-controlled period for subjects randomized to the placebo group in Study 109 will be analyzed using a similar negative binomial regression model without the treatment in the model. Note the placebo rate might be slightly different from that estimated in Study 109 final CSR analyses, which included two arms (placebo and active) instead of the placebo arm only in this model.

The annualized (in 48 weeks) event rate of pulmonary exacerbation, defined as number of pulmonary exacerbations divided by total exposure in each study period, will be summarized and plotted using boxplot. In addition, number of events per patient-year with 95% CI from the model will be provided.

Time-to-first pulmonary exacerbation (109 Subjects Only)

Time-to-first pulmonary exacerbation will be analyzed and plotted using the estimates from Kaplan-Meier analysis (KM analysis) in two approaches:

- KM approach 1 includes two treatment groups: 1) L200/I-L/I based on 109 FAS including time-to-first event in the Cumulative Study Period; and 2) P-L/I based on 109 ROS including time-to-first event in the Current Study Period;
- KM approach 2 includes one treatment group, placebo, based on 109 FAS including time-to-first event in the Previous Study Period only.

Both on-treatment events and events after treatment discontinuation will be considered. For subjects enrolled in the Treatment Cohort Period 1 of Study 110, any subject without a pulmonary exacerbation before completion of the eligible analysis period will be considered censored at the end of the analysis period. For subjects not enrolled into the Study 110, any subject without a pulmonary exacerbation before withdrawal from Study 109 will be considered

censored at the time of withdrawal, and any subject who completes Study 109 without a pulmonary exacerbation will be considered censored at the last dose date in Study 109.

Event of having at least 1 pulmonary exacerbation (109 Subjects Only)

Number and percentage of subjects with at least one pulmonary exacerbation will be summarized for treatment groups: 1) L200/I-L/I based on 109 FAS including events in the Cumulative Study Period; and 2) P-L/I based on 109 ROS including events in the Current Study Period.

Number and percentage of subjects with at least one pulmonary exacerbation will also be summarized for Placebo based on 109 FAS including events in the Previous Study Period in a separate column.

Subjects who have no exacerbations through the end of the corresponding Study Period will be considered as having no event. A bar chart summarizing the percentage of subjects with at least one pulmonary exacerbation will be provided.

Rate of change in $LCI_{2.5}$, $LCI_{5.0}$ (Subjects from LCI Set Only) and $ppFEV_1$

Linear mixed-effects (LMM) analyses will be conducted to estimate the overall rate of change in $LCI_{2.5}$, $LCI_{5.0}$, and $ppFEV_1$ during the Cumulative Study Period based on the LCI Set or 110 LCI Set for LCI measurements and FAS or 110 FAS for $ppFEV_1$.

For analysis of the rate of change in $LCI_{2.5}$, the dependent variable will be postbaseline value and the model will include treatment groups as the fixed effect (Placebo and L/I Overall), random intercept and slope for treatment duration (in patient years) and interaction of treatment groups and treatment duration. Model will adjust for previous study (Study 109 versus Study 011B), weight (<25 kg versus ≥25 kg) and $ppFEV_1$ severity (<90 versus ≥90), both as determined at screening in the previous study; and adjust for previous study baseline $LCI_{2.5}$ as a continuous covariate. Rate of change in $LCI_{5.0}$ will be analyzed similarly.

For analysis of the rate of change in $ppFEV_1$, the analysis will be similar to those specified for the LMM analysis of $LCI_{2.5}$, with the postbaseline value of $ppFEV_1$ as dependent variable; and removing the baseline $LCI_{2.5}$ as the continuous covariate. For visits with both predose and postdose measurements, only predose measurements will be included.

In the LMM, measurements at and after Week 2 of Studies 109 or 011B for subjects randomized/enrolled in L200/I in Studies 109 or 011B, and measurements at and after Week 2 of Study 110 for subjects randomized in Placebo in Study 109, will be included to estimate the rate of change for L/I Overall; measurements at and after Week 2 up to Week 24 of Study 109 for subjects randomized in Placebo in Study 109 will be included to estimate the rate of change for Placebo. The rate of change will be reported as an annualized rate of change using patient years; 95% will also be provided.

10.3.2.3 Multiplicity Adjustment

This is a safety study. All efficacy/PD endpoints are secondary endpoints. No multiplicity adjustment will be implemented for these endpoints and the corresponding *P*-values generated for them will be nominal.

[redacted]

10.4 Safety Analysis

Treatment Cohort Period 1

Evaluating safety of long-term treatment with lumacaftor in combination with ivacaftor in the Treatment Cohort Period 1 is the primary objective of this study. The overall safety profile of study drug will be assessed in terms of the following safety and tolerability endpoints:

- Adverse events
- Clinical laboratory values (hematology, serum chemistry, coagulation studies, and urinalysis)
- Standard digital electrocardiograms (ECGs)
- Vital signs
- Pulse oximetry
- Ophthalmological examinations
- Spirometry

Only descriptive analysis of safety will be performed (i.e., no statistical testing will be performed).

10.4.1 Adverse Events

Observational Cohort

For the Observational Cohort, a listing will be presented for all SAEs.

Treatment Cohort Period 1

For Treatment Cohort Period 1, TEAEs will be summarized following the presentation format in Section 10.1.2.1, Table 10-3.

1) Previous Study Period based on Safety Set by treatment groups (L200/I and Placebo);

2) Current Study Period based on 110 Safety Set by treatment groups (L200/I-L/I and P-L/I) and Overall;

3) Cumulative Study Period based on Safety Set with L200/I-L/I, and Current Study Period based on 110 Safety Set with P-L/I, pooled together. The pooled treatment group is presented as L/I Overall.

In TEAE summaries, number and percentage of subjects, as well as exposure-adjusted number of events, will be provided.

For analysis purposes, AEs will be classified as pretreatment AEs, TEAEs, or post-treatment AEs.

- **Pretreatment AE:** any AE that started in the pre-treatment period. The pre-treatment AE will be the same for Previous Study Period and Cumulative Study Period.
- **TEAE:** any AE that increased in severity or that was newly developed in the treatment-emergent period.
- **Post-treatment AE:** any AE that increased in severity or that was newly developed in the post-treatment period.

For AEs with missing or partial start dates, if there is no clear evidence that the AEs started before or after study treatment, then the AEs will be classified as TEAEs. Details regarding handling rules of missing dates are included in Appendix J.

An overview table of the TEAE profile for Treatment Cohort Period 1 will be provided, including total number of TEAEs, with number and percent of subjects and exposure-adjusted number of events in 100PY for the following categories:

- All TEAEs
- Grade 3/4 TEAEs
- TEAEs by relationship
- TEAEs by maximum severity
- TEAEs leading to treatment interruption
- TEAEs leading to treatment discontinuation

- Serious TEAEs
- Related serious TEAEs
- TEAE leading to death

Adverse events summary tables will be presented for the aforementioned TEAEs. The summary will be presented by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT) using frequency counts, percentages (i.e., number and percentage of subjects with one or more events) and exposure-adjusted number of events (i.e., number of events per 100PY). When summarizing the number and percentages of subjects, subjects with multiple occurrences of the same adverse event or a continuing adverse event will be counted once, and only the maximum severity level will be presented in the severity summaries, and the worst/highest relationship level in the relationship summaries.

Additional summary tables will be presented for TEAEs showing number and percentage of subjects, as well as exposure-adjusted number of events per 100PY:

- Any TEAE by PT
- TEAE with a frequency of ≥5% at the PT level in any treatment group by PT

For subjects in Study 110 exposed to LUM 400 mg q12h/IVA 250 mg q12h, an overview of the TEAE profile summarizing TEAEs occurring during the treatment-emergent period will be provided, [redacted]

In addition, a listing containing individual subject adverse event data for TEAEs leading to treatment interruption, TEAEs leading to treatment discontinuation, SAEs and all deaths will be provided separately, with a flag indicating the TEAE status for SAEs and deaths.

Analysis of AEs of special interest (AESI) categories:

The following AESIs are defined:

1. Elevated Transaminases

   The AESI of elevated transaminases is defined by the AEs whose PTs falls into any of the following:

   - Alanine aminotransferase abnormal
   - Alanine aminotransferase increased
   - Aspartate aminotransferase abnormal
   - Aspartate aminotransferase increased
   - Transaminases abnormal
   - Transaminases increased
   - Liver function test abnormal
   - Liver function test increased

- Hypertransaminasaemia
- Hepatic enzyme increased
- Hepatic enzyme abnormal

2. Respiratory Symptom AESI

   The respiratory symptoms AESI is defined by the AEs whose PTs fall into any of the following:

   - Chest Discomfort
   - Dyspnoea
   - Respiration abnormal

3. Respiratory events AESI

   The respiratory event AESI is defined by the AEs whose PTs fall into any of the following:

   - Asthma
   - Bronchial hyperreactivity
   - Bronchospasm
   - Chest Discomfort
   - Dyspnoea
   - Respiration abnormal
   - Wheezing

Treatment-emergent AESIs will be summarized

- Showing number and percentage of subjects by PT;
- Showing number and percentage of subjects by maximum severity;
- Summary of duration of events (days) with descriptive summary;
- Summary of time-to-first onset (relative to first dose date);
- Showing number and percentage of subjects with 1) TEAE leading to treatment interruption; 2) TEAE leading to treatment discontinuation; 3) serious TEAEs; 4) related serious TEAEs; and 5) TEAE leading to death.

[redacted]

Treatment Cohort Period 2

For Treatment Cohort Period 2, AEs will be classified as TEAEs or post-treatment AEs.

- **TEAE:** any AE that increased in severity or that was newly developed in the treatment-emergent period of Treatment Cohort Period 2.
- **Post-treatment AE:** any AE that increased in severity or that was newly developed in the post-treatment period of Treatment Cohort Period 2.

For AEs with missing or partial start dates, if there is no clear evidence that the AEs started before or after study treatment, then the AEs will be classified as TEAEs. Details regarding handling rules of missing dates are included in Appendix J.

An overview table of the TEAE profile will be provided, including total number of TEAEs, with number and percent of subjects in Treatment Cohort Period 2 for the following categories:

- All TEAEs
- Grade 3/4 TEAEs
- TEAEs by relationship
- TEAEs by maximum severity
- TEAEs leading to treatment interruption
- TEAEs leading to treatment discontinuation
- Serious TEAEs
- Related serious TEAEs
- TEAE leading to death

TEAE tables summarizing number and percentage of subjects with one or more events by SOC and PT will be provided for the following:

- All TEAEs
- Serious TEAEs

When summarizing the number and percentages of subjects, subjects with multiple occurrences of the same adverse event or a continuing adverse event will be counted once, and only the maximum severity level will be presented in the severity summaries, and the worst/highest relationship level in the relationship summaries.

In addition, a listing containing individual subject adverse event data for all AEs, TEAEs leading to treatment interruption, TEAEs leading to treatment discontinuation, and SAEs will be provided separately, with a flag indicating the TEAE status for AEs and SAEs listings.

10.4.2 Clinical Laboratory

Treatment Cohort Period 1

For the laboratory measurements, the raw values and change from previous study baseline of the continuous hematology and chemistry results will be summarized in System International (SI) units at each scheduled time point in the Cumulative Study Period based on the Safety Set.

The number and percentage of subjects meeting the defined threshold criteria during the treatment-emergent period will be summarized. The threshold criteria are provided in Appendix H. For LFT results (alanine aminotransferase [ALT], aspartate aminotransferase [AST], serum alkaline phosphatase [ALP], and total bilirubin), the following analyses will be conducted:

- The mean values (95% CI) will be plotted against visit for all the visits in the Cumulative Study Period for ALT and AST.

- A listing for subjects with elevated LFT results during the treatment-emergent period of the Cumulative Study Period will be presented. The listing will include all parameters of the LFT assessment at all visits.

The number and percentage of subjects with shift changes from baseline in ALT, AST, ALP and total bilirubin (normal/missing, high, low, according to the reference range), based on the worst on-treatment laboratory evaluation, will be tabulated.

Results of urinalysis and the serum pregnancy test will be listed in individual subject data listings only. A listing containing individual subject hematology, chemistry, and coagulation values will be provided with a column indicating outside reference range or not. This listing will include data from scheduled and unscheduled time points.

Treatment Cohort Period 2

For Treatment Cohort Period 2 LFT results (ALT, AST, ALP, and total bilirubin), the following analyses will be conducted:

- The number and percentage of subjects meeting the defined threshold criteria during the treatment-emergent period of Treatment Cohort Period 2 will be summarized. The threshold criteria are provided in Appendix H.
- A listing for subjects with all LFT results during the treatment-emergent period of the Treatment Cohort Period 2 will be presented. The listing will include all parameters of the LFT assessment at all visits.

Results of urine pregnancy test will be listed in individual subject data listing.

10.4.3 Standard Digital ECG

Treatment Cohort Period 1

For the ECG measurements, a summary of raw values and change from previous study baseline will be provided at each scheduled time point in the Cumulative Study Period based on the Safety Set for the following standard digital ECG measurements: PR, QT, and QT corrected for HR (QTc) intervals (Fridericia's correction [$QTcF = QT/RR^{1/3}$]), QRS duration, and HR. In addition, the mean QTcF values will be plotted against visits in the Cumulative Study Period.

The number and percentage of subjects meeting at least one threshold analysis criterion during the treatment-emergent period will be summarized following the presentation format in Section 10.1.2. The threshold analysis criteria are provided in Appendix H. The number and percentage of subjects with heart rate (bpm) < 40, < 50 and >90 will be summarized. A listing containing individual subject ECG measurements including all parameters and assessments at all visits will be provided. A separate listing of subjects meeting at least 1 threshold analysis criterion during the treatment-emergent period will also be presented.

The number and percentage of subjects with shift changes from baseline, based on the worst on-treatment overall ECG evaluation, will be tabulated.

10.4.4 Vital Signs

Treatment Cohort Period 1

For the vital signs measurements, the raw values and change from previous study baseline values will be summarized at each scheduled time point in the Cumulative Study Period based on the Safety Set: systolic and diastolic blood pressure (mm Hg), body temperature (^{o}C), HR (beats per minute), respiratory rate (breaths per minute), weight (kg), height(m) and BMI (kg/m^2).

The number and percentage of subjects meeting at least 1 threshold analysis criterion during the treatment-emergent period will be provided following the presentation format in Section 10.1.2. The threshold criteria are provided in Appendix H. A listing containing individual subject vital signs measurements including all parameters and assessments at all visits will be provided.

In addition, number and percentage of subjects for the following categories during the treat-emergent period will be summarized.

Table 10-7 Additional Vital Signs Categorical Analyses

Meeting criteria	SBP (mmHg)	DBP (mmHg)	Heart rate (bpm)
For at least once	>140	>90	<40
	>140 and >10 increase from baseline	>90 and >5 increase from baseline	<50
	>140 and >20 increase from baseline	>90 and >10 increase from baseline	>90
	>10 increase from baseline	>5 increase from baseline	
	>20 increase from baseline	>10 increase from baseline	
	>120	>80	
For at least twice	>140	>90	
	>120	>80	

Number and percentage of subjects with SBP >120 mmHg at each visit and those with DBP > 80 mmHg at each visit in the Cumulative Study Period will be provided.

Potentially abnormal SBP and DBP by their percentiles adjusted for sex, age and height will be provided, including

- Number and percentage of subjects with categories ≥90%-<95%, ≥95%-<99% + 5 mmHg and ≥99% + 5 mmHg)
- Number and percentage of subjects with SBP and DBP percentiles ≥95% once and twice during the treatment-emergent period will be provided.
- Number and percentage of subjects with SBP and DBP percentiles ≥95% at each visit will also be provided.

The height adjustment will be based on height-for-age-z-scores and their corresponding percentiles using the standard normal distribution. The height percentiles will be further mapped per the following rules:

Table 10-8 Grouped Percentiles for Height-for-age Z-scores

Calculated Percentiles (%)	Grouped Percentiles (%)
0 – <7.5	5
7.5 – <17.5	10
17.5 – <37.5	25
37.5 – <62.5	50
62.5 – <82.5	75
82.5 – <92.5	90
92.5 – 100	95

The sex and age-adjusted normal range for SBP and DBP for each grouped height percentiles is based on the SBP/DBP table in Appendix K per the National Heart, Lung, and Blood Institute (NHLBI) website (http://www.nhlbi.nih.gov/health-pro/guidelines/current/hypertension-pediatric-jnc-4/blood-pressure-tables). A listing of subjects with potentially abnormal SBP or DBP will be provided.

10.4.5 Pulse Oximetry

Treatment Cohort Period 1

The raw values and change from previous study baseline in percent of oxygen saturation measurements at each scheduled time point during the Cumulative Study Period will be summarized with two treatment groups: L200/I-L/I and P-L/I based on the Safety Set. In addition, the mean value at each visit will be plotted for the percent of oxygen saturation.

The number and percentage of subjects with shift changes from previous study baseline (normal/missing and low according to the reference range) to the lowest percent of oxygen saturation during the treatment-emergent period will be tabulated following the safety presentation format in Section 10.1.2.

10.4.6 Ophthalmological Examinations

Treatment Cohort Period 1

For the analysis of slit lamp lens, the number and percentage of subjects with shift changes from previous study baseline (normal versus abnormal) will be tabulated for the Previous Study Period based on the Safety Set, Current Study Period based on 110 Safety Set, and Cumulative Study Period based on the Safety Set at each scheduled time point following the safety presentation format in Section 10.1.2. Ophthalmological examination findings will also be presented as a data listing.

Treatment Cohort Period 2

Ophthalmological examination findings in Treatment Cohort Period 2 will be presented as a data listing.

10.4.7 Physical Examination

Physical examination findings will be presented as a data listing for Cumulative Study Period in Treatment Cohort Period 1.

10.4.8 Spirometry

Treatment Cohort Period 1

Analysis of Predose Spirometry at Each Postdose Visit

Spirometry data will be summarized descriptively as safety-supporting data at each visit during the Cumulative Study Period by treatment group (L200/I-L/I and P-L/I) based on the Safety Set. The following summary (number and percentage of subjects) will be provided:

- Absolute change from previous study baseline in predose $ppFEV_1 \leq -5$ percentage points
- Absolute change from previous study baseline in predose $ppFEV_1 \leq -10$ percentage points
- Relative change from previous study baseline in predose $ppFEV_1 \leq -5$ %
- Relative change from previous study baseline in predose $ppFEV_1 \leq -10$ %
- Absolute change from previous study baseline in predose $FEV_1 \leq -0.05$L
- Absolute change from previous study baseline in predose $FEV_1 \leq -0.10$L
- Relative change from previous study baseline in predose $FEV_1 \leq -5$%
- Relative change from previous study baseline in predose $FEV_1 \leq -10$%

Subjects with ≥5 percentage points decrease in absolute change from previous study baseline in $ppFEV_1$ or ≥0.05 L decrease in absolute change from previous study baseline in FEV_1 at any visit during the Cumulative Study Period will be listed based on the Safety Set. The listing will include raw values and absolute/relative changes from previous study baseline in $ppFEV_1$ and FEV_1 at all visits during the Cumulative Study Period.

Analysis of Serial Spirometry

Based on the 110 Safety Set for the Current Study Period, raw values and absolute change from predose assessment in postdose $ppFEV_1$ and FEV_1 will be summarized by visit and by time point. The number and percentage of subjects with ≥5, ≥10, ≥15, and ≥20 percentage points decrease in the absolute change from predose to postdose in $ppFEV_1$ will also be summarized by visit and time point.

The summary tables will include two treatment groups (L200/I-L/I and P-L/I). For treatment L200/I-L/I, separate summaries will also be provided by previous studies (Study 109 and 011B). For both of the summaries, the mean values along with the 95% CIs based on Normal approximation will be plotted against visits and time points.

10.5 Narratives Listings

Narratives listings will be provided for subjects with any of the following events that occurred by the study cutoff date in the Cumulative Study Period of Treatment Cohort Period 1 and the study cutoff date of the Treatment Cohort Period 2 separately.

- Death
- Serious AEs
- TEAEs leading to treatment discontinuation
- Pregnancy
- LFT elevations meeting at least 1 of the following criteria:
  - ALT or AST >5xULN (regardless of total bilirubin) during the treatment-emergent period
  - ALT or AST >3xULN and total bilirubin >2xULN during the treatment-emergent period

11 INTERIM AND DMC ANALYSES

11.1 Interim Analysis

Two Interim Analysis (IAs) were conducted:

1. IA1 (Study 011B subjects only): Data cut as of 01 Aug 2016, when all subjects from Study 011B have completed 24 weeks of treatment in Study 110.
2. IA2 (Study 109 and Study 011B subjects): Data cut as of 03 Apr 2017, when all subjects have completed the 24 weeks of treatment in Study 110.

Details of the interim analysis were described in the separate IA SAPs.

11.2 DMC Analysis

An independent data monitoring committee (DMC) was formed using the [redacted].

Safety and tolerability data was reviewed by the independent DMC to ensure the safety of the subjects in the study based on the same data cut used for IA2. Procedural details of the independent DMC's structure and function and data planned for review is outlined in the independent DMC charter. The statistical analysis methodology was specified in the IA2 SAP, which was used as a substitute for the DMC SAP because the DMC analyses were similar to the IA2 safety analyses. DMC charter and IA2 SAP were finalized before the DMC review meeting.

12 REFERENCES

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13 APPENDICES

Appendix A Schedule of Assessments

Schedules of Assessments are shown in Table 13-1 (Treatment Cohort Period 1), Table 13-2, (optional Treatment Cohort Period 2), and Table 13-3 (Observational Cohort). All visits are to be scheduled relative to the Day 1 Visit (first dose of study drug). For example, the Week 8 (± 1 week) Visit would occur after 8 weeks of study drug administration has been completed (i.e., Day 57, first day of Week 9).

Table 13-1 Study VX15-809-110: Treatment Cohort Period 1

Event/Assessment[a]	Treatment Period								Early Treatment Termination Visit[d,e]	Safety Follow-up Visit (4 weeks [± 7 days] After Last Dose)[d,e]
	Day 1[b]	Day 3 (± 1 day)	Day 15 (± 3 days) and Week 4 (± 1 week)	Week 8, Week 16, Week 24, Week 36, Week 48 (± 1 week)	Week 12, Week 20 (± 1 week)	Week 60 Week 84 (± 1 week)	Week 72 (± 1 week)	Week 96[c] (± 1 week)		
Clinic visit	X		X	X	X[f,g]	X	X	X	X	X
Telephone contact[h]		X			X[g,i]					

[a] All assessments will be performed before study drug dosing unless noted otherwise (Protocol Section 11.1).

[b] The Day 1 Visit of Study 110 will be on the **same day** as the Week 24 Visit (last Treatment Period visit) of Study 109 or the Week 26 Visit (Safety Follow-up Visit) of Study 011B for subjects at Study 110 sites that have been activated by the time the Week 24 Visit (Study 109) or the Week 26 Visit (Study 011B) has been completed. Subjects at these active sites will NOT have to repeat any Study 110 Day 1 assessments that were specified to be performed at the Week 24 Visit (Study 109) or the Week 26 Visit (Study 011B). Subjects at these active sites may return within 1 calendar day to complete the remaining Day 1 assessments (including administration of the Day 1 dose for subjects who receive the last Study 109 dose at the Week 24 Visit [see Protocol Section 10.2]) specific to Study 110. If study drug administration occurs when a subject returns the following calendar day, predose vital sign and spirometry assessments must be repeated before dosing. Subjects who were enrolled but had Day 1 study drug administration procedures (Protocol Section 10.2) delayed more than 1 calendar day will have to repeat all assessments (with the exception of the ophthalmologic examination if performed within the last 3 months before) that were specified to be performed at the Day 1 visit before receiving their first dose of study drug. The Day 1 Visit of Study 110 **will NOT coincide** with the Week 24 Visit (last Treatment Period visit) of Study 109 or the Week 26 Visit (Safety Follow-up Visit) of Study 011B for subjects at Study 110 sites that have NOT been activated by the time the Week 24 Visit (Study 109) or the Week 26 Visit (Study 011B) has been completed. Subjects at these nonactive sites will have to repeat any Study 110 Day 1 assessments (in addition to completing Study 110-specific Day 1 events/assessments) that were specified to be performed at the Week 24 Visit (Study 109) or the Week 26 Visit (Study 011B) except for the ophthalmologic examination (if the ophthalmologic examination was performed within the last 3 months before the visit).

[c] For subjects 6 through 11 years of age who elect to enter Treatment Cohort Period 2, the Week 96 visit will also serve as the first study visit for the optional Treatment Cohort Period 2.

[d] Subjects who prematurely discontinue study drug treatment during the Treatment Cohort Period 1 in Study 110 will be asked to complete the Early Treatment Termination Visit and the Safety Follow-up Visit (Protocol Section 8.1.1.3). The Early Treatment Termination Visit should be scheduled as soon as possible after the subject decides to terminate study treatment. If the Early Treatment Termination Visit occurs 3 weeks or later following the last dose of study drug, then the Safety Follow-up Visit will replace the Early Treatment Termination Visit (i.e., the assessments performed will be those specified for the Safety Follow-up Visit in Table 13-1), and an Early Treatment Termination Visit will not be required. Subjects who enter Treatment Cohort Period 2 do not need to complete the Safety Follow-up Visit.

[e] With the exception of [redacted] subjects who cannot access the commercial product after regulatory approval because reimbursement by the subject's insurance carrier (whether government or private payer) is not yet available or because the subject lacks insurance coverage, subjects who become eligible to receive commercially-available LUM/IVA by prescription of a physician may be discontinued from study drug dosing and will complete the Early Treatment Termination Visit (before commercially-available LUM/IVA dosing begins). The Safety Follow-up Visit will not be required if the subject immediately continues on commercially-available LUM/IVA.

[f] LFTs (ALT, AST, GGT, ALP, and total bilirubin) will be performed at these visits. Although blood samples are to be collected and analyzed at a central laboratory, a local laboratory may be used if a subject cannot return to the clinical study site for the blood draw (Protocol Section 11.7.3).

[g] A urine pregnancy test will be performed for all female subjects of childbearing potential before the Week 12 and Week 20 telephone contacts, and the results made available before the contact. The urine pregnancy test may be performed at home or at the site.

[h] Telephone contacts will be made to assess the subject's status, any AEs, concomitant medications, treatments, and procedures.

Table 13-1 Study VX15-809-110: Treatment Cohort Period 1

Event/Assessment[a]	Treatment Period								Early Treatment Termination Visit[d,e]	Safety Follow-up Visit (4 weeks [± 7 days] After Last Dose)[d,e]
	Day 1[b]	Day 3 (± 1 day)	Day 15 (± 3 days) and Week 4 (± 1 week)	Week 8, Week 16, Week 24, Week 36, Week 48 (± 1 week)	Week 12, Week 20 (± 1 week)	Week 60 Week 84 (± 1 week)	Week 72 (± 1 week)	Week 96[c] (± 1 week)		
Informed consent (and assent, if applicable)	X									
Inclusion/exclusion criteria review	X									
Urine β-hCG[j,k]	X		X	X	X[g]	X	X	X	X	X
CFQ-R[l]	X		X	Weeks 16, 24, 48				X	X[m]	X
TSQM[l]	X		X	Weeks 16, 24, 48				X	X[m]	X
Height and weight[n]	X		X	X		X	X	X	X	X
Vital signs[o]	X		X	X		X	X	X	X	X
Pulse oximetry[o]	X		X	X		X	X	X	X	X

i If a subject returns to the site for the Week 12 and/or Week 20 laboratory assessments, assessment of the subject's status, any AEs, concomitant medications, treatments, and procedures may be done in the clinic and telephone contact will not be required.

j Pregnancy tests will be performed for all female subjects who are of childbearing potential from the time of the Day 1 Visit or at any point through the Safety Follow-up Visit (Protocol Section 11.7.8).

k See Protocol Section 11.7.2 for details.

l All questionnaires should be completed before the start of any other assessments. The CFQ-R (Protocol Section 11.6.5) should be completed first, followed by the TSQM (Protocol Section 11.6.6).

m Subjects will need to complete the questionnaires at the Early Treatment Termination Visit if it has been 2 weeks or more since they last completed the questionnaire.

n Height and weight will be measured before study drug dosing with shoes off (Protocol Section 11.6.4). BMI will be derived from this assessment.

o Vital signs and pulse oximetry will be collected before study drug dosing after the subject has been at rest (seated or supine) for at least 5 minutes (Protocol Section 11.7.4).

Table 13-1 Study VX15-809-110: Treatment Cohort Period 1

Event/Assessment[a]	Treatment Period								Early Treatment Termination Visit[d,e]	Safety Follow-up Visit (4 weeks [± 7 days] After Last Dose)[d,e]
	Day 1[b]	Day 3 (± 1 day)	Day 15 (± 3 days) and Week 4 (± 1 week)	Week 8, Week 16, Week 24, Week 36, Week 48 (± 1 week)	Week 12, Week 20 (± 1 week)	Week 60 Week 84 (± 1 week)	Week 72 (± 1 week)	Week 96[c] (± 1 week)		
Ophthalmologic examination[p]	X			Week 48[q]				X[q,r]	X[q,r]	X[q,r]
Full physical examination[s]	X							X	X	X
Standard 12-lead ECG[t]	X[u]		X	Weeks 8, 16, 24, 48			X	X	X	X
Serum β-hCG[j,k]	X									
Serum chemistry[k,v]	X		X	X	X[f,w] LFTs only	X[f,w] LFTs only	X	X	X	X
Hematology[k]	X		X	X			X	X	X	X
Coagulation studies[k]	X		X	Weeks 16, 24, 48				X		X
Urinalysis[k]	X			Weeks 16, 24, 48				X		X

p An ophthalmologic examination will be conducted by a licensed ophthalmologist or optometrist (Protocol Section 11.7.6). Subjects with documentation of bilateral lens removal do not need the ophthalmologic examination. If a cataract or lens opacity is identified and determined to be clinically significant by a licensed ophthalmologist or optometrist at the Day 1 examination (also see Footnote b), the subject will be notified. After discussion with the site principal investigator and in collaboration with the Vertex medical monitor, the subject may elect to participate or not to participate in the study. If the subject continues in the study, more frequent ophthalmologic monitoring should be considered. If a cataract or lens opacity is identified and determined to be clinically significant by a licensed ophthalmologist or optometrist after dosing, the subject will be notified. After discussion with the site principal investigator, and in collaboration with the Vertex medical monitor, the subject may elect to continue or discontinue the study. If the subject discontinues study drug, they should complete the Early Treatment Termination Visit and Safety Follow-up Visit (see Protocol Section 8.1.1.3 for Early Treatment Termination). If the subject continues, more frequent ophthalmologic monitoring should be considered.

q Subjects may complete the ophthalmologic examination within ± 1 week of the scheduled visit.

r An ophthalmologic examination will be conducted by a licensed ophthalmologist or optometrist at the Week 96 Visit (or the Early Treatment Termination Visit if the subject does not have a Week 96 Visit) OR the Safety Follow-up Visit (Protocol Section 11.7.6). Subjects with documentation of bilateral lens removal do not need the ophthalmologic examination.

s Symptom-directed physical examinations will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator (Protocol Section 11.7.4).

t All standard 12-lead ECGs will be performed before study drug dosing and after the subject has been seated or supine for at least 5 minutes (Protocol Section 11.7.5). The ECG will be performed before any other procedures that may affect heart rate (e.g., blood draws).

u ECGs collected on Day 1 before study drug dosing will be performed in triplicate.

v LFTs (ALT, AST, GGT, ALP, and total bilirubin) must be performed at the scheduled visits and every 4 weeks (± 1 week) in between scheduled visits through Week 24 (Weeks 12 and 20) (Protocol Section 11.7.3). After this point, LFTs will be collected at subsequent scheduled clinic visits (Weeks 24, 36, 48, 60, 72, 84, and 96). Although blood samples are to be collected and analyzed at a central laboratory, a local laboratory may be used if a subject cannot return to the clinical study site for the blood draw.

w The liver function testing at Weeks 12, 20, 60, and 84 may be completed pre- or postdose.

Table 13-1 Study VX15-809-110: Treatment Cohort Period 1

Event/Assessment[a]	Treatment Period								Early Treatment Termination Visit[d,e]	Safety Follow-up Visit (4 weeks [± 7 days] After Last Dose)[d,e]
	Day 1[b]	Day 3 (± 1 day)	Day 15 (± 3 days) and Week 4 (± 1 week)	Week 8, Week 16, Week 24, Week 36, Week 48 (± 1 week)	Week 12, Week 20 (± 1 week)	Week 60 Week 84 (± 1 week)	Week 72 (± 1 week)	Week 96[c] (± 1 week)		
[redacted]										
Sweat chloride[z]	X		X	Week 24				X	X	
Lung clearance index (subjects from Study 109 and the Study 011B LCI Substudy only)[aa]	X		X	Weeks 24, 48				X	X	
Spirometry[bb]	X[cc]		X[cc]	X		X	X	X	X	X
Other events related to outcome (subjects from Study 109 only)[dd]	X		X	X		X	X	X	X	

[redacted]

z Sweat collection will be done approximately at the same time as predose blood collections (Protocol Section 11.6.2).

aa The LCI assessment will be performed pre-bronchodilator and before study drug dosing (Protocol Section 11.6.1). The assessment will be performed in triplicate and before the spirometry assessment.

bb Spirometry will be performed pre-bronchodilator for all spirometry assessments and before study drug dosing unless noted otherwise (Protocol Section 11.6.3).

cc On Days 1 and 15, spirometry will be performed before study drug dosing and at 2 hours (± 30 minutes) and 4 hours (± 30 minutes) postdose (Protocol Section 11.6.3).

dd Other events related to outcome include assessments relating to pulmonary exacerbations, administration of antibiotic therapy for sinopulmonary signs or symptoms, and hospitalizations (Protocol Section 11.6.7)

Table 13-1 Study VX15-809-110: Treatment Cohort Period 1

Event/Assessment[a]	Treatment Period								Early Treatment Termination Visit[d,e]	Safety Follow-up Visit (4 weeks [± 7 days] After Last Dose)[d,e]
	Day 1[b]	Day 3 (± 1 day)	Day 15 (± 3 days) and Week 4 (± 1 week)	Week 8, Week 16, Week 24, Week 36, Week 48 (± 1 week)	Week 12, Week 20 (± 1 week)	Week 60 Week 84 (± 1 week)	Week 72 (± 1 week)	Week 96[c] (± 1 week)		
[redacted]										
Meal(s) or snack(s) at site[gg]	X		X	X		X	X	X		
Study drug dosing[hh,gg]	**LUM 200 mg q12h/IVA 250 mg q12h OR LUM 400 mg q12h/IVA 250 mg q12h[ii]**									
Observation 4 hours after the first dose	X									
Study drug count			X	X		X	X	X		
Concomitant medications	**Continuous, from signing of ICF (and assent form, if applicable) through Safety Follow-up Visit**									
Concomitant treatments and procedures	**Continuous, from signing of ICF (and assent form, if applicable) through Safety Follow-up Visit**									
AEs and SAEs[jj]	**Continuous, from signing of ICF (and assent form, if applicable) through Safety Follow-up Visit**									

AE: adverse event; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; β-hCG: beta-human chorionic gonadotropin; BMI: body mass index; CF: cystic fibrosis; CFQ-R: CF Questionnaire-Revised; [redacted]; ECG: electrocardiogram; GGT: gamma glutamyl transpeptidase; ICF: informed consent form; IEC: independent ethics committee; IRB: institutional review board; [redacted]; IVA: ivacaftor; LCI: lung clearance index; LFT: liver function test; LUM: lumacaftor; [redacted]; q12h: every 12 hours; SAE: serious adverse event; TSQM: Treatment Satisfaction Questionnaire for Medication.

[redacted]

gg Fat-containing food such as a standard CF high-fat, high-calorie meal or snack (Protocol Section 10.2) will be provided at the site to subjects after all predose assessments have occurred.

hh The study drug should be administered every 12 hours (± 2 hours) within 30 minutes of consuming fat-containing food (Protocol Section 10.2). On days of scheduled visits, the dose of study drug will be administered at the site after predose assessments have been completed. The last dose of study drug will be administered at the Week 96 Visit.

ii Subjects who turn 12 years of age in the previous study or Day 1 of this rollover study will begin receiving LUM 400 mg q12h/IVA 250 mg q12h on Day 1. Subjects who turn 12 years of age after the Day 1 Visit of this rollover study will begin receiving LUM 400 mg q12h/IVA 250 mg q12h at their next scheduled visit.

jj SAEs that occur after the Safety Follow-up Visit and are considered related to study drug(s) will be reported to Vertex GPS **within 24 hours** as described in Protocol Section 13.1.2.2.

Table 13-2 Study VX15-809-110: Optional Treatment Cohort Period 2

Event/Assessment[a]	Treatment Period[b] **Week 108 (± 1 week) Week 120 (± 1 week) Week 132 (± 1 week) Week 144 (± 1 week) Week 156 (± 1 week) Week 168 (± 1 week)**	**Early Treatment Termination Visit[c]**
Clinic visit	X	X
Urine β-hCG (all female subjects of childbearing potential from the time of the Day 1 Visit or at any point through the Safety Follow-up Visit (Protocol Sections 11.7.2and 11.7.8)	X Week 168 only	X
Vital signs[d]	X Week 168 only	X
Full physical examination[e]	X Week 168 only	X
Ophthalmologic examination[f]	X Week 168 only	X
Serum chemistry; LFTs only (ALT, AST, GGT, ALP, and total bilirubin)	X Weeks 144 and 168 only	X
Study drug dosing[g]	**LUM 200 mg q12h/IVA 250 mg q12h**	
Study drug count	X	X
AEs and SAEs[h]	**Continuous, from signing of ICF (and assent form, if applicable) through end of study**	

[a] All assessments will be performed before study drug dosing unless noted otherwise (Protocol Section 11.1). Data from unscheduled assessments may be evaluated by Vertex.

[b] Week 96 is the first visit for subjects 6 through 11 years of age who complete Treatment Cohort Period 1 and elect to enter Treatment Cohort Period 2 (Table 13-1).

[c] Subjects who prematurely discontinue study drug treatment will be asked to complete the Early Treatment Termination Visit. The Early Treatment Termination Visit should be scheduled as soon as possible after the subject decides to terminate study treatment.

[d] Vital signs will be collected before study drug dosing after the subject has been at rest (seated or supine) for at least 5 minutes (Protocol Section 11.7.4).

[e] Symptom-directed physical examinations will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator or health care provider (Protocol Section 11.7.4).

[f] An ophthalmologic examination will be conducted by a licensed ophthalmologist or optometrist (Protocol Section 11.7.6). Subjects with documentation of bilateral lens removal do not need the ophthalmologic examination. If a cataract or lens opacity is identified and determined to be clinically significant by a licensed ophthalmologist or optometrist at the Week 96 (Treatment Cohort Period 1) examination (also see Footnote b), the subject will be notified. After discussion with the site principal investigator, the subject may elect to continue or discontinue the study. If the subject discontinues study drug, they should complete the Early Treatment Termination Visit (Protocol Section 8.1.1.3). If the subject continues, more frequent ophthalmologic monitoring should be considered.

[g] The study drug should be administered every 12 hours (± 2 hours) within 30 minutes of consuming fat-containing food (Protocol Section 10.2). On days of scheduled visits, the dose of study drug will be administered at the site after predose assessments have been completed. The last dose of study drug will be administered at the Week168 Visit.

[h] SAEs that occur after the ETT Visit and are considered related to study drug(s) will be reported to Vertex GPS **within 24 hours** as described in Protocol Section 13.1.2.2.

Table 13-3 Study VX15-809-110: Observational Cohort

Event/Assessment	Day 1[a]	Long-term Follow-up	
		Approximately Every 3 to 4 Months for the First Year	Approximately 2 Years (± 4 weeks)
Clinic visit	X		
Telephone contact		X	X
Informed consent/assent	X		
Inclusion criteria review	X		
Serious adverse events	**Continuous, from signing of ICF (and assent form, if applicable) through the last telephone contact**		

ICF: informed consent form.

[a] The Day 1 Visit of Study 110 will be on the **same day** as the Week 24 Visit (last Treatment Period visit) of Study 109 or the Week 26 Visit (Safety Follow-up Visit) of Study 011B for subjects at Study 110 sites that have been activated by the time the Week 24 Visit (Study 109) or the Week 26 Visit (Study 011B) has been completed. Subjects at these active sites will NOT have to repeat any Study 110 Day 1 assessments that were specified to be performed at the Week 24 Visit (Study 109) or the Week 26 Visit (Study 011B). The Day 1 Visit of Study 110 **will NOT coincide** with the Week 24 Visit (last Treatment Period visit) of Study 109 or the Week 26 Visit (Safety Follow-up Visit) of Study 011B for subjects at Study 110 sites that have NOT been activated by the time the Week 24 Visit (Study 109) or the Week 26 Visit (Study 011B) has been completed. Subjects at these nonactive sites will have to repeat any Study 110 Day 1 assessments (in addition to completing Study 110-specific Day 1 events/assessments) that were specified to be performed at the Week 24 Visit (Study 109) or the Week 26 Visit (Study 011B).

Appendix B Precisions of Summary for Continuous Variables

Table 13-4 Precision of Special Summary Statistics for Continuous Variables in CF Studies

Variables	Statistics	Decimal Places
Percent Predicted FEV_1	Mean, LS mean, 95% CI	1
FEV_1 (L)	Mean, LS mean, 95% CI	3
CFQ-R	Mean, LS mean, 95% CI	1
Sweat Chloride (mmol/L)	Mean, LS mean, 95% CI	1
BMI (kg/m^2)	Mean, LS mean, 95% CI	2
Weight (kg)	Mean, LS mean, 95% CI	1
Normalized days with event	Mean	1
Number of events	Event rate	2
LCI	Mean, LS mean, 95% CI	1

The precision of the Safety Lab Data will follow the latest standard from the Biometrics Standardization Committee.

The precision of the measurement in raw data for other continuous variables will be used to determine the number of decimal places to present in tables, figures, and derived listings. Minimum and maximum values will be reported with the same precision as the units of measure. The mean, median, SD and SE will be reported to 1 greater decimal place.

Any values that require transformation to standard units (metric or SI) will be converted with the appropriate corresponding precision.

Categorical Variables: Percentages will be presented to 1 decimal place.

Appendix D Analysis Visit Window Mapping Rules for Efficacy and Safety Measurements

Table 13-5 Visit Window Mapping Rules for Study 110 Visits

Assessments	Study 110 Visit	Target Study Day	Visit Window (in Study Days)
• Spirometry (see special handling below) • Weight and height • Vital Signs • Pulse Oximetry	110 Day 15	15	(1, 22]
	110 Week 4	29	[23, 43]
	110 Week 8	57	[44, 85]
	110 Week 16	113	[86, 141]
	110 Week 24	169	[142, 211]
	110 Week 36	253	[212, 295]
	110 Week 48	337	[296, 379]
	110 Week 60	421	[380, 463]
	110 Week 72	505	[464, 547]
	110 Week 84	589	[548, 631]
	110 Week 96	673	[632, 687]
	110 Follow-up	701	Nominal Visit
• Labs ○ Chemistry (Except LFT) ○ Hematology	110 Day 15	15	(1, 22]
	110 Week 4	29	[23, 43]
	110 Week 8	57	[44, 85]
	110 Week 16	113	[86, 141]
	110 Week 24	169	[142, 211]
	110 Week 36	253	[212, 295]
	110 Week 48	337	[296, 421]
	110 Week 72	505	[422, 589]
	110 Week 96	673	[590, 687]
	110 Follow-up	701	Nominal Visit
• Chemistry (LFT)	110 Day 15	15	(1, 22]
	110 Week 4	29	[23, 43]
	110 Week 8	57	[44, 71]
	110 Week 12	85	[72, 99]
	110 Week 16	113	[100, 127]
	110 Week 20	141	[128, 155]
	110 Week 24	169	[156, 211]
	110 Week 36	253	[212, 295]
	110 Week 48	337	[296, 379]
	110 Week 60	421	[380, 463]
	110 Week 72	505	[464, 547]
	110 Week 84	589	[548, 631]
	110 Week 96	673	[632, 687]
	110 Follow-up	701	Nominal Visit
• Coagulation • CFQR, TSQM	110 Day 15	15	(1, 22]
	110 Week 4	29	[23, 71]
	110 Week 16	113	[72, 141]

• TSQM	110 Week 24	169	[142, 253]
• TSQM	110 Week 48	337	[254, 505]
	110 Week 96	673	[506, 687]
	110 Follow-up	701	Nominal Visit
• Urinalysis (including urine microscopy)	110 Week 16	113	(1, 141]
	110 Week 24	169	[142, 253]
	110 Week 48	337	[254, 505]
	110 Week 96	673	[506, 687]
	110 Follow-up	701	Nominal Visit
• Ophthalmologic examination	110 Week 48	337	[254, 505]
	110 Week 96	673	[506, 687]
	110 Follow-up	701	Nominal Visit
• Standard ECG	110 Day 15	15	(1, 22]
	110 Week 4	29	[23, 43]
	110 Week 8	57	[44, 85]
	110 Week 16	113	[86, 141]
	110 Week 24	169	[142, 253]
	110 Week 48	337	[254, 421]
	110 Week 72	505	[422, 589]
	110 Week 96	673	[590, 687]
	110 Follow-up	701	Nominal Visit
• Sweat Chloride	110 Day 15	15	(1, 22]
	110 Week 4	29	[23, 99]
	110 Week 24	169	[100, 421]
	110 Week 96	673	[422, 687]
• LCI	110 Day 15	15	(1, 22]
	110 Week 4	29	[23, 99]
	110 Week 24	169	[100, 253]
	110 Week 48	337	[254, 505]
	110 Week 96	673	[506, 687]

Special handling for spirometry assessments:

- For serial spirometry, 110 Day 1 pre-/post-dose and 110 Day 15 pre-/post-dose measurements by hour, assign analysis visit = nominal visit.
- For the 110 Week 4 visit, the window will be (study day of 110 Day 15 visit, 43), where the spirometry post the 110 Day 15 nominal serial spirometry will be considered in the window of 110 Week 4 visit.
- For the other post-dose visits on or after 110 Week 8, visit window approach will be applied. No 110 Day 1 post-dose and 110 Day 15 pre-/post-dose measurements will be remapped to derive the other post-dose visits on or after 110 Week 8.

Appendix E Imputation Rules for Missing Prior/Concomitant Medication Dates

The following rules will be applied for every treatment-emergent period:

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

- Missing or partial medication start date:
  - If only DAY is missing, use the first day of the month.
  - If DAY and Month are both missing, use the first day of the year.
  - If DAY, Month and Year are all missing, use a date before the first dose date.
- Missing or partial medication stop date:
  - If only DAY is missing, use the last day of the month.
  - If DAY and Month are both missing, use the last day of the year.
  - If DAY, Month and year are all missing, leave the stop date as missing; the medication will be considered 'continuing' at the study exit.

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

Table 13-6 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 Treatment-Emergent Period**	**> End Date of Treatment-Emergent Period**
< First dose date of study drug	P	PC	PCA
≥ First dose date and ≤ End date of Treatment-Emergent period	-	C	CA
> End date of Treatment-Emergent period	-	-	A

A: Post; C: Concomitant; P: Prior

Appendix F Coefficients for 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[1] and Wang[2] standards.

The Wang standard applies to male subjects 6 to 17 years and female subjects 6 to 15 years of age. Wang's standard will be used to calculate the predicted spirometry parameters for the population enrolled in to this study.

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

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

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 subject's sex, race, and age as shown in Table 13-7 and Table 13-8.

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 13-7 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

Source: Reference 1 (Tables 2 and 3)

Table 13-8 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

Source: Reference 2 (Tables 4 and 5)

Appendix H Criteria for Threshold Analysis

Table 13-9 Threshold Analysis Criteria for Laboratory Tests

Parameter	Threshold Analysis	Comments
Clinical Chemistry		
ALT	≤3xULN >3x - ≤ 5xULN >5x - ≤ 8xULN >3xULN >5xULN >8xULN	FDA DILI Guidance Jul 2009.
AST	≤3xULN >3x - ≤ 5xULN >5x - ≤ 8xULN >3xULN >5xULN >8xULN	FDA DILI Guidance Jul 2009.
ALT or AST	ALT>3xULN or AST>3xULN	Vertex LFT working group 2014
Alkaline Phosphatase	>1.5xULN	FDA DILI Guidance Jul 2009.
Total Bilirubin	>1.5x - ≤2xULN >2xULN	FDA DILI Guidance Jul 2009.
ALT and Total Bilirubin	ALT>3xULN and TBILI>2xULN	FDA DILI Guidance Jul 2009. To be counted within a same treatment phase, whatever the interval between measurement.
AST and Total Bilirubin	AST>3xULN and TBILI>2xULN	FDA DILI Guidance Jul 2009. To be counted within a same treatment phase, whatever the interval between measurement.
(ALT or AST) and Total Bilirubin	(ALT>3xULN or AST>3xULN) and TBILI>2×ULN	Vertex LFT working group 2014
CPK	>3x - ≤ 10xULN >10xULN	FDA Feb 2005. Am J Cardiol April 2006.
Creatinine	≥150 µmol/L (Adults) ≥30% change from baseline ≥100% change from baseline	Benichou C., 1994.
Creatinine Clearance (Cokcroft's formula)	<30 ml/min (severe renal impairment) ≥30 - <50 ml/min (moderate renal impairment) ≥50 - ≤80 ml/min (mild renal impairment)	FDA criteria May 1998.
Uric Acid Hypouricemia Hyperuricemia	 <120 µmol/L >408 µmol/L	Harrison- Principles of internal Medicine 17th Ed., 2008.
Blood Urea Nitrogen	≥17 mmol/L	
Chloride	<85 mmol/L >115 mmol/L	
Sodium	≤129 mmol/L ≥150 mmol/L	

Table 13-9 Threshold Analysis Criteria for Laboratory Tests

Parameter	Threshold Analysis	Comments
Potassium	<3 mmol/L ≥5.5 mmol/L	FDA Feb 2005.
Total Cholesterol	≥7.74 mmol/L	Threshold for therapeutic intervention.
Triglycerides	≥4.6 mmol/L	Threshold for therapeutic intervention.
Glucose		
Hypoglycaemia	≤3.9 mmol/L and <LLN	ADA May 2005.
Hyperglycaemia	≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted)	ADA Jan 2008.
HbA1c	>8%	
Albumin	≤25 g/L	
CRP	>2xULN or >10 mg/L (if ULN not provided)	FDA Sept 2005.
Hematology		
WBC	<3.0 Giga/L (Non-Black); <2.0 Giga/L (Black) ≥16.0 Giga/L	Increase in WBC: not relevant. To be interpreted only if no differential count available.
Lymphocytes	>4.0 Giga/L	
Neutrophils	<1.5 Giga/L (Non-Black);<1.0 Giga/L (Black)	International Consensus meeting on drug-induced blood cytopenias, 1991. FDA criteria.
Monocytes	>0.7 Giga/L	
Basophils	>0.1 Giga/L	
Eosinophils	>0.5 Giga/L or >ULN (if ULN≥0.5 Giga/L)	Harrison- Principles of internal Medicine 17th Ed., 2008.
Hemoglobin	≤115 g/L (Male); ≤95 g/L (Female) ≥185 g/L (Male); ≥165 g/L (Female) Decrease from Baseline ≥20 g/L	Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).
Hematocrit	≤0.37 v/v (Male) ; ≤0.32 v/v (Female) ≥0.55 v/v (Male) ; ≥0.5 v/v (Female)	
RBC	≥6 Tera/L	
Platelets	<100 Giga/L ≥700 Giga/L	International Consensus meeting on drug-induced blood cytopenias, 1991.

Table 13-10 Threshold Analysis Criteria for ECGs

CRITERIA for THRESHOLD ANALYSIS of ECGs Ref.: CPMP 1997 guideline.		
Parameter	**Threshold Analysis**	**Comments**
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	
PR	≥220 ms and increase from baseline ≥20 ms	
QRS	≥120 ms	
QTc Borderline Prolonged* Additional	Absolute values (ms) Borderline: 431-450 ms (Male); 451-470 ms (Female) Prolonged: >450 ms (Male); >470 ms (Female) ≥500 ms Increase from baseline Borderline: Increase from baseline 30-60 ms Prolonged: Increase from baseline >60 ms	To be applied to any kind of QT correction formula.

Table 13-11 Threshold Analysis Criteria for Vital Signs

CRITERIA for THRESHOLD ANALYSIS of VITAL SIGNS		
Parameter	**Threshold Analysis**	**Comments**
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Orthostatic Hypotension Orthostatic SBP Orthostatic DBP	 ≤-20 mmHg ≤-10 mmHg	
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.

Appendix I Important Protocol Deviation Programming Rules (Based on the Clinical Database)

Important protocol deviations during the Treatment Period for Treatment Cohort Period 1

- Compliance < 80% during the Treatment Cohort Period 1 of Study 110.

Important protocol deviations during the Treatment Period for Treatment Cohort Period 2

- Compliance < 80% during the Treatment Cohort Period 2 of Study 110.

Appendix J Handling of Missing Dates in Adverse Events for Each Treatment-emergent Period

For AEs with missing or partial start dates, if there is no clear evidence that the AEs started before the corresponding study period as appropriate, then the AEs will be classified as TEAEs.

As an intermediate step for programming purpose, imputation rules for missing or partially missing AE start/end dates are defined below.

If Year of AE start date is missing:

If year of the AE start date is missing, then 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.

If Year of AE start date is not missing:

If both day and month of the AE start date are missing:

- If year of the AE start date = the year of the first dose date, impute the missing day and month of the AE start date using the day and month of the first dose date. If this leads to a date after the AE end date, then impute the missing day and month of the AE start date using the day and month of the AE end date. Note:
  - If the AE ended before first dose date, then the AE will be classified as a pre-treatment AE. If the AE ended after the first dose date, then there is not enough evidence to determine whether the AE is a TEAE or not, and to be conservative, the AE will be classified as a TEAE.
- If year of the AE start date ≠ the year of the first dose date, impute the missing day and month of the AE start date using the 1 and Jan.
  - If the year is before the year of the first dose date, then by imputing the missing day and month of the AE start date January 1, TEAE status will be pre-treatment.
  - If the year is after the year of the first dose date, then by imputing the missing day and month of the AE start date January 1, TEAE status will be TEAE if AE start date is on or before the last dose date +28 days; and will be post-treatment AE start date is after the last dose date+28 days.

If only day of the AE start date is missing:

- If the year of the AE start date = the year of the first dose date = the year of the AE end date, and the month of the AE start date = the month of the first dose date = the month of the AE end date, then impute the missing day of AE start date using the smaller non-missing value of (day of the first dose, day of the AE end date).
- If (the year of the AE start date = the year of the first dose date), and (the month of the AE start date = the month of the first dose date), and (the year of the AE start date < the year of the AE end date, or the month of the AE start date < the month of the AE end date), then impute the missing day of AE start date using the day of the first dose.

- If (the year of the AE start date = the year of the first dose date), and (the month of the AE start date = the month of the first dose date), and the AE is ongoing, then impute the missing day of AE start date using the day of the first dose.
- Otherwise, impute the missing day of the AE start date as 1.

Missing or partially missing AE stop date will not be imputed.