Protocol CTX-4430-CF-201

A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety, and Tolerability of CTX-4430 Administered Orally Once-Daily for 48 Weeks in Adult Patients with Cystic Fibrosis

Statistical Analysis Plan

Prepared for:
Celtaxsys

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Prepared by:

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VERSION HISTORY OF IMPLEMENTED PLANS

Version	Date	Revision Author	Comments
1.0	6 June 2018	██████████	Final Version
2.0	15 June 2018	██████████	Updated window convention for Week 48 and Week 52. Change done prior to unblinding.

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1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1: Abbreviations and Definitions of Terms

AE	adverse event
ANOVA	analysis of variance
BMI	body mass index
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire - Revised
CFTR	cystic fibrosis transmembrane regulator
CFU	colony forming unit
CI	confidence interval
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
FAP	Full Analysis Population
$FEF_{25-75\%}$	forced expiratory flow during the middle portion of the forced vital capacity
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
HIV	human immunodeficiency virus
HRQOL	health-related quality of life
hs-CRP	high-sensitivity C-reactive protein
ICF	informed consent form
IDMC	Independent Data Monitoring Committee
IP	investigational product
IWRS	interactive Web randomization system
LOCF	last observation carried forward
LTA4H	leukotriene A4 hydrolase
LTB4	leukotriene B4
PK	pharmacokinetic
PP	Per-protocol Population
SAE	serious adverse event
SD	standard deviation
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
WBC	white blood cell

2. INTRODUCTION

This document presents the statistical analysis plan (SAP) for Celtaxsys Protocol CTX-4430-CF-201: A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety, and Tolerability of CTX-4430 Administered Orally Once-Daily for 48 Weeks in Adult Patients with Cystic Fibrosis.

Cystic fibrosis (CF) is one of the most important causes of chronic pulmonary disease. About 70,000 individuals are affected by CF worldwide.[1] CF pathology is characterized by a cycle of infection, inflammation, and airway obstruction.

Leukotriene B4 (LTB4) is a powerful attractant and activator of inflammatory immune cells, particularly neutrophils. CF lung disease is characterized by significant neutrophilic infiltrates in the small airways and elevation of LTB4 in the airways.[2,3] In destructive pulmonary diseases such as CF, inhibition of LTB4 production has the potential to reduce both neutrophil influx and release of damaging neutrophil-derived enzymes such as elastase.[4,5]

CTX-4430 is a novel synthetic, small-molecule, LTA4H inhibitor being developed to address the underlying pulmonary inflammation in CF by reducing LTB4 production.

This analysis plan is based on the final protocol Version 5.0 Amendment 4 dated 04MAY2016.

The SAP provides the description of the analysis for the final analyses.

3. STUDY OBJECTIVES

The primary objectives of this study are:

- To evaluate the safety and tolerability of CTX-4430 administered orally once-daily to CF subjects for 48 weeks

- To evaluate the efficacy of CTX-4430 administered orally once-daily to CF subjects for 48 weeks as determined by the absolute change from Baseline in FEV_1 (forced expiratory volume in 1 second) percent predicted.

The secondary objectives of this study are:

- To evaluate the efficacy of CTX-4430 administered orally once-daily to CF subjects for 48 weeks as determined by the relative change from Baseline in FEV_1 percent predicted

- To evaluate the effect of CTX-4430 administered orally once-daily to CF subjects for 48 weeks on forced vital capacity (FVC) percent predicted and forced expiratory flow during the middle portion of the forced vital capacity ($FEF_{25-75\%}$) percent predicted

- To evaluate the effect of CTX-4430 administered orally once-daily to CF subjects for 48 weeks on time to first pulmonary exacerbation while in the study

- To evaluate the effect of CTX-4430 administered orally once-daily to CF subjects for 48 weeks on the number of pulmonary exacerbations

- To evaluate the effect of CTX-4430 administered orally once-daily to CF subjects for 48 weeks on specified biomarkers (sputum deoxyribonucleic acid [DNA] and elastase and serum high-sensitivity C-reactive protein [hs-CRP]).

The exploratory objectives of this study are:

- To evaluate the effect of CTX-4430 administered orally once-daily to CF subjects for 48 weeks on sputum bacterial density

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- To evaluate the change from Baseline in subject's health-related quality of life (HRQOL) while on CTX-4430 administered orally once daily for 48 weeks as measured by the Cystic Fibrosis Questionnaire - Revised (CFQ-R).

4. STUDY DESIGN

4.1 General Design

This study is a Phase 2, double-blind, randomized, placebo-controlled, parallel-group, multicenter study to evaluate the safety and efficacy of CTX-4430 administered once-daily for 48 weeks for treatment of CF. A total of 195 pulmonary CF subjects who meet all the inclusion and no exclusion criteria and provide written informed consent will be randomized to receive 50 mg CTX-4430, 100 mg CTX-4430, or placebo in a 1:1:1 ratio for 48 weeks.

Subjects will be screened to assess eligibility criteria within 21 days before Baseline (first dose of investigational product [IP]). At the screening visit, subjects will consent to participation in the study and all study procedures by signing the study informed consent form (ICF). Upon determination that a subject meets all inclusion and no exclusion criteria, the subject will be randomized at Baseline to the treatment assignment via an interactive Web randomization system (IWRS). Follow-up visits will be conducted approximately every 4 weeks from Week 4 to Week 52 (4 weeks after completion of treatment).

An Independent Data Monitoring Committee (IDMC) will periodically (approximately every 8 weeks) review the accumulating study data. The primary responsibility of the IDMC will be to monitor subject safety (including pulmonary exacerbations) and study conduct. The IDMC will have access to both safety and efficacy data. The IDMC will be requested to avoid formal evaluations of efficacy for the purpose of discontinuing the trial early for benefit. As such, no adjustment for multiple testing will be required. The IDMC will review the study data in accordance with a written charter.

4.2 Discussion of Study Design

A trial of 48 weeks is warranted for study of anti-inflammatory treatments in CF, even at the Phase 2 stage, since the expected major impact of this class of treatment will be to reduce the rate decline in FEV_1. Current Cystic Fibrosis Foundation registry data (see Table 2) indicate that the expected rate of FEV_1 decline is in the range of 3.3 to 5.1 % per year in subjects with at least one pulmonary exacerbation in the prior year. Variability (as coefficient of variation, CV) of FEV_1 percent predicted in CF trials typically ranges from 7 to 10%, meaning that CV will be on the order of twice the size of the anticipated FEV_1 change over the course of a year. Thus, 48 weeks is the optimum duration for discerning an effect on rate of FEV_1 decline that enables projection of anticipated effect size and powering for Phase 3 studies while minimizing total patient enrollment in Phase 2.

Table 2 Annual Change in FEV_1 in CF Patients Aged 18 to 30 Years

Baseline FEV_1 Range (Percent Predicted)	N	Mean	25% Percentile	50% Percentile	75% Percentile
50 to 59	531	-3.3	-6.8	-3.0	0.7

60 to 79	965	-3.3	-7.5	-2.9	1.2
80 to 99	598	-3.8	-7.0	-3.2	0.5
≥100	94	-5.1	-8.0	-3.0	0.1

Source: Cystic Fibrosis Foundation registry data.

4.3 Method of Assignment of Subjects to Treatment Groups

Upon determination that a subject meets all eligibility criteria, the subject will be randomized to treatment assignment via an IWRS. Each subject will be assigned to CTX-4430 50 mg, CTX-4430 100 mg, or placebo in a blinded 1:1:1 fashion by means of a computer-generated randomization list stratified by FEV_1 percent predicted at the Screening visit (50 to 75% and >75%), number of pulmonary exacerbations in the 12 months before Screening (1 or >1), and use of cystic fibrosis transmembrane regulator (CFTR) modulating therapy such as ivacaftor or ivacaftor + lumacaftor (yes/no).

A centralized randomization schedule will be generated by the unblinded statistician ███████ ████████████████████████████ who will not be involved in the conduct or analysis of the study, using a validated system. The schedule will have randomization numbers assigned to the 3 study treatments in blocks of 3 to achieve a 1:1:1 ratio of study treatment (i.e., an equal number of subjects in each treatment group). Each eligible subject will be assigned to the next sequential randomization number based upon the stratification factors above and will receive the corresponding study treatment. The randomization schedule will be kept strictly confidential and accessible only to authorized persons if unblinding of individual subjects becomes necessary in cases of emergency or for expedited reporting. Only when the study has been completed and the study database locked will the randomization schedule be made available for analysis.

4.4 Blinding

Investigators, subjects, and all study staff with direct subject contact will be blinded to treatment assignment.

The investigator will ensure that blinding is broken only in accordance with the protocol conditions for unblinding due to medical necessity or safety reasons.

There is an IDMC for this study that reviews unblinded data approximately every 8 weeks with a focus towards monitoring subject safety (including pulmonary exacerbations) and study conduct. The IDMC will have access to unblinded safety and efficacy data to enable risk-benefit assessments but will be requested to avoid formal evaluations of efficacy for the purpose of discontinuing the trial early for benefit.

This report to the IDMC will be prepared by the Sponsor's CRO/designee (i.e., an independent statistician who will be responsible for preparing the unblinded study results) and will include a summary of adverse event (AE) rates by treatment group. AEs will be tabulated by body system, severity, and their relationship to the trial drug. Serious adverse events (SAEs) will be similarly presented. This report will also include tabulation of pulmonary exacerbations and their severity, and their relationship to the trial drug. Additionally, data will be provided on subject weight, neutrophil counts, other safety labs and sputum microbiology, as the data become available.

4.5 Determination of Sample Size

The sample size calculation was performed with the following assumptions:

- 1:1:1 ratio of 50 mg CTX-4430, 100 mg CTX-4430, and placebo (2:1 ratio of CTX-4430 to placebo)
- Difference between average treatment effect (change from baseline) of 50 mg/100 mg CTX-4430 versus placebo of 3.5 percentage points in FEV_1 percent predicted at 48 weeks with a Common standard deviation (SD) of 7 percentage points
- Power of at least 90%
- One-sided alpha = 0.05.

Using a two-sample t-test for the mean difference with the above assumptions, a sample size of 156 subjects (52:52:52) is required for the primary, overall comparison of CTX-4430 versus placebo. Although the primary analysis will be based upon the Full Analysis Population (FAP), it is also of interest to be able to have a sufficient number of subjects to support analyses in the Per-protocol Population (PP). It is expected that approximately 80% of randomized subjects will be included in the PP. As such, the number of randomized subjects is increased to 195 (65:65:65).

5. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

5.1 Changes in the Conduct of the Study

There were no changes in the conduct of the study at the time of preparing this statistical analysis plan.

5.2 Changes from the Analyses Planned in the Protocol

In the event that a subject does not have data for Week 48, the primary analysis will use the last recorded data from Week 32 to Week 48 rather than basing the primary analysis solely on values from Week 48 (i.e., the analysis window has been expanded from that described in Section 6.2).

Sensitivity analyses of the primary analysis are being added to:
- Exclude any subject that experienced a pulmonary exacerbation between Week 32 and Week 48 inclusive
- Include a mixed model repeated measures analysis of absolute change from baseline in FEV_1 percent predicted
- Exclude any data collected more than 1 week after discontinuing study treatment.

The primary endpoint will be summarized within groups formed by the number of pulmonary exacerbations recorded during the course of the study: 0 exacerbations, 1 exacerbation or more than 1 pulmonary exacerbation during the study.

 For simplicity, the repeated measures analysis for the primary endpoint will not include terms for the randomization strata. The protocol indicates that data will be collected for subjects who discontinue treatment early and remain in the study after study treatment discontinuation. The analysis of the rate of exacerbation and the time to first exacerbation will be repeated after excluding data collected more than one week after study treatment discontinuation. If a CFTR modulator is started during the course of the study, that subject will be excluded from the Per-Protocol population.

Change from Baseline in body mass index (BMI) at Week 48 is being added as a secondary analysis.

6. BASELINE, EFFICACY AND SAFETY EVALUATIONS

6.1 Schedule of Evaluations

Table 3: Assessments Conducted at each Scheduled Visit

Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
Visit Name/Week[a]	Screening	Baseline	4	6	8	12	16	20	24	28	32	36	40	44	48	52	Early Term
Informed consent (study ICF ▮▮)	X																
Demographics & disease characteristics	X																
Medical history	X	X															
Physical exam [c]	X[c]	X	X		X	X	X	X	X		X		X		X[c]	X	X
12-lead ECG	X	X	X		X	X			X		X		X		X		X
Height, calculation of BMI	X																
Weight	X	X	X		X	X	X	X	X		X		X		X	X	X
Vital signs	X	X[d]	X		X	X	X	X	X		X		X		X	X	X
Pulse oximetry	X	X	X		X	X	X	X	X		X		X		X	X	X
CFQ-R[e]		X				X			X						X		X
Spirometry	X	X	X		X	X	X		X		X		X		X	X	X
Pulmonary exacerbation checklist		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Sputum sample [f]		X			X				X						X		X
Hematology	X	X	X		X	X			X		X		X		X	X	X
Serum chemistry	X	X	X	X	X	X	X	X	X		X		X		X	X	X
hs-CRP		X	X		X	X			X		X		X		X	X	X
Serum pregnancy test [g]	X																
HIV & HCV antibodies, HBsAg	X																
Urinalysis	X	X	X		X	X			X		X		X		X	X	X
Urine pregnancy test [g]		X	X		X	X	X	X	X		X		X		X	X	X
Urine alcohol and drug screen	X																
Randomization		X															
▮▮▮▮▮▮		X[h]	X[h]		X[h]												
IP dispensing		X	X		X	X	X	X	X[i]		X[i]		X[i]				
IP collection and capsule count			X		X	X	X	X	X		X		X		X		X
AE & concomitant medication recording	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

AE = adverse event; BMI = body mass index, CFQ-R = Cystic Fibrosis Questionnaire – Revised; ECG = electrocardiogram; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus, hs-CRP = high-sensitivity C-reactive protein: ICF = informed consent form; IP = investigational product; ▮▮▮▮▮▮▮▮
HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus, ▮▮▮▮▮▮▮▮
a   Baseline visit within 21 days of Screening, window for other visits: ±5 days
b   Visits 10, 12, and 14 will be conducted via phone call.
c   Complete physical exam at Screening and Week 48, focused physical exam at all other visits
d   Pre-dose and before discharge
e   To be administered before spirometry and sample collection
f   After spirometry
g   For women of childbearing potential
▮   ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮)
i   2 bottles of IP must be dispensed

6.2 Time Point Algorithms

6.2.1. Relative Study Day

The date of first dose of study drug will be considered relative Day 1, and the day before the first dose of study drug will be relative Day -1. Relative days will be calculated as follows only when the full assessment date is known (i.e., partial dates will have missing relative days):

For days on or after the first dose of study drug:
Date of Assessment – Date of First Dose of Study Drug + 1.

For days before the first dose of study drug:
Date of Assessment – Date of First Dose of Study Drug.

6.2.2. Analysis Visit Windows

For the purpose of analysis, the visit numbers will be recalculated according to the parameter's scheduled assessments to be analyzed and the relative study day as defined above. All efficacy data collected at scheduled visits, unless otherwise noted, will be used in the analyses, including data collected after a subject discontinued study medication. For safety analyses, data collected up to 28 days post-treatment will be used. Baseline is defined as the latest assessment obtained prior to first dose of study medication. The lower bound of the window for the first post-baseline assessment will be set to relative study Day 2. The window for the last scheduled post-baseline assessment will be defined with only a lower bound. All other lower and upper bounds are determined by the following algorithm:

Let x_i = scheduled day for assessment i.
Let x_{i+1} = scheduled day for assessment i+1.

The lower bound for assessment i+1 is defined as:

$$LB_{i+1} = x_i - \text{round} ([x_{i+1} - x_i]/2)$$

The upper bound for assessment i for Week 4 through Week 40 is defined as:

$$UB_i = LB_{i+1} - 1$$

For Week 48 the upper bound will be the maximum of the treatment stop day + 7 days or study day 350, which is the value determined by the upper bound formula for this visit. For Week 52, the lower bound will be the maximum of (the treatment stop day + 7 or study day 350) + 1 day.

For example, spirometry is scheduled to be collected at Screening, Baseline, Weeks 4, 8, 12, 16, 24, 32, 40, 48, 52 and, if applicable, early termination. The analysis windows for spirometry assessments is given below.

Table 4: Analysis Windows for Spirometry

Scheduled Visit	Scheduled Study Day	Visit Window for Analysis (Days)
Baseline	1	≤ 1
Week 4	29	2 – 42
Week 8	57	43 – 70
Week 12	85	71 – 98
Week 16	113	99 – 140
Week 24	169	141 – 196
Week 32	225	197 – 252
Week 40	281	253 – 308
Week 48	337	309 – maximum of treatment end day + 7 or study day 350
Week 52	365	≥ maximum of (treatment end day + 7 or study day 350) + 1

For analyses conducted by analysis visit window, if 2 visits have the same distance from the scheduled study day, the data of the visit labeled as the scheduled visit will be used and data from the visit labeled Unscheduled will not be used.

Descriptive analysis visits for other parameters are defined similarly. The only exception to this rule is for vital signs at the Baseline visit. When both are collected on relative study Day 1, the pre-dose assessment will be assigned as baseline and the assessment prior to discharge will be summarized as a separate time point.

6.3 Baseline Assessments

Baseline is defined as the latest assessment obtained prior to first dose of study drug.

The following baseline assessments will be conducted:

- Demographics (age [years], gender, race, ethnicity)
- Medical history
- Physical examination
- 12-lead ECG
- Assessment of CFQ-R
- Vital signs (heart rate, systolic/diastolic blood pressure, respiratory rate)
- Pulse oximetry
- Height, weight and BMI
- Laboratory tests (hematology, chemistry, urinalysis)
- Spirometry (FEV_1 [absolute value and percent predicted], FVC percent predicted, $FEF_{25-75\%}$ percent predicted)
- Biomarkers (sputum DNA concentration, sputum elastase concentration, serum hs-CRP)
- Disease characteristics

6.4 Efficacy Variables

6.4.1. Primary Efficacy Variable

The primary efficacy variable is FEV_1 percent predicted and is collected at Screening, Baseline, and Weeks 4, 8, 12, 16, 24, 32, 40, 48, 52, and, if applicable, early termination. In addition to visit values, absolute change in FEV_1 percent predicted from baseline will be calculated for each post-baseline assessment, according to windowing rules specified in Section 6.2.2.

Absolute change from baseline is defined as the Week 48 (using the visit window defined previously) visit value minus the Baseline visit value. The percent predicted value for all spirometry measures will be determined with the NHANES III database using the equations of Hankinson et al. 1999[8].

6.4.2. Secondary Efficacy Variables

6.4.2.1. Spirometry

Spirometry variables FEV_1 percent predicted, FVC percent predicted and $FEF_{25-75\%}$ percent predicted which will be collected at Screening, Baseline, and Weeks 4, 8, 12, 16, 24, 32, 40, 48, 52, and, if applicable, early termination. Visit values are assigned using the windowing method specified in Section 6.2.2. Absolute and relative or percent change from baseline will also be calculated at each post-baseline assessment. Relative or percent change from baseline is defined as 100 times the absolute change from baseline divided by the Baseline visit value.

6.4.2.2. Pulmonary exacerbations

The time to first protocol defined pulmonary exacerbation and number of protocol defined pulmonary exacerbations are determined by the pulmonary exacerbation checklist. The pulmonary exacerbation checklist is collected at every post-Screening visit except at Week 6. Any pulmonary exacerbation that occurs after first dose of study medication will be included in the analysis.

Pulmonary exacerbations are defined as treatment with oral, inhaled, or intravenous antibiotic(s) for ≥4 of symptoms/signs listed below per the modified Fuchs criteria[6]. The onset date is defined as the date that antibiotics were initiated and as reflected on the pulmonary exacerbation checklist. If the same pulmonary exacerbation spans 2 or more study visits, it will be considered as one exacerbation. The pulmonary exacerbation checklist will capture the date of onset, the signs/symptoms listed below as well as the treatment with oral, inhaled, or intravenous antibiotics:

- Change in sputum
- New or increased hemoptysis
- Increased cough
- Increased dyspnea
- Malaise, fatigue, or lethargy
- Temperature >38°C
- Anorexia or weight loss
- Sinus pain or tenderness
- Change in sinus discharge
- Change in physical examination of the chest
- 10% or more absolute decrease in FEV_1 percent predicted from the previously recorded value
- Radiographic changes indicative of pulmonary infection.

6.4.2.3. Biomarkers

Biomarker variables sputum DNA, elastase, and serum hs-CRP. Sputum DNA and elastase will be collected at Baseline and Weeks 8, 24, 48, and, if applicable, early termination. Serum hs-CRP will be collected at Baseline and Weeks 4, 8, 12, 24, 32, 40, 48, 52, and, if applicable, early termination. Visit values are assigned using the windowing method specified in Section 6.2.2. Absolute change from baseline will be calculated for all biomarkers at each collected study week. For sputum elastase and sputum DNA, change from baseline will be calculated using log_{10} transformed absolute values at baseline and Week 48. If there are any values below the limit of detection, they will be imputed using a value half of the lower limit of detection (LOD). For elastase the LOD is 0.25 mcg/mL and for DNA the LOD is 0.625 mcg/mL.

6.4.2.4. BMI

BMI will be recorded at Screening and will be calculated for data analysis at Baseline and Weeks 4, 8, 12, 20, 24, 32, 40, 48, 52, and, if applicable, early termination. BMI will be calculated as:

Weight in kilograms collected at each visit / (height in meters)^2 collected at screening

Visit values are assigned using the windowing method specified in Section 6.2.2. Absolute change from baseline will be calculated.

6.4.3. Additional Variables

The exploratory variables are sputum bacterial density and quality of life as assessed by the CFQ-R instrument. Sputum bacterial density will be collected at Baseline and Weeks 8, 24, 48, and, if applicable, early termination. Sputum bacterial density is measured by the presence (including, if present, number of colony forming units [CFUs] per gram of sputum) or absence of *Pseudomonas aeruginosa*, *Burkholderia cepacia complex*, *Achromobacter xylosoxidans*, *Stenotrophomonas maltophilia*, and *Staphylococcus aureus* (including methicillin–resistant *S. aureus* and small colony variants of *S. aureus*). Presence of a pathogen is assessed by the number of subjects with a viable sample testing positive for the given pathogen at each collection point. Absence of a pathogen is determined by taking the difference of the total number of subjects with a viable sample and the number of subjects with a viable sample testing positive for the given pathogen at each collection point. CFU counts will be transformed using the log_{10} transformation and summarized using the arithmetic mean.

The CFQ-R consists of 9 quality of life domains (physical, role/school, vitality, emotion, social, body image, eating, treatment burden, health perceptions) and 3 symptom domains (weight, respiratory, and digestion). A standardized score for each domain is computed based on the individual components with a range of 0 to 100 (higher scores indicating better health). The standardized domain score is only computed when at least 50% of the individual components are not missing. See Appendix 1 in Section 11.1 for more details on the derivation.

Visit values are assigned using the windowing method specified in Section 6.2.2. Absolute change from baseline will be calculated for each domain of the CFQ-R and CFUs for bacterial density.

6.6 Safety Assessments

6.6.1. Extent of Exposure and Compliance to Study Treatment

The expected number of study medication doses will be calculated as:

For subjects who complete treatment, the number of expected doses = date of last study medication dose - date of first dose of study medication + 1. For subjects who discontinue treatment, the number of expected doses = the earliest of date of Week 48 visit or date of study drug discontinuation - date of first dose of study medication + 1.

The number of bottles dispensed, each containing 36 capsules, will be recorded. An investigational site staff member will count the capsules returned by each subject. Subjects will be questioned in relation to any capsules which may have been lost or destroyed to gain a full understanding of the number of capsules taken during the treatment period. The number of capsules taken is calculated as:

Doses taken = number of capsules dispensed - number of capsules returned.

Percent compliance will be calculated as:

Percent compliance = (doses taken / expected doses) * 100%. The expected number of doses is the number of capsules that should have been taken as discussed above. Subjects will be considered compliant with study medication if they take at least 80% of expected doses.

If a bottle is dispensed but the bottle is not returned, then the doses taken for the unreturned bottle will be imputed as follows:

1. Percent compliance for each subject will be calculated as above using only bottles with return information.
2. For unreturned bottles, the number of doses taken will be set to the integer value of 36 x (percent compliance from step 1 / 100).

Percent compliance will then be calculated as above using the imputed doses taken for unreturned bottles.

6.6.2. Adverse Events

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and does not necessarily have a causal relationship with this product. For purposes of this trial, AEs will be reported from the signing of the study ICF through study completion or early termination. A treatment emergent AE (TEAE) is an AE that occurs after the first dose of study medication through 28 days after the last dose, whether this occurs at the final dosing visit at Week 48, or earlier in the study if study drug was permanently discontinued.

AEs will be attributed to treatments according to the following algorithm:
- If the start date of an AE is known, then:
  - If the AE starts at any time prior to Day 1 then the AE will not be summarized and hence will not be attributed to any treatment.

- o For AE's starting on Day 1 (day of first dose), the AE will be classified as treatment emergent for the purposes of reporting. These will be captured in a separate listing,
- o If the AE starts after Day 1 and on or prior to 28 days after the last dose of study medication, then the AE is considered treatment emergent and assigned to the actual treatment received.
- If the start day of an AE is unknown but the month and year are known, then:
  - o If the month and year are the same or later than the month and year of randomization, the AE will be considered treatment emergent and assigned to the actual treatment received.
- If year is present, but month and day are missing
  - o If the year is the same or later than the year of randomization, the AE will be considered treatment emergent and assigned to the actual treatment received.
- Any other type of partial missing AE start date is considered to be treatment emergent.

The investigator's verbatim term of each AE will be mapped to system organ class and preferred term using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) adverse event dictionary.

The Investigator will assess the severity of each AE as either mild, moderate, or severe. If severity is missing, the AE severity will not be imputed (i.e., will be not be included in AE summaries requiring severity but the relevant AE will appear in all other summaries).

The Investigator will assess the relationship of each AE to the study medication as either not related, unlikely related, possibly related, probably related, or definitely related. If relationship is missing, the attribution will not be imputed.

6.6.3. Clinical Laboratory Evaluations

Safety blood and urine specimens (see Table 5) will be collected from all subjects at Screening, Baseline, and Weeks 4, 6, 8, 12, 16, 20, 24, 32, 40, 48, 52, and, if applicable, early termination.

Visit values are assigned using the windowing method specified in Section 6.2.2. Absolute change from baseline will be calculated for continuous lab parameters. Laboratory values will also be classified as normal (if the value is within normal reference range) or abnormal (if the value is either below or above the normal reference range). Values that are three times below the normal lower reference range or three times above the normal upper reference range will be summarized.

Table 5   Hematology, Chemistry, and Urinalysis Tests

Hematology	Chemistry	Urinalysis
Hematocrit	Albumin	Bilirubin
Hemoglobin	Alkaline phosphatase	Blood
Platelet count	Alanine aminotransferase	Glucose
Red blood cell count	Aspartate aminotransferase	Ketones
White blood cell (WBC) count	Bicarbonate	Leukocyte esterase
WBC differential (absolute count and %)	Bilirubin (total and direct)	Nitrites
Neutrophils	Blood urea nitrogen	pH
Lymphocytes	Calcium	Protein
	Chloride	
Monocytes	Creatinine	Specific gravity
Eosinophils	Gamma glutamyl transferase	
Basophils	Glucose	
	Phosphorus	
	Potassium	
	Sodium	
	Uric acid	
	Total protein	
	hs-CRP	

6.6.4. Vital Signs

Temperature, heart rate, systolic and diastolic blood pressure, and respiratory rate will be measured after the subject has been seated for 10 minutes at Screening, Baseline (pre-dose and prior to discharge), and Weeks 4, 8, 12, 16, 20, 24, 32, 40, 48, 52, and, if applicable, early termination. Visit values are assigned using the windowing method specified in Section 6.2.2. Absolute change from baseline will be calculated.

6.6.5.Weight and Pulse Oximetry

Weight and pulse oximetry will be measured at Screening, Baseline, and Weeks 4, 8, 12, 16, 20, 24, 32, 40, 48, 52 and, if applicable, early termination. Visit values are assigned using the windowing method specified in Section 6.2.2. Absolute change from baseline will be calculated.

6.6.6.Electrocardiogram

An ECG will be performed at Screening, Baseline, and Weeks 4, 8, 12, 24, 32, 40, 48 and, if applicable, early termination. ECG parameters include mean RR duration, mean heart rate, mean PR duration, mean QRS duration, mean QT Duration, mean QTcB – Bazett's Correction Formula, and mean QTcF – Fridericia's Correction Formula. Visit values are assigned using the windowing method specified in Section 6.2.2. Absolute change from baseline will be calculated. The overall interpretation of the ECG will be classified as normal or abnormal.

6.6.7.Physical Examination

A complete physical exam will be performed at Screening and at Week 48. A physical exam focused on any medical complaints will be performed as required at Baseline, Weeks 4, 8, 12, 16, 20, 24, 32, 40, and 52, and, if applicable, early termination.

Any physical exam abnormality deemed clinically significant by the Investigator at Screening or Baseline (before dosing) will be reported as medical history. Any physical exam abnormality emergent after the administration of study medication, or abnormality that has worsened since Screening or Baseline reporting, that is deemed clinically significant by the Investigator, will be reported as an AE.

7. STATISTICAL METHODS

7.1 General Methodology

Standard statistical methods will be employed to analyze all data. Data collected in this study will be reported using summary tables and subject data listings. For categorical variables, frequencies, and percentages will be presented. For continuous variables, the number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum will be presented. Unless otherwise indicated, confidence intervals (CIs) will be 95% 2-sided intervals.

Complete listings of all clinical data will be provided to supplement further investigation of tabulated values. Version 9.2 or later of the SAS® statistical software package will be used to provide all statistical analyses.

7.2 Adjustments for Covariates

Other than the adjustment for the randomization stratification factors for the analysis of the primary endpoint calculated using the 48-week analysis window, no adjustment for covariates is planned in this study.

7.3 Handling of Dropouts or Missing Data

Subjects who terminate the study prematurely after randomization may not be replaced, regardless of the reason for withdrawal. The handling of missing data will be discussed throughout Section 8, where relevant. A number of imputation strategies will be investigated for the primary endpoint. Secondary endpoint analyses will be based upon the observed data.

7.4 Pooling of Strata

For the purpose of data analysis, randomization strata (FEV_1 percent predicted at the Screening visit (50 to 75% and >75%), number of pulmonary exacerbations in the 12 months before Screening (1 or >1), and use of cystic fibrosis transmembrane regulator (CFTR) modulating therapy such as ivacaftor or ivacaftor + lumacaftor (yes/no)) will be combined with smaller strata to have at least 10 subjects total within a stratum. This is a multi-center study with approximately 78 sites planned. Therefore, it is expected to have approximately only 2.5 subjects per site (195 subjects / 78 sites). Subjects were not stratified by site for the purpose of randomization. Due to the expected small number of subjects at each site, the treatments will not be formally compared within site.

7.5 Multiple Comparisons/Multiplicity

The primary analysis will be based upon an analysis of variance (ANOVA) in which the average of the Week 48 change from Baseline in FEV_1 percent predicted for the 2 CTX-4430 doses is compared to that in the placebo group using a 1-sided 0.05 level of significance. If the primary analysis (aggregate CTX-4430 effect vs. placebo) reaches the 0.05 level of significance (1-sided), the individual CTX-4430 doses will be compared to the placebo arm using Dunnett's procedure at the 0.05 (2-sided) alpha level. This procedure maintains the type I error at the usual 0.05 (2-sided) level for the individual dose comparisons with placebo while allowing a proof of concept test for the pooled comparison at the 0.05 (1-sided). This approach is consistent with the Fleming and Richardson[7] approach to Phase 2 screening trials in which a screening trial, if positive at the more stringent 0.05 2-sided level after preliminary testing, can be treated as providing a more definitive statistical test and may reduce the amount of additional confirmatory trial data that is needed. No other adjustments for multiplicity will be used and other statistical analyses will be viewed as supportive.

The IDMC for the study will be requested to avoid formal evaluations of efficacy for the purpose of discontinuing the trial early for benefit. As such, no adjustment for multiple testing will be required.

8. STATISTICAL ANALYSIS

8.1 Disposition of Subjects

The number of screened subjects, randomized subjects, treated subjects, subjects who completed the study, and subjects who discontinued the study drug early will be summarized by treatment group. For subjects who discontinue study drug, the subjects who discontinue study drug and the study, and those who discontinue study drug but stay in the study will be separately summarized. Reasons for discontinuation will also be summarized.

The number of randomized subjects in each subject analysis population and the reasons for inclusion in the FAP but not in the PP will be summarized by treatment group. Additionally, a summary of the

concordance between the randomization strata as recorded in the IVRS system and the clinical database will be provided.

8.2 Protocol Violations

Protocol violations will be summarized.

8.3 Analysis Populations

8.3.1. Randomized Population

All subjects randomized to an active treatment or placebo will be included in the Randomized Population. Subjects in the Randomized Population will be analyzed according to their randomized treatment group.

8.3.2. Full Analysis Population

All subjects randomized to and receiving at least 1 dose of assigned treatment will be included in the FAP. Subjects in the FAP will be analyzed according to their randomized treatment group.

8.3.3. Safety Population

All subjects randomized to and receiving at least 1 dose of assigned treatment will be included in the Safety Population. All safety analyses will be performed using the Safety Population according to the actual treatment received.

8.3.4. Per-Protocol Population

Subjects in the FAP who meet all study inclusion/exclusion criteria, are assessed at the Week 48 visit, receive at least 80% of assigned treatment doses at the time of their Week 48 assessment, and do not start a CFTR modulator during the course of the study will be included in the PP. All subjects in the PP will be analyzed according to the actual treatment received.

8.4 Demographic and Other Baseline Characteristics

Sex, race, and ethnicity will be summarized using counts and percentages. Age, height (cm), weight (kg), and BMI will be summarized with descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum) overall and by treatment group.

The investigator's verbatim term of each medical history item will be mapped to system organ class and preferred term using the latest version of MedDRA. Medical history will be summarized by system organ class and preferred term; a subject will only be counted once per system organ class and once per preferred term within a treatment.

8.5 Prior and Concomitant Therapy

The World Health Organization (WHO) Drug Dictionary will be used to classify medications by preferred term and WHO Anatomical Therapeutic Chemical (ATC) classification of ingredients.

The following applies to all data collected on the prior and concomitant electronic case report form (eCRF) page and will be reported by each category separately.

Where a medication start date is missing, this medication will be assumed to be concomitant for reporting purposes, unless the end date is prior to the first administration of study treatment. Partial dates will not be imputed.

Descriptive statistics, such as frequency counts and percentages will be provided to summarize the use of medications other than the study drug reported throughout the study. The number and percent of subjects who took other therapy will be shown by WHO ATC classification of ingredients and by preferred term.

8.6 Analysis of Efficacy Parameters

8.6.1. Analysis of Primary Efficacy Variable

The primary efficacy analysis of change from Baseline to Week 48 in FEV_1 percent predicted will be performed on the FAP. The primary efficacy evaluation will compare the combined, average absolute change from Baseline in FEV_1 percent predicted of the 50 mg and 100 mg CTX-4430 treatment groups versus the placebo group.

For the primary efficacy analysis, the last data point (including early termination visit) recorded between Week 32 and Week 48 will be used in calculating the change from baseline. Subjects with no recorded data between Week 32 and Week 48 will be treated as missing the primary endpoint. Missing primary endpoint values will be imputed using the average placebo (according to the randomized treatment assignment) change from baseline to Week 48.

The primary analysis will be based upon an analysis of variance (ANOVA) in which the average of the Week 48 absolute change from Baseline in FEV_1 percent predicted for the 2 CTX-4430 doses is compared to that in the placebo group using a 1-sided test with a 0.05 level of significance. The ANOVA model will contain a separate term for each dose group with the average over the 2 CTX-4430 doses created by averaging the parameters estimates within the ANOVA model (i.e., through the use of the LSMESTIMATE statement in SAS PROC MIXED with terms proportionate to [0.5, 0.5 and -1], for the active arms and placebo, respectively). Weighting for these averages will be based on the number of subjects with a non-missing response in each randomization stratum for the FAP (using the OM option in PROC MIXED). In addition to terms for treatment group, the ANOVA will include a term for the stratification factors used for randomization (pooled strata based upon Section 7.4) and a term for the interaction between treatment group and pooled strata. Simple descriptive statistics will be presented by treatment group and averaged CTX-4430 dose.

If the 1-sided null hypothesis (comparison of CTX-4430 combined active doses vs placebo) is rejected, the individual CTX-4430 doses will be compared to the placebo arm using Dunnett's procedure at the 0.05 (2-sided) alpha level. This procedure maintains the type I error at the usual 0.05 (2-sided) level for the individual dose comparisons with placebo while allowing a proof of concept test for the pooled comparison at the 0.05 (1-sided). This approach is consistent with the Fleming and Richardson[7] approach to Phase 2 screening trials in which a screening trial, if positive at the more stringent 0.05 2-sided level after preliminary testing, can be treated as providing a more definitive statistical test and may reduce the amount of additional confirmatory trial data that is

needed.[7] If the combined active dose comparison to placebo does not reject the null hypothesis at the 1-sided 5% level, the pairwise comparisons (100 mg CTX-4430 vs placebo and 50 mg CTX-4430 vs placebo) will be treated as descriptive analyses for the purpose exploring the dose response relationship for CTX-4330. No other adjustments for multiplicity will be used and other statistical analyses will be viewed as supportive.

The following sensitivity analyses for the primary analysis will be conducted:

1.) The primary analysis will be repeated on the PP population.

2.) The primary analysis will be repeated with missing values for FEV_1 percent predicted imputed using last observation carried forward (LOCF; i.e., values for Weeks 4-28 will be used in the primary analysis if the primary endpoint is missing before the Week 32 visit).

3.) The primary analysis will be repeated with missing values excluded from the analysis (i.e., observed data analysis)

4.) The primary analysis will be repeated using a rank based transformation where missing values are imputed as the worst rank (Lachin, 1999).[9] In this procedure, subjects are pooled over treatment and then ranks are assigned from 1-N where N is the number of subjects in the full analysis population. Ranks 1-K will be assigned a value of (K+1)/2.

5.) A mixed model repeated measures analysis of absolute change from Baseline in FEV_1 percent predicted using all post-baseline data to explore the consistency of the treatment effect over time. The model will include treatment (2 doses and placebo), visit, and treatment-by-visit interaction. The comparison between treatments will be made using means estimated by this model for the 48-week analysis window.

6.) The primary analysis will be repeated excluding any subject who experienced a protocol defined pulmonary exacerbation that began between the Week 32 and Week 48 visits, inclusive.

7.) The primary analysis will be repeated excluding any data collected more than 1 week after discontinuing study treatment.

8.6.2. Analysis of Secondary Efficacy Variables

The absolute change from baseline at Week 48 in the spirometric measures FVC percent predicted and $FEF_{25-75\%}$ percent predicted and percent change (relative change) from baseline in FEV_1 percent predicted, will be analyzed using ANOVA as described above for the primary efficacy variable. The overall comparison of the combined active doses vs. placebo as well as the comparisons between each active dose and placebo will be made. These analyses will be limited to the observed data on the FAP.

The time to first protocol defined pulmonary exacerbation will be analyzed using a Cox proportional hazards model (SAS PROC PHREG). The model will contain terms for treatment. For simplicity, an unstratified analysis will be performed. The two active doses will be compared to placebo individually as well as pooled together using a contrast statement similar to that used for the primary analysis. Time in study will be defined as the date of the Week 48 or Early Termination visit – treatment start date + 1. Plots of the distribution of time to first exacerbation will be produced using Kaplan-Meier (KM) methodology. In these analyses, subjects will be censored as of their last assessment for pulmonary exacerbations. The estimated hazard ratios with 95% 2-sided CIs will be summarized in a forest plot. These analyses will be limited to the observed data on the FAP and PP population.

The number of protocol-defined pulmonary exacerbations reported through the Week 48/Early Termination visit will be annualized where a year is defined by 52 weeks and will be analyzed using a

negative binomial regression (SAS PROC GENMOD). The two active doses will be compared to placebo individually as well as pooled together using a contrast statement similar to that used for the primary analysis. The model will include factors for treatment group and the natural log of time in study as an offset variable. Time in study will be defined as the date of the Week 48 or Early Termination visit – treatment start date + 1. Point estimates, standard errors, and 95% CIs for the mean of number of pulmonary exacerbations will be presented. The difference in means between each CTX-4430 group from placebo will be presented along with standard errors and 95% CIs. The estimated treatment effect along with standard errors and 95% CIs will also be calculated for the combined active doses. In these analysis, subjects will be censored as of their last assessment for pulmonary exacerbations. The estimated differences between the arms with 95% 2-sided CIs will be summarized in a forest plot. These analyses will be limited to the observed data on the FAP and PP population.

To examine the impact of early treatment discontinuation on the treatment effect, the overall analyses of the time to first exacerbation and the rate of exacerbations will be repeated censoring more than 1 week after treatment discontinuation. For this analysis, the same negative binomial model will be used, but time in study will be defined as the treatment end date – treatment start date + 7.

Additionally, the number of protocol-defined pulmonary exacerbations leading to hospitalizations and those necessitating the administration of intravenous antibiotics will be annualized where a year is defined as 52 weeks and assessed between the combined active doses and placebo arms and between each active dose and placebo. The analysis will be done using negative binomial regression as described for the analysis of all protocol-defined pulmonary exacerbations.

Descriptive statistics for the spirometric measures will also be presented on observed data for the visit values, percent and absolute change from baseline for each scheduled visit. The 95% CIs for the mean differences between the CTX-4430 groups and placebo will also be presented on the absolute and percent changes from baseline.

The change from baseline at Week 48 in serum hs-CRP will be summarized using ANOVA to estimate the means and 95% CIs for each individual treatment group and the pooled CTX-4430 treatment groups and the mean differences between the CTX-4430 groups (individual and pooled) and placebo. The model will contain a term for treatment, a term for the stratification factors used for randomization (pooled strata based upon Section 7.4), and a term for the interaction between treatment group and pooled strata. Weighting for the means will be based on the number of subjects with a non-missing response in each randomization stratum for the FAP (using the OM option in PROC MIXED). Additionally, serum hs-CRP will be summarized using descriptive statistics by treatment group (individual and pooled) for each scheduled visit (per Table 5). The summary will be done on the FAP using observed data with no imputation for missing data.

Sputum DNA and elastase data will be transformed using the $\log_{10}$ transformation and summarized using the same methods as serum hs-CRP.

The change from baseline at Week 48 in BMI will be summarized using ANOVA to estimate the means and 95% CIs for each individual treatment group and the pooled CTX-4430 treatment groups and the mean differences between the CTX-4430 groups (individual and pooled) and placebo. The model will contain a term for treatment, a term for the stratification factors used for randomization (pooled strata based upon Section 7.4), and a term for the interaction between treatment group and pooled strata. The summary will be done on the FAP. In case of missing data, the last data recorded starting from the Week 32 to the Week 48/Early Termination visit, inclusive, will be used.

8.6.3. Subgroup Analyses

The primary endpoint (both by individual dose and combined active doses) will be examined for subgroups formed by the following variables:

Stratification factors at randomization:

- Baseline FEV_1 percent predicted (≤75% and >75%)
- Number of pulmonary exacerbations in the 12 months before Screening (1 or >1)
- Use of CFTR-modulating therapy, such as ivacaftor or ivacaftor + lumacaftor (yes/no)

Additional factors:

- Baseline FEV_1 percent predicted (≤pooled median, >pooled median)
- Age (≤pooled median, >pooled median)
- Number of pulmonary exacerbations in the 12 months before Screening (≤2 or >2)
- Use of azithromycin (yes/no)
- Number of protocol defined pulmonary exacerbations experienced during the study (0, 1, or >1)

The time to first exacerbation and the rate of pulmonary exacerbations will be examined (both by individual dose and combined active doses) within subgroups formed on the basis of the following variables:

- Baseline FEV_1 percent predicted of ≤ 75% and > 75%
- Pulmonary Exacerbations in the past 12 months prior to screening categorized as 1 or >1 exacerbation
- Use of CFTR-modulating therapy such as ivacaftor or ivacaftor + lumacaftor (yes/no)
- Number of pulmonary exacerbations in the 12 months before Screening (≤2 or >2)
- Use of azithromycin in the past 12 months (yes/no)

Subgroup analyses will be based upon observed data (without imputation) by the presentation of simple, descriptive statistics and CIs within the subgroups.

Additionally, for the secondary endpoint of time to first protocol defined pulmonary exacerbation, The Cox proportion hazards model as described in section 8.6.2 will be used to estimate the hazard rate and the corresponding 95% CIs within the subgroups. For the secondary endpoint of number of protocol-defined pulmonary exacerbations, negative binomial regression will be used as described in Section 8.6.2 to estimate the annualized rate of exacerbations and the corresponding 95% CIs within the subgroups.

Forest plots will be used to graphically display the means and CIs for each subgroup for the primary endpoint and the secondary endpoint of number of protocol-defined pulmonary exacerbations.

8.6.4. Exploratory Analyses

CFUs for sputum bacterial density and change from baseline in CFU will be analyzed descriptively by treatment group at Weeks 8, 24 and 48. CFUs will be transformed using the log_{10} transformation and summaries of the transformed CFU counts will be provided at each visit for total CFU counts and

CFU counts for each pathogen (*P aeruginosa*, *Burkholderia cepacia* complex, *Achromobacter xylosoxidans, Stenotrophomonas maltophilia, and Staphylococcus aureus* (including methicillin–resistant *S aureus* and small colony variants of *S aureus*)). In addition to the basic descriptive statistics, 95% CIs for the mean differences between the CTX-4430 groups and placebo for the absolute change from baseline for both total bacterial load and organism will be presented.

CFQ-R domain scores will be analyzed descriptively by treatment group. In addition to the basic descriptive statistics, 95% CIs for the mean differences between the CTX-4430 groups and placebo for the absolute change from baseline will be presented

8.7 Analysis of Safety

All safety analyses will be performed on the Safety Population.

8.7.1. Extent of Exposure and Compliance to Study Treatment

- **Extent of Exposure**

The extent of subject exposure to study medication will be quantified using the parameters expected doses and taken doses, which will be summarized using descriptive statistics (N, mean, SD, median, minimum, maximum) by treatment group.

- **Measurements of Treatment Compliance**

Percent compliance will be summarized using descriptive statistics (N, mean, SD, median, minimum, maximum) by treatment group. Percent compliance will also be summarized in the categories of <80% and ≥80%.

8.7.2. Adverse Events

The investigator's verbatim term of each AE will be mapped to system organ class and preferred term using the latest version of the MedDRA dictionary.

TEAEs will be summarized by system organ class and preferred term; a subject will only be counted once per system organ class and once per preferred term within a treatment. Subject counts and percentages will be presented for each treatment group and totaled for all treatment groups for the following:

- All TEAEs
- All TEAEs by severity
- All TEAE by relationship
- All treatment emergent SAEs
- TEAEs leading to discontinuation of study participation

Listings will be presented by subject for all TEAEs, all treatment-emergent SAEs, TEAEs with death as the outcome, and TEAEs leading to discontinuation from the study.

AEs recorded between the screening and baseline visit will be listed separately. In addition, AEs occurring on Day 1 (baseline visit) will be listed separately.

For the summary of AEs by severity, if a subject has multiple events occurring in the same body system or same preferred term, then the event with the highest severity will be counted. For AEs by relationship to study drug, if a subject has multiple events occurring in the same body system or same preferred term, the event with the highest association to study drug will be summarized. AEs potentially related to study drug are defined as a subset of adverse events with a relationship to study drug of either possible, probable, definite, or unknown.

No statistical inference between the treatments will be performed on adverse events.

8.7.3. Clinical Laboratory Evaluations

Clinical laboratory results at each time point and change from Baseline will be summarized using summary statistics (n, mean, SD, median, minimum and maximum values) by treatment group to each scheduled assessment. In addition, shift tables of specified clinical laboratory evaluations will be presented to display the shift in the normal range categories (low, normal, high) from Baseline to each scheduled assessment. For hematology, WBC, hematocrit, hemoglobin, platelet count, and absolute neutrophil count will be summarized. For chemistry, alkaline phosphatase; alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase, bilirubin (total and direct), blood urea nitrogen, creatinine, glucose, and uric acid

Listings of laboratory data will also be presented for all tests. Within each listing, laboratory values outside the normal ranges will be flagged as either high or low.

8.7.4. Vital Signs

Values at each time point and absolute change from Baseline for vital sign measurements (systolic and diastolic blood pressure, pulse, respiration rate, and temperature), will be summarized with descriptive statistics (n, mean, SD, median, minimum, and maximum) at each scheduled visit by treatment group. Listings of these data will also be presented.

8.7.5. Weight, BMI, and Pulse Oximetry

Values at each time point and absolute change from Baseline for weight, BMI, and pulse oximetry measurements, will be summarized with descriptive statistics (n, mean, SD, median, minimum, and maximum) at each scheduled visit by treatment group. Listings of these data will also be presented.

8.7.6. Physical Examination Findings

Any physical examination abnormality deemed clinically significant by the Investigator at Screening or Baseline will be reported as medical history. Any physical exam abnormality emergent after the administration of study medication, or abnormality that has worsened since Screening or Baseline reporting, that is deemed clinically significant by the Investigator, will be reported as an AE. Listings of these data will be presented.

8.7.7. Electrocardiogram

Values at each time point and absolute change from Baseline for ECG measurements (mean RR duration, mean heart rate, mean PR duration, mean QRS duration, mean QT duration, QTcB, and QTcF), will be summarized with descriptive statistics (n, mean, SD, median, minimum, and maximum) at each scheduled visit by treatment group. In addition, shift tables will be presented to display the

shift in the overall interpretation categories (normal or abnormal) from Baseline to each scheduled assessment. Listings of these data will also be presented.

9. Amendment History

Prior to unblinding, the windowing convention for Week 48 was updated to include subjects that had a valid Week 48 visit but were being excluded from the Week 48 window.
- In Version 1, the Week 48 window was defined as any assessment occurring between study days 309 and 350 inclusive.
- In Version 2, the upper bound for the Week 48 visit was changed to the maximum of study day 350 or the treatment end day + 7 days. The lower bound for the Week 52 visit was also adjusted accordingly.

10. Computer Software

For continuous variables, descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum) will be generated. For categorical variables, the number and proportion of subjects will be displayed.

11. REFERENCES

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12. APPENDICES

12.1   APPENDIX 1: VARIABLE DEFINITIONS

Weight will be displayed in kilograms (kg), height will be displayed in centimeters (cm), and temperature will be displayed in Celsius (C). Weights, heights, or temperatures recorded in alternate units will be converted to the units being displayed using standard conversion formulas.

- CFQ-R

The CFQ-R is comprised of 50 individual questions contributing to 12 domains. The 50 questions are classified to domains as follows:

Question 1 = phys1
Question 2 = phys2
Question 3 = phys3
Question 4 = phys4
Question 5 = phys5
Question 6 = vital6
Question 7 = emot7
Question 8 = emot8
Question 9 = vital9
Question 10 = vital10
Question 11 = vital11
Question 12 = emot12
Question 13 = phys13
Question 14 = eat14
Question 15 = treat15
Question 16 = treat16
Question 17 = treat17
Question 18 = health18
Question 19 = phys19
Question 20 = phys20
Question 21 = eat21
Question 22 = social22
Question 23 = social23
Question 24 = body24
Question 25 = body25
Question 26 = body26
Question 27 = social27
Question 28 = social28
Question 29 = social29
Question 30 = social30
Question 31 = emot31
Question 32 = health32
Question 33 = emot33
Question 34 = health34
Question 35 = role35
Question 36 = role36
Question 37 = role37

Question 38 = role38
Question 39 = weight39
Question 40 = resp40
Question 41 = resp41
Question 42 = resp42
Question 43 = resp43
Question 44 = resp44
Question 45 = resp45
Question 46 = resp46
Question 47 = digest47
Question 48 = digest48
Question 49 = digest49
Question 50 = eat50

Each response to an individual question is on an ordinal scale from 1 to 4. However, due to the phrasing of responses to certain questions, some responses need to be reversed ordered (1 recoded to 4, 2 recoded to 3, 3 recoded to 2, and 4 recoded to 1). This can be done via the following code:

```
vital6   =      5-vital6;
vital10  =      5-vital10;
phys13 =        5-phys13;
treat15 =       5-treat15;
treat17 =       5-treat17;
health18        =       5-health18;
social23        =       5-social23;
social28        =       5-social28;
social30        =       5-social30;
health32        =       5-health32;
health34        =       5-health34;
role35  =       5-role35;
resp43          =    5-resp43;
```

The domain scores can then be calculated using the following code:

```
if nmiss (phys1, phys2, phys3, phys4, phys5, phys13, phys19, phys20) <= 4 then
physical = (mean (phys1, phys2, phys3, phys4, phys5, phys13, phys19, phys20)-1)/3*100;

if nmiss (role35, role36, role37, role38) <= 2 then
role = (mean (role35, role36, role37, role38)-1)/3*100;

if nmiss (vital6, vital9, vital10, vital11) <= 2 then
vitality = (mean (vital6, vital9, vital10, vital11)-1)/3*100;

if nmiss (emot7, emot8, emot12, emot31, emot33) <= 2 then
emotion = (mean (emot7, emot8, emot12, emot31, emot33)-1)/3*100;

if nmiss (social22, social23, social27, social28, social29, social30) <= 3 then
social = (mean (social22, social23, social27, social28, social29, social30)-1)/3*100;

if nmiss (body24, body25, body26) <= 1 then
body = (mean (body24, body25, body26)-1)/3*100;

if nmiss (eat14, eat21, eat50) <= 1 then
```

eat = (mean (eat14, eat21, eat50)-1)/3*100;

if nmiss (treat15, treat16, treat17) <= 1 then
treat = (mean (treat15, treat16, treat17)-1)/3*100;

if nmiss (health18, health32, health34) <= 1 then
health = (mean (health18, health32, health34)-1)/3*100;

if nmiss (weight39) = 0 then
weight= (mean (weight39)-1)/3*100;

if nmiss (resp40, resp41, resp42, resp44, resp45, resp46) <= 3 then
respirat = (mean (resp40, resp41, resp42, resp44, resp45, resp46)-1)/3*100;

if nmiss (digest47, digest48, digest49) <= 1 then
digest = (mean (digest47, digest48, digest49)-1)/3*100;

12.2   APPENDIX 2: STATISTICAL ANALYSIS AND PROGRAMMING DETAILS

ANOVA Analysis

The SAS procedure MIXED will be used in the ANOVA analysis for change from baseline at Week 48.

```
proc summary data=ADEF nway;                 *find unique strata/treatment combinations;
    Where xxx;                               *where conditions provided by table shell;
    class STRATA TRT01P;
    var xxx;                                 *xxx is numeric variable being summarized;
    output out=cells (keep=STRATA TRT01P)  n=n;  *n being output is not used, forces creation of 1
                                                  record per stratum;
run;

proc summary data=ADEF nway;                 *find count of nonmissing within stratum;
    class STRATA;
    var ;
    output out=STRATA (keep=STRATA n) n=n;    *n used as weight;
run;

data om;               * make dataset with strata/treatment combinations each having
                       * number of records as stratum size ;
                       *there will be 2 times the number of records as in the original
                       * dataset;
merge cells strata;
        by strata;
        do i=1 to n;
                output;
        end;
        keep STRATA TRT01Pt;
run;

ods output DIFFS=outstat;
```

```
proc mixed data=ADEF;
   class TRTPN  STRATA;
   model <RESP> = TRTPN  STRATA TRTPN  *STRATA;
   lsmeans TRTPN  / pdiff tdiff cl om=om   diff=control('xxx');
   lsmestimate TRTPN 'Placebo' 0 0 1 / om=om cl;
   lsmestimate TRTPN 'Combined' 0.5 0.5 / om=om cl;
   lsmestimate TRTPN 'Combined vs. Placebo' 0.5 0.5 -1 / om=om cl;
 run;
```

Where the ordering of TRTPN is 1 = 50 mg CTX-4430, 2 = 100 mg CTX-4430, and 3 = Placebo.
<RESP> corresponds to absolute change, percent change or rank of absolute change.

Mixed Model Repeated Measures Analysis

The SAS procedure MIXED will be used in the repeated measures analysis.

```
PROC MIXED DATA=ADSP;
   WHERE PARAMCD = <VALUE>;
   CLASS TRTPN AVISITN USUBJID;
   MODEL <RESP> = TRTPN AVISITN AVISITN*TRTPN;
   LSMEANS TRTPN / CL DIFF=CONTROL('3') ADJUST=DUNNETT;
   LSMEANS TRTP*AVISITN / CL diff;
   LSMEANS TRTP*AVISITN / CL diff=control('3' '48') adjust=dunnett;
   IsmESTIMATE TRTPN*AVISITN 'Combined at Week 4' .5 0 0 0 0 0 0 0 .5 / CL;
   IsmESTIMATE TRTPN*AVISITN 'Combined at Week 8' 0 .5 0 0 0 0 0 0 0 .5 / CL;
   IsmESTIMATE TRTPN*AVISITN 'Combined at Week 12' 0 0 .5 0 0 0 0 0 0 0 .5 / CL;
   IsmESTIMATE TRTPN*AVISITN 'Combined at Week 16' 0 0 0 .5 0 0 0 0 0 0 .5 / CL;
   IsmESTIMATE TRTPN*AVISITN 'Combined at Week 24' 0 0 0 0 .5 0 0 0 0 0 .5 / CL;
   IsmESTIMATE TRTPN*AVISITN 'Combined at Week 32' 0 0 0 0 0 .5 0 0 0 0 0 .5 / CL;
   IsmESTIMATE TRTPN*AVISITN 'Combined at Week 40' 0 0 0 0 0 0 .5 0 0 0 0 0 .5 / CL;
   IsmESTIMATE TRTPN*AVISITN 'Combined at Week 48' 0 0 0 0 0 0 0 .5 0 0 0 0 0 0 .5 / CL;
   IsmESTIMATE TRTPN 'Combined' .5 .5 0 / CL;
   IsmESTIMATE TRTPN*AVISITN 'Combined vs Placebo at Week 4' .5 0 0 0 0 0 0 0 .5 0 0 0 0 0 0 0 -1 / CL;
   IsmESTIMATE TRTPN*AVISITN 'Combined vs Placebo at Week 8' 0 .5 0 0 0 0 0 0 0 .5 0 0 0 0 0 0 0 -1 / CL;
   IsmESTIMATE TRTPN*AVISITN 'Combined vs Placebo at Week 12' 0 0 .5 0 0 0 0 0 0 .5 0 0 0 0 0 0 0 -1 / CL;
   IsmESTIMATE TRTPN*AVISITN 'Combined vs Placebo at Week 16' 0 0 0 .5 0 0 0 0 0 0 .5 0 0 0 0 0 0 0 -1 / CL;
   IsmESTIMATE TRTPN*AVISITN 'Combined vs Placebo at Week 24' 0 0 0 0 .5 0 0 0 0 0 0 .5 0 0 0 0 0 0 0 -1 / CL;
   IsmESTIMATE TRTPN*AVISITN 'Combined vs Placebo at Week 32' 0 0 0 0 0 .5 0 0 0 0 0 0 .5 0 0 0 0 0 0 0 -1 / CL;
   IsmESTIMATE TRTPN*AVISITN 'Combined vs Placebo at Week 40' 0 0 0 0 0 0 .5 0 0 0 0 0 0 .5 0 0 0 0 0 0 0 -1 / CL;
   IsmESTIMATE TRTPN*AVISITN 'Combined vs Placebo at Week 48' 0 0 0 0 0 0 0 .5 0 0 0 0 0 0 .5 0 0 0 0 0 0 0 -1 / CL;
   IsmESTIMATE TRTPN 'Combined vs. Placebo' 0.5 0.5 -1 / CL;
   REPEATED AVISITN / SUBJECT=USUBJID TYPE=UN;
RUN;
```

Cox Proportional Hazards Analysis

The SAS procedure PHREG will be used in the Cox proportional hazards analysis. The following code will be used for the time to first pulmonary exacerbation.

```
proc phreg data=ADTTE;
   WHERE PARAMCD = <value);
   class TRTPN(param=effect);
   model AVAL*CNSR(1) = TRTPN;
   lsmeans TRTPN;
   contrast '50 mg vs Placebo' TRTPN   2   1 / estimate=exp;
   contrast '100 mb vs Placebo' TRTPN   1   2 / estimate=exp;
   contrast 'Combined vs Placebo' TRTPN 3   3 / estimate=exp;
run;
```

Negative Binomial Regression Analysis

The SAS procedure GENMOD will be used in the negative binomial regression analysis. The following code will be used for the number of pulmonary exacerbations.

```
PROC GENMOD DATA=ADSP;
   WHERE PARAMCD = <VALUE>;
   CLASS TRTPN;
   MODEL <RESP> = TRTPN/ DIST=NEGBIN LINK=LOG OFFSET=OFFSET;
   estimate '50mg' intercept 1 TRTPN 1 0 0 / exp;
   estimate '100mg' intercept 1 TRTPN 0 1 0 / exp;
   estimate 'Combined' intercept 1 TRTPN .5 .5 0 / exp;
   estimate 'Placebo' intercept 1 TRTPN 0 0 1 / exp;
 RUN;
```

Where RESP is the count of exacerbations and lnyear is the natural log of years of follow-up for each subject. Estimates of the differences from placebo will be obtained using the SAS macros NLMeans and NLEstimate

Kaplan Meier Analysis

The SAS procedure LIFETEST will be used in the Kaplan-Meier analysis. The following code will be used for the time to first pulmonary exacerbation.

```
PROC LIFETEST DATA=ADTTE METHOD=KM CONFTYPE=LOGLOG;
   STRATA TPTPN;
   TIME AVAL*CNSR(1);
RUN;
```

Where CNSR = 0 for subjects with a pulmonary exacerbation and CNSR = 1 for subjects without a pulmonary exacerbation.