STATISTICAL ANALYSIS PLAN

Study Title:	Randomized, Double-Blind, Phase 3B Trial to Evaluate the Safety and Efficacy of 2 Treatment Regimens of Aztreonam 75 mg Powder and Solvent for Nebulizer Solution / Aztreonam for Inhalation Solution (AZLI) in Pediatric Subjects with Cystic Fibrosis (CF) and New Onset Respiratory Tract *Pseudomonas aeruginosa* (*PA*) Infection/Colonization **A**ztreonam **L**ysine for **P**seudomonas **IN**fection **E**radication 2 (ALPINE 2) Study
Name of Test Drug:	Aztreonam 75 mg powder and solvent for nebulizer solution (European Union [EU]) or Aztreonam for Inhalation Solution (United States [US]) (AZLI)
Study Number:	GS-US-205-1850
Protocol Version (Date):	Original: 11 November 2016 Amendment 1: 31 March 2017 Amendment 2: 06 November 2017 Amendment 3: 15 April 2020
Analysis Type:	Final Analysis
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Analysis Plan Author(s):	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF ABBREVIATIONS

AE	adverse event
ATC	anatomical therapeutic chemical
AZLI	Aztreonam 75 mg powder and solvent for nebulizer solution (European Union [EU]); aztreonam for inhalation solution (US)
BID	twice daily
BMI	body mass index
CF	cystic fibrosis
CFU	colony forming units
CI	confidence interval
CRF	case report form
CSR	clinical study report
DMC	data monitoring committee
eCRF	electronic case report form
ET	early termination
EU	European Union
FAS	full Analysis Set
FEF_{25-75}	forced expiratory flow from 25% to 75% of the forced vital capacity
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
HLT	high-level term
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
ID	Identification
ITT	intent to treat
IWRS	Interactive Web Response System
IV	intravenous
KM	Kaplan-Meier
LLT	lower-level term
LOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MH	Mantel-Haenszel

MIC	minimum inhibitory concentration
MMRM	mixed-effect model for repeated measures
NLP	Natural Language Processing
PA	*Pseudomonas aeruginosa*
PP	Per-protocol
PT	preferred term
PTM	placebo to match
Q1, Q3	first quartile, third quartile
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SI (units)	international system of units
SOC	system organ class
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
TNS	tobramycin nebulizer solution
ULN	upper limit of normal
TID	3 times daily
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) in the clinical study report (CSR) for Study GS-US-205-1850. This SAP is based on the study protocol amendment 3 dated 15 April 2020 and the electronic case report form (eCRF). The SAP will be finalized before the database finalization. Any changes made after the finalization of the SAP will be documented in the CSR.

1.1. Study Objectives

The primary objective of this study is as follows:

To evaluate the safety and efficacy of a 14-day course vs a 28-day course of Aztreonam 75 mg powder and solvent for nebulizer solution (European Union [EU]); aztreonam for inhalation solution (US) (AZLI) 75 mg three times a day (TID) in subjects with new onset *Pseudomonas aeruginosa (PA)* respiratory tract colonization/infection as determined by *PA* eradication over a 28-day post-treatment follow-up period.

The secondary objectives of this study are as follows:

- To evaluate the time from primary eradication to *PA* recurrence over a 108-week post-treatment follow-up period
- To compare the efficacy of AZLI 75 mg TID for 14 days vs historical pooled tobramycin nebulizer solution (TNS) two times a day (BID) for 28 days as determined by *PA* eradication over a 28-day post-treatment follow-up period
- To evaluate the time to *PA* recurrence for a sub-group of subjects matching the population in the TNS ELITE Study {Ratjen 2010} over a 108-week post-treatment follow-up period

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1.2. Study Design

This is a randomized, double-blind, multi-center study in pediatric subjects age 3 months to less than 18 years with CF and newly detected *PA* respiratory tract colonization/infection. Subjects will be randomized in 1:1 ratio in AZLI 28-day or AZLI 14-day treatment arm. The randomization will be stratified by age group (3 months to < 2 years, 2 to < 6 years, and 6 to < 18 years).

The study schedule will consist of a minimum of 13 visits: Screening, Day 1 (Baseline and Randomization), Day 29, Weeks 6, 8, 16, and at 12-week intervals thereafter through Week 112. Subjects may be screened up to 14 days prior to the Baseline visit to determine eligibility for participation in the study. Screening and Baseline may occur on the same day for subjects.

Initial Eradication Phase (Primary Endpoint):

At the Baseline visit (Day 1), eligible subjects will be randomized to a 28-day course of AZLI 75 mg TID or a 14-day course of AZLI 75 mg TID followed by a 14-day course of placebo to match (PTM) TID. Note: AZLI and PTM will both be considered "study drug treatment".

After completing study drug treatment, subjects will be followed through Week 8 for safety and recurrence of *PA* (cultures obtained at Day 29, Week 6, and Week 8).

Follow-Up Culture Phase:

Following the end of the Initial Eradication Phase, subjects will continue in the Follow-Up Culture Phase, with study visits and *PA* cultures obtained at Week 16 and then every 12 weeks for 112 weeks total study duration.

Re-Treatment Phase:

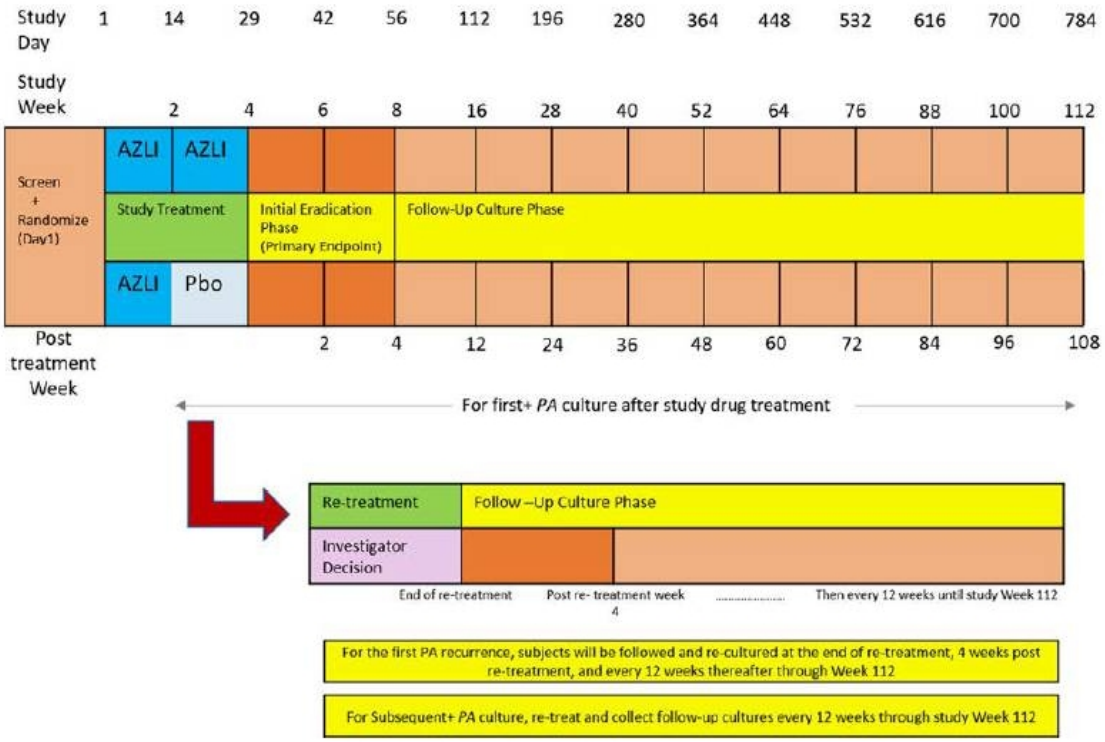
Subjects with *PA* recurrence after study drug treatment should be re-treated with a standard of care antipseudomonal antibiotic regimen at the discretion of the Investigator. A non-exclusive list of re-treatment regimen options include:

- Inhaled AZLI (Cayston®) 75 mg TID x 28 days
- Inhaled tobramycin 300 mg BID x 28 days
- Inhaled colistin 2 million units BID x 28 days (with or without oral ciprofloxacin)
- Any intravenous (IV) antibiotic regimen (with or without additional inhaled or oral antibiotics)
- Other antipseudomonal antibiotic regimen at the discretion of the Investigator (to be documented)

For the first *PA* recurrence, subjects will be followed and re-cultured at the end of re-treatment, 4 weeks post re-treatment, and every 12 weeks thereafter through Week 112. If subjects have subsequent *PA* recurrences post re-treatment, they will be treated at the Investigator's discretion and have continued follow-up cultures collected every 12 weeks through Week 112.

The total study period will be 112 weeks (4 weeks study drug treatment + 4 weeks Initial Eradication Phase + 104 weeks Follow-Up Culture Phase).

A schedule of the study design is provided below.



1.3. Sample Size and Power

A maximum feasible sample size of 130 evaluable subjects (65 subjects per treatment arm) will provide 75% power to show that treatment with AZLI for 14 days is not inferior to treatment with AZLI for 28 days with a 20% noninferiority margin at a 1-sided significance level of 0.025, assuming PA eradication rates for both AZLI treatment groups is 75% {Tiddens 2015}. Assuming a non-evaluability rate of 5 to 7%, up to 140 subjects needed to be enrolled to obtain 130 evaluable subjects for the efficacy analysis.

2. TYPE OF PLANNED ANALYSIS

2.1. Data Monitoring Committee Analyses

An external multidisciplinary Data Monitoring Committee (DMC) will review the progress of the study and perform interim reviews of the safety data in order to protect subject welfare and preserve study integrity. To ensure the best interests of the participants, the DMC will make recommendations to the sponsor if the nature, frequency, and severity of adverse effects associated with the study treatment warrant the early termination of the study, the continuation of the study, or the continuation of the study with modifications.

DMC data review meetings are scheduled via teleconference format. The initial DMC data review meeting is based on data collected after approximately 25% of planned subjects either have provided *PA* cultures through Week 8 or have discontinued the study. Additional meetings will be scheduled every 3 to 6 months following the initial data review meeting. The timing of these meetings may be modified at the discretion of the DMC based on enrollment rates and availability of data.

The DMC's role and responsibilities and the scope of analysis to be provided to the DMC are documented in a mutually agreed upon charter, which defines the DMC membership, meeting logistics, and meeting frequency.

2.2. Primary Analysis

Primary analysis of the primary endpoint is the test of non-inferiority of the 14-day AZLI course compared to the 28-day AZLI course based on the Evaluable Analysis Set. Primary analysis was to be performed after all subjects have completed Week 8, or Week 16 if Week 8 culture data are missing, or are early terminated, and the data have been cleaned and finalized for the analysis. However, due to the challenges brought by COVID-19 pandemic resulting in inability to clean and finalize the data for the primary analysis as required by the study protocol, the primary analysis will be combined with the final analysis.

2.3. Final Analysis

After all subjects have completed the study through Week 112 or are early terminated, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized, the final analysis of the data was to be performed.

However, during ongoing COVID-19 pandemic, the risk of continuing the trial in this vulnerable CF paediatric patient population considerably outweighed the benefits of trial continuation. Therefore, the study was terminated early on September 23rd, 2021. At the time of study termination, all evaluable subjects completed the initial eradication period and provided data for the primary analysis, more than 60% of subjects evaluable for the primary analysis also completed 108-weeks follow-up period, in line with the terms of the agreed Pediatric Investigational Plan (PIP) for Cayston issued by the Pediatric Committee (PDCO) of the European Medicines Agency (EMA).

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of subjects in each category will be presented; for continuous variables, the number of subjects (n), mean, standard deviation (SD) or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

All statistical tests will be 2-sided and performed at the 5% significance level unless otherwise specified.

By-subject listings will be presented for all subjects in the Intent-to-treat (ITT) Analysis Set and sorted by subject ID number, visit date, and time (if applicable). Data collected on log forms, such as AEs, will be presented in chronological order within the subject. The treatment group to which subjects were randomized will be used in the listings. Age, sex at birth, race, and ethnicity will be included in the listings.

3.1. Analysis Sets

Analysis sets define the subjects to be included in an analysis. Analysis sets, and their definitions are provided in this section. Subjects included in each analysis set will be determined before the study blind is broken for analysis. The analysis set will be identified and included as a subtitle of each TFL.

For each analysis set, the number and percentage of subjects eligible for inclusion, as well as the number and percentage of subjects who were excluded and the reasons for their exclusion, will be summarized by treatment group.

A listing of reasons for exclusion from analysis sets will be provided by subject.

3.1.1. Intent-to-treat (ITT) Analysis Set

Intent-to-treat (ITT) Analysis Set includes all subjects who were randomized in the study. The ITT analysis set will be used in a sensitivity analysis of the primary endpoint to evaluate the impact of the treatment regimens on the treatment effect and in data listings.

3.1.2. Evaluable Analysis Set

The evaluable analysis set for the primary efficacy analysis will include all randomized subjects who complete AZLI treatment with at least 75% compliance (prescribed adherence to AZLI, defined in Section 4.2.2.1) and do not use any anti-*PA* antibiotics while on study treatment with AZLI. Evaluability of subjects with missing *PA* culture result through last dose of AZLI + 28 days is determined after applying missing data imputation rules described in Section 3.6.1. After imputation, subjects with missing data in both central and local lab will not be included in the evaluable analysis set unless those subjects have positive *PA* culture from Week 4 to Week 6 for AZLI 14 Days group, or from Week 4 to Week 8 for AZLI 28 Days group.

3.1.3. ELITE Study Matching Analysis Set

The ELITE Study matching analysis set will consist of subjects from Evaluable Analysis Set who also satisfy the published criteria for efficacy analysis population in ELITE Study {Ratjen 2010}. The criteria for subject's inclusion in the ELITE study matching analysis set are:

- Subjects must be 6 months and older at randomization
- No anti-*PA* IgG Antibody Interpretation at Screening/Baseline = positive, and no history of positive anti-*PA* antibody on record
- Did not use anti-pseudomonal antibiotics through 28 days after completion of active treatment (Week 6 or Week 8 visit, depending on treatment assignment)
- Non-missing *PA* culture result at 28 days after last dose of AZLI (Week 6 or Week 8 visit, depending on treatment assignment)
- *PA* negative through 28 days after completion of active treatment (Week 6 or Week 8 visit, depending on treatment assignment)
- No important protocol deviation related to compliance with study drug administration (IPD TA01 "Subject administered more/less medication than required"), no violation of inclusion criterion #3 and exclusion criterion #1
  - — Inclusion criterion #3: Documented new onset of positive respiratory tract culture for *PA* within 30 days of Screening defined as either first lifetime documented *PA*-positive culture, or *PA* recovered after at least a 2-year history of *PA*-negative respiratory cultures (at least 2 cultures per year)
  - — Exclusion criterion #1: Use of IV or inhaled antipseudomonal antibiotics within 2 years of Screening

3.1.4. Per-Protocol Analysis Set

The Per-Protocol (PP) Analysis Set includes subjects in the Evaluable Analysis Set who did not have any important protocol deviations that impacted the primary outcome evaluation, including and not limited to violation of inclusion criterion #3 or exclusion criterion #1, non-compliance with study drug regimen specified in the protocol (IPD TA01 "Subject administered more/less medication than required") or taking prohibited medication (IPD XM01 "Subject took a medication prohibited by the protocol").

The PP Analysis Set is the secondary analysis set for the efficacy analyses.

3.1.5. Safety Analysis Set

The Safety Analysis Set includes subjects randomized and who received at least one dose of study drug. This is the primary analysis set for safety analyses.

3.2. Subject Grouping

For analyses based on the ITT Analysis Set, Evaluable Analysis Set, the ELITE Study Matching Analysis Set and the PP Analysis Set, subjects will be grouped according to the treatment to which they were randomized. For analyses based on the Safety Analysis Set, subjects will be grouped according to the actual treatment received. The actual treatment received will differ from the randomized treatment only when subject's actual treatment differs from randomized treatment for the entire treatment duration.

3.3. Strata and Covariates

Subjects will be randomly assigned to treatment groups via the interactive web response system (IWRS) in a 1:1 ratio using a stratified randomization schedule. Stratification will be based on three age groups (3 months to < 2 years; 2 to < 6 years; and 6 to < 18 years).

If there are discrepancies in stratification factor values between the IWRS and the clinical database, the values recorded in the clinical database will be used for analyses.

Analyses performed using mixed-effect model repeated measures (MMRM), such as pulmonary function test analyses, will include baseline value in the model. Although the randomization is stratified by age group, age group will not be used as a covariate in the analysis model because spirometry assessment is done for subjects 6 years and older.

3.4. Examination of Subject Subgroups

The primary endpoint will be summarized for all subjects and by age group (3 months to < 2 years, 2 to < 6 years, 6 to < 18 years), gender, *PA* infection history (first *PA* infection, recurrent *PA* infection).

3.5. Multiple Comparisons

The primary endpoint will be tested at the 1-sided significance level of 0.025.

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3.6. Missing Data and Outliers

3.6.1. Missing Data

In general, missing data will not be imputed unless methods for handling missing data are specified. Exceptions are presented in this document.

To determine Evaluable Analysis Set, for subjects with missing central microbiology culture results at post-baseline visits during primary eradication period the local microbiology culture results will be used from the same analysis visit, if available. If both central and local microbiology results are missing for any visit, the missing data will be imputed using the next immediate visit. If the result at the next immediate visit is negative, then the negative result will be assigned. If the result at the next immediate visit is positive or missing then no imputation will be done, and the result will remain as missing.

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If Screening and Day 1 visits are performed on the same day and Day 1 pre-dose spirometry assessment is not provided, then the pre-dose analysis time point will be assigned to the Screening visit measurement.

Missing microbiology cultures colony forming units (CFU) data in which the pathogen is absent as determined by culture samples will be set to 0. Otherwise, missing CFU data will not be imputed.

For missing last dosing date of study drug, imputation rules are described in Section 4.2.1. The handling of missing or incomplete dates for AE onset is described in Section 7.1.5.2, and for prior and concomitant medications in Section 7.5.

3.6.2. Outliers

No data will be excluded from the analyses, including any outliers.

3.7. Data Handling Conventions and Transformations

The following conventions will be used for the imputation of date of birth when it is partially missing or not collected:

- If only month and year of birth is collected, then "15" will be imputed as the day of birth
- If only year of birth is collected, then "01 July" will be imputed as the day and month of birth
- If year of birth is missing, then date of birth will not be imputed

In general, age collected at Day 1 (in years) will be used for analyses and presented in listings. If age at Day 1 is not available for a subject, then age derived based on date of birth and the Day 1 visit date will be used instead. If an enrolled subject was not dosed with any study drug, the randomization date will be used instead of the Day 1 visit date. For screen failures, the date the first informed consent was signed will be used for the age derivation. Age required for longitudinal and temporal calculations and analyses (eg, estimates of creatinine clearance, age at date of AE) will be based on age derived from date of birth and the date of the measurement or event, unless otherwise specified.

Data that are continuous in nature but are less than the lower limit of quantitation (LOQ) or above the upper LOQ will be imputed as follows:

- A value that is 1 unit less than the LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "< x" (where x is considered the LOQ). For example, if the values are reported as < 50 and < 5.0, values of 49 and 4.9, respectively, will be used to calculate summary statistics. An exception to this rule is any value reported as < 1 or < 0.1, etc. For values reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively, will be used to calculate summary statistics.

- A value that is 1 unit above the LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "> x" (where x is considered the LOQ). Values with decimal points will follow the same logic as above.

- The LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "≤ x" or "≥ x" (where x is considered the LOQ).

CFU data will be transformed using the base 10 logarithm before calculating changes. To account for zero values, 1 will be added to each CFU measurement before being transformed. Any CFU data values where the pathogen (eg, *PA*) was not isolated from a valid culture will be set to zero (0).

3.8. Study Day and Analysis Visit Assignment

Data obtained after the follow-up culture phase visits will be excluded from the summaries but will be included in the listings.

For subjects who prematurely withdraw from the study, the early termination (ET) data (except respiratory culture records) will be assigned to what would have been the next scheduled visit where the respective data were scheduled to be collected (eg, for subjects with early withdrawals between Visit 3 and 4, the data collected at the ET visit will be summarized at the Visit 4 timepoint).

3.8.1. Definition of Study Day

Study day will be calculated from the first dosing date of study drug and derived as follows:

- For post-dose study days: Assessment Date – First Dosing Date + 1
- For days prior to the first dose: Assessment Date – First Dosing Date

Therefore, study Day 1 is the day of first dose of study drug administration.

3.8.2. Analysis Visit Windows

Subject visits might not occur on protocol-specified days. In general, the values obtained at the nominal visit will be used for analysis, with exception to respiratory culture results.

Any data obtained at unscheduled visits will not be assigned to a particular visit or time point.

The following rules will be applied for respiratory culture results:

- A visit prior to the first dosing of study drug may be included in the calculation of the baseline value, if applicable. If there are multiple *PA* culture results of central or local labs on or prior to the study drug first dose date, priority will go to the record with positive result, then central lab, if available, and then the result closest to first dosing of study drug.
- Respiratory culture records will be assigned to the analysis visit according to analysis visit windows presented in Table 3-1, regardless of whether visit is a regular scheduled visit, unscheduled or Early Termination visit.

Table 3-1. Analysis Visit Windows

Nominal Visit	Nominal Study Day	Lower Limit	Upper Limit
Baseline	1	-43	1
Week 4	29	Date of last dose of AZLI treatment-Date of treatment start date +1	32
Week 6	42	33	45
Week 8	56	46	59
Week 16	112	60	126
Week X (X= 28, 40, 52, 64, 76, 88, 100, 112	X*7	(X-12)*7 +15	X*7 +14

3.8.3. Selection of Data in the Event of Multiple Records in an Analysis Visit Window

Depending on the statistical analysis method, single values may be required for each analysis window. For example, change from baseline by visit usually requires a single value, whereas a time-to-event analysis would not require 1 value per analysis window.

If multiple valid, nonmissing, continuous measurements exist in an analysis window, records will be chosen based on the following rules if a single value is needed:

- In general, the baseline value will be the last nonmissing value on or prior to the first dosing date of study drug, unless specified differently. If multiple measurements occur on the same day, the last nonmissing value prior to the time of first dosing of study drug will be considered as the baseline value. If these multiple measurements occur at the same time or the time is not available, the average of these measurements (for continuous data) will be considered the baseline value.

- For non-microbiology (e.g. spirometry) assessments, the postbaseline values will be assigned using the following priority order:

  — Non-missing nominal visit

  — The record closest to the nominal day for that visit will be selected

  — If there are 2 records that are equidistant from the nominal day, the later record will be selected

  — If there is more than 1 record on the selected day, the worst will be taken, unless otherwise specified.

If multiple valid, nonmissing, non-microbiology categorical measurements exist in an analysis window, records will be chosen based on the following rules if a single value is needed:

- For baseline, the last available record on or prior to the date of the first dose of study drug will be selected. If there are multiple records with the same time or no time recorded on the same day, the value with the lowest severity will be selected.

- For post-baseline visits, if there are multiple records with the same time or no time recorded on the same day, the value with the worst severity within the window will be selected.

For the respiratory culture data, when multiple records of central or local labs are mapped to the same nominal visit, for visits through Week 8, local lab result will only be used when central lab result from the same visit is missing; for visits after Week 8, priority will go to the record with positive result, and then the earliest result. If multiple central laboratory records are mapped to the same nominal visit then the priority will go to the record with positive respiratory culture result, and next to the scheduled visit record. If there are the same *PA* culture results from central and local lab done on the same day, then the priority is given to the central lab result.

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

A summary of subject enrollment will be provided by treatment group for each country, investigator within a country, and overall. The summary will present the number and percentage of subjects enrolled. For each column, the denominator for the percentage calculation will be the total number of subjects analyzed for that column.

A similar enrollment table will be provided by stratification factor stratum. The denominator for the percentage of subjects in the stratum will be the total number of randomized subjects. If there are discrepancies in the value used for stratification assignment between the IWRS and the clinical database, the value collected in the clinical database will be used for the summary. A listing of subjects with discrepancies in the value used for stratification assignment between the IWRS and the clinical database at the time of data finalization will be provided.

The randomization schedule used for the study will be provided as an appendix to the CSR.

A summary of subject disposition will be provided by treatment group. This summary will present the number of subjects screened, the number of subjects who met all eligibility criteria but were not randomized with reasons subjects not randomized, the number of subjects randomized, and the number of subjects in each of the categories listed below:

- Safety Analysis Set
- Per-Protocol Analysis Set
- ITT Analysis Set
- Evaluable Analysis Set
  - Did not meet evaluability criteria due to < 75% compliance
  - Did not meet evaluability criteria due to use of anti-*PA* antibiotics while on AZLI treatment
  - Did not meet evaluability criteria due to missing *PA* culture result during initial eradication phase
- The ELITE Study Matching Analysis Set
- Completed study drug
- Did not complete study drug with reasons for premature discontinuation of study drug
- Completed study
- Did not complete the study with reasons for premature discontinuation of study

For the status of study drug and study completion and reasons for premature discontinuation, the number and percentage of subjects in each category will be provided. The denominator for the percentage calculation will be the total number of subjects in the Safety Analysis Set corresponding to that column. In addition, a flowchart will be provided to depict the disposition.

The following by-subject listings will be provided by subject identification (ID) number in ascending order to support the above summary tables:

- Reasons for premature study drug or study discontinuation
- Lot number and kit ID of assigned study drugs

4.2. Extent of Study Drug Exposure and Adherence

Extent of exposure to study drug will be examined by assessing the total duration of exposure to study drug and the level of adherence to the study drug specified in the protocol.

4.2.1. Duration of Exposure to Study Drug

Total duration of exposure to study drug will be defined as last dosing date minus first dosing date plus 1, regardless of any temporary interruptions in study drug administration, and will be expressed in days using up to 1 decimal place (eg, 10.5 days). If the last study drug dosing date is missing, the latest date among the study drug end date, clinical visit date, laboratory sample collection date, and vital signs assessment date that occurred during the on-treatment period will be used.

The total duration of exposure to active AZLI treatment will be summarized using descriptive statistics and using the number (ie, cumulative counts) and percentage of subjects exposed through the following time periods: ≥ 1 day, ≥ 8 days, ≥ 15 days, and ≥ 29 days. Summaries will be provided by treatment group for the Safety Analysis Set.

No formal statistical testing is planned.

4.2.2. Adherence to Study Drug

The total number of vials of AZLI administered will be summarized using descriptive statistics.

The presumed total number of vials administered to a subject will be determined by the data collected on the drug accountability CRF using the following formula:

$$\text{Total Number of Vials Administered} = \left(\sum \text{No. of Vials Dispensed}\right) - \left(\sum \text{No. of Vials Returned}\right)$$

Total dose (mg) taken will be calculated as 75 times the number of vials taken.

In general, unreturned missing vials will be assumed to have not been inhaled. Subjects without a vial return record are assumed to have taken one dose at clinic (at day 1 visit) and their total number of inhaled vials equals one.

4.2.2.1. Prescribed Adherence

The level of prescribed adherence to the AZLI treatment will be determined by the total amount of study drug administered relative to the total amount of study drug specified by the protocol for a subject who completes treatment in the study.

The level of prescribed adherence will be expressed as a percentage using the following formula:

$$\text{Prescribed Adherence (\%)} = \left(\frac{\text{Total Amount of Study Drug Administered}}{\text{Total Amount of Study Drug Specified by Protocol}} \right) \text{ x } 100$$

Specifically, the Prescribed Adherence (%) of AZLI 14 Days group will be calculated as:

$$\text{Prescribed Adherence (\%)}_{14} = \min[100, 100^* \text{ (total number of inhaled vials)}/(3*14)]$$

The Prescribed Adherence of AZLI 28 Days group will be calculated as:

$$\text{Prescribed Adherence (\%)}_{28} = \min[100, 100^* \text{ (total number of inhaled vials)}/(3*28)]$$

The prescribed adherence to AZLI and overall prescribed adherence (regardless of treatment assignment) will be provided in the listing.

Descriptive statistics for the level of prescribed adherence with the number and percentage of subjects belonging to adherence categories (eg, < 75, ≥ 75 to $< 80\%$, ≥ 80 to $< 85\%$, ≥ 85 to $< 90\%$, ≥ 90 to $< 95\%$, $\geq 95\%$) will be provided by treatment group for the Safety Analysis Set.

Total number of used vials will be summarized (mean, median, SD, minimum, maximum, and n).

Subjects are defined as treatment compliant if they used at least 75% of the vials they were supposed to use based on Prescribed Adherence calculations above.

No formal statistical testing is planned.

A by-subject listing of study drug administration and drug accountability will be provided separately by subject ID number (in ascending order) and visit (in chronological order).

4.3. Protocol Deviations

Subjects who did not meet the eligibility criteria for study entry but enrolled in the study will be summarized regardless of whether they were exempted by the sponsor or not. The summary will present the number and percentage of subjects who did not meet at least 1 eligibility criterion and the number of subjects who did not meet specific criteria by treatment group based on the ITT Analysis Set. A by-subject listing will be provided for those subjects who did not meet at least 1 eligibility (inclusion or exclusion) criterion. The listing will present the eligibility criterion (or criteria if more than 1 deviation) that subjects did not meet and related comments, if collected.

Protocol deviations occurring after subjects entered the study are documented during routine monitoring. The number and percentage of subjects with important protocol deviations by deviation reason (eg, nonadherence to study drug, violation of select inclusion/exclusion criteria) will be summarized by treatment group for the ITT Analysis Set. A by-subject listing will be provided for those subjects with important protocol deviation.

4.4. Assessment of COVID-19 Impact

This study was ongoing during the novel coronavirus (COVID-19) pandemic which had an impact on the study conduct. Some subjects were unable to attend onsite visits due to shelter in place guidelines, site closures, or other reasons. This section describes how special situations due to COVID-19 will be handled in the analysis.

4.4.1. Study Drug or Study Discontinuation Due to COVID-19

A by-subject listing of reasons for premature study drug or study discontinuation due to COVID-19 will be provided, if applicable.

4.4.2. Protocol Deviations Due to COVID-19

A by-subject listing will be provided for subjects with important protocol deviations related to COVID-19. A separate listing will be provided for subjects with non-important protocol deviations related to COVID-19.

4.4.3. Missed and Virtual Visits due to COVID-19

An overall summary of the number and percentage of subjects with missed or virtual visits (e.g., at least 1, with 1, 2, 3 or more visits) due to COVID-19 will be provided by treatment group and overall. The denominator for the percentage calculation will be the total number of subjects in the safety population for that column.

A by-subject listing of subjects with missed or virtual visits due to COVID-19 will be provided by subject ID number in ascending order.

Information regarding missed or virtual visits due to COVID-19 will be collected as free text in the CRF comment fields. The determination of missed or virtual visits due to COVID-19 will be done using Natural Language Processing (NLP) to search the CRF comment fields. A detailed explanation of the algorithm is given in Appendix 2.

4.4.4. COVID-19 Adverse Events

AEs of COVID-19 will be included in analyses of AEs if applicable, which will be determined through COVID-19 SMQ broad search. A by-subject listing of AEs of COVID-19 will be provided, if applicable.

4.4.5. Overall Assessment of COVID-19 Pandemic Impact

For subjects affected by COVID-19 infection and/or pandemic while participating in the study, a listing of the following individual COVID-19 related outcome categories will be provided:

- Death due to COVID-19
- Adverse event of COVID-19, as determined by COVID-19 SMQ broad search
- Hospitalization (using data from AE eCRF) due to adverse event of COVID-19 as defined above
- Study drug discontinuation due to COVID-19
- Study discontinuation due to COVID-19
- Missed visits due to COVID-19
- Missed *PA* culture collection due to COVID-19

In addition, composite broad COVID-19 impact indicator will be derived based on the following individual categories defined above: death, adverse event, hospitalization, study drug discontinuation, study discontinuation, missed visits, and missed key assessments. Composite specific COVID-19 impact indicator will be derived based on death and specific adverse event.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Subject demographic variables (ie, age, sex, race, and ethnicity) and baseline characteristics (body weight [in kg], height [in cm], body mass index [BMI; in kg/m^2], vital signs) will be summarized by treatment group and overall using descriptive statistics for continuous variables and using number and percentage of subjects for categorical variables. The summary of demographic data will be provided for the Safety Analysis Set for the following:

- Age (on the first dose date of any study drug) as a continuous variable
- Age group (3 months to < 2 years; 2 to < 6 years; and 6 to < 18 years)
- Sex (male, female)
- Race (American Indian or Alaska Native, Asian, Black or African American, White or Other)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, Not permitted)
- body weight [in kg]
- height [in cm]
- body mass index [BMI in kg/m^2]
- vital signs (blood pressures in mmHg, pulse in beats/min, temperate in C°)

A by-subject demographic listing, including the informed consent date, will be provided by subject ID number in ascending order.

5.2. Other Baseline Characteristics and CF Disease Characteristics

Other baseline characteristics include:

[redacted]

- Respiration Rate at baseline (breaths/min)

- O_2 Saturation (%) at baseline
- Chest Auscultation at baseline
- Presence of *PA* at baseline (Present or Absent)
- *PA* mucoid phenotype (mucoid *PA*, non-mucoid *PA*)
- Log10 *PA* CFU for Patients with Positive *PA*
- MIC of Aztreonam for All *PA* Isolates
- Highest Aztreonam MIC for *PA* (ug/mL)
- Infection history (first *PA* infection, recurrence)
- Anti-*PA* IgG antibodies (interpretation categories: negative, borderline, positive)
- CF Disease characteristics:
  - Sweat Chloride Test (mEq/L)
  - Sweat Sodium (mEq/L)
  - CF Genotype (Total, Homozygous, Heterozygous, Unidentified, Other, Missing)
    1) Homozygous if both of the results are 'Delta F508'
    2) Heterozygous if one result is 'Delta F508' and one is 'other', 'unidentified', or missing
    3) Unidentified if both of the two results are 'unidentified', or if one result is 'unidentified' and one is 'missing'
    4) Other if one result is 'other' and one is 'other', 'unidentified', or missing
    5) Missing if both results are missing

These baseline and CF disease characteristics will be summarized by treatment group and overall using descriptive statistics for continuous variables and using number and percentage of subjects for categorical variables. The summary of baseline characteristics will be provided for the Safety Analysis Set.

In addition, the number and percent of subjects with positive result for pathogens detected from nasal swabs obtained at baseline visit using Biofire assay will be summarized.

A by-subject listing of other baseline characteristics will be provided by subject ID number in ascending order.

5.3. Medical History

Disease-specific medical history will be collected on the CRFs and will be summarized using descriptive statistics (sample size, mean, SD, median, Q1, Q3, minimum, and maximum) for continuous data, by the number and percent of subjects for categorical data, and by total counts for multiple records data.

Summaries of previous *PA* infection history will be provided for the safety analysis set. Summaries of previous *PA* infection history will include number of subjects with first *PA* infection and recurrent *PA* infection. Subcategories of the number of subjects with 1, 2, 3, 4, and ≥ 5 additional previous *PA* infections (ie, not including the infection to qualify for the study) will be included within the category of recurrent *PA* infection. The number of subjects with available data will be used as the denominator in the summaries.

General medical history data will be collected at screening and listed only. General medical history data will not be coded.

6. EFFICACY ANALYSES

6.1. Primary Efficacy Endpoint

6.1.1. Definition of the Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects with *PA*-negative cultures through 28 days post-treatment in the 14-day treatment group vs 28-day treatment group. Evaluable Analysis Set of the primary efficacy endpoint is defined in Section 3.1.2. Subjects with no *PA*-positive culture at Week 4 through Week 6 (for 14-day AZLI treatment group) or Week 8 (for 28-day AZLI treatment group) analysis visit will be considered to be a responder for the primary endpoint (analysis visits are defined in Section 3.8.2, handling of missing *PA* culture results are described in Section 3.8.3).

6.1.2. Analysis of the Primary Efficacy Endpoint

Primary analysis of the primary endpoint is the test of non-inferiority of the 14-day AZLI course compared to the 28-day AZLI course based on the Evaluable Analysis Set. The proportion of evaluable subjects with *PA*-negative cultures through 28 days post-treatment (Week 6 visit for subjects in the 14-day treatment group and Week 8 visit for subjects in the 28-day group) for each treatment group will be presented with 2-sided exact 95% confidence interval (CI). The difference in proportions between treatment groups, and the associated 95% CIs will be constructed based on stratum-adjusted Mantel-Haenszel (MH) proportions, using age group (as in IWRS) as stratification factor, as follows {Koch 1989}:

$$p_A - p_B \pm Z_{(1-\alpha/2)} * SE(p_A - p_B),$$

where

- $(p_A - p_B) = \frac{\sum w_h d_h}{\sum w_h}$, is the stratum-adjusted MH proportion difference, where $d_h = p_{Ah} - p_{Bh}$ is the difference in the proportion of subjects who met the endpoint between 14-day AZLI and 28-day AZLI groups in age stratum h.
- $w_h = \frac{n_{Ah} n_{Bh}}{n_{Ah} + n_{Bh}}$, is the weight based on the harmonic mean of sample size per treatment group for each stratum where n_{Ah} and n_{Bh} are the sample sizes of 14-day AZLI and 28-day AZLI in age stratum h.
- $SE(p_A - p_B) = \sqrt{\frac{\sum w_h^2 \left[\frac{p^*_{Ah}(1-p^*_{Ah})}{n_{Ah}-1} + \frac{p^*_{Bh}(1-p^*_{Bh})}{n_{Bh}-1} \right]}{(\sum w_h)^2}}$, where

- $p^*_{Ah} = \frac{m_{Ah} + 0.5}{n_{Ah} + 1}$ and $p^*_{Bh} = \frac{m_{Bh} + 0.5}{n_{Bh} + 1}$, and
- m_{Ah} and m_{Bh} are the number of subjects who met the endpoint in14-day AZLI and 28-day AZLI in age stratum h.
- $\alpha = 0.05$ for the calculation of 95% CI
- $Z_{(1-\alpha/2)} = Z_{0.975}$ is the 97.5th percentile of the normal distribution
- Z score = $\frac{(p_A - p_B)}{SE_{(p_A - p_B)}}$

Evaluable Analysis Set of primary efficacy endpoint is defined in Section 3.1.2. Non-inferiority of the 14-day treatment regimen will be claimed if the lower bound of 1-sided 97.5% confidence limit of the treatment difference (14-day course group vs 28-day course group) is above the non-inferiority margin of -20%.

The primary endpoint will be summarized for all subjects and by age group (3 months to < 2 years, 2 to < 6 years, 6 to < 18 years) and for gender, infection history (first *PA* infection, recurrent *PA* infection), and presence of *PA* at baseline (presence, absence) subgroups, In each subgroup analysis, the proportion of evaluable subjects with *PA*-negative cultures at all time points through Week 8 for each treatment group will be summarized (n and percentage) and an exact 95% CI will be provided based on this sensitivity analysis population of subjects. The difference in proportions between treatment groups, and the associated 95% CIs will be constructed based on stratum-adjusted MH method using age as stratification factor, except for the by-age subgroup analysis, where the difference in proportions between treatment groups, and the associated 95% CIs will be calculated without age stratum adjustment.

To evaluate the robustness of the treatment effect, the following sensitivity analyses of the primary endpoint will be conducted:

- Sensitivity analysis 1 will be based on the ITT analysis Set and will use the same definition of primary efficacy endpoint as in Section 6.1
- Sensitivity analysis 2 will be based on PP Analysis Set and will use the same definition of primary efficacy endpoint as in Section 6.1.
- In sensitivity analysis 3, subjects with any anti-pseudomonal antibiotic use through 28 days after completion of AZLI treatment (Week 6 or Week 8 visit), or with a *PA*-positive culture at Week 4 through Week 6 or Week 8, depending on treatment assignment, will be defined as treatment failures. Analysis will be based on Evaluable Analysis Set.
- In sensitivity analysis 4, subjects with a *PA*-positive culture from either central or local lab at Week 4 through Week 6 or Week 8, depending on treatment assignment, will be defined as treatment failures. Analysis will be based on Evaluable Analysis Set.

The proportion of evaluable subjects with *PA*-negative cultures at all time points through Week 8 for each treatment group will be summarized (n and percentage) and an exact 95% CI will be provided based on this sensitivity analysis population of subjects. The difference in proportions between treatment groups, and the associated 95% CIs will be constructed based on stratum-adjusted MH method using age as stratification factor, as well.

6.2. Secondary Efficacy Endpoints

6.2.1. Definition of Secondary Efficacy Endpoints

The secondary efficacy endpoints of this study are:

- Time from primary eradication to *PA* recurrence over a 108-week post-treatment follow-up period
- The proportion of subjects with *PA*-negative cultures through 28 days post-treatment in the 14-day treatment group vs historical pooled data for *PA* eradication at 28 days post-treatment in subjects treated with TNS
- Time to *PA* recurrence after primary eradication for a sub-group of subjects matching the population in the TNS ELITE Study over a 108-week post-treatment follow-up period

6.2.2. Analysis Methods for Secondary Efficacy Endpoints

For time to recurrence secondary endpoint, local lab *PA* presence will be considered and will override a central lab *PA* absence result, if they are mapped to the same clinical visit. The actual date of the lab, whether unscheduled or at scheduled clinic visit will be used as the event date of the recurrence of *PA* after the primary eradication. Recurrence after *PA* eradication is defined as first positive *PA* culture result in subject who met the primary endpoint and had no local lab *PA*-positive culture from Week 4 to Week 6 for AZLI 14 Days group, or from Week 4 to Week 8 for AZLI 28 Days group. The end of the primary eradication period will be calculated as following: the date of last dose of AZLI + 28 days. The first day of follow-up period will be derived as the date of last AZLI administration + 29 days.

Time (in days) to the event will be calculated as [earliest date of event – (last AZLI dose date +28 days) +1].

Subjects without *PA* recurrence will be censored at the last lab visit date with PA culture result.

Time (in days) to censoring will be calculated as [last lab visit date – (last AZLI dose date +28 days) +1].

The median time to *PA* recurrence after the primary eradication over the 108-week post-treatment follow-up period will be assessed using un-stratified Kaplan-Meier (KM) method. In addition to median time, the KM estimates of recurrence probability and 95% CIs will be

presented for each 12-week interval post-primary eradication by treatment group based on the Evaluable Analysis Set. Additional summaries of time to PA recurrence will be provided in months and by age subgroups (3 months to < 2 years, 2 years to < 6 years, and 6 to < 18 years). The corresponding KM figures will be provided.

The median time to *PA* recurrence and 95% CI will be presented for ELITE-matching analysis set as described in Section 3.1.3, and compared descriptively with the published result from ELITE Study (median time to recurrence after 28-day treatment with tobramycin is 26.12 months with 95% CI [14.69 to NA]).

The proportion of subjects with *PA*-negative cultures during 28 days post-treatment period in the 14-day course group will be summarized at each visit (n and percent) and be presented with exact 95% CI and compared descriptively with historical pooled data for proportion of subjects with *PA* eradication at 28 days post-treatment with TNS. The historical data for the proportion of subjects with *PA*-negative cultures during 28 days post-treatment period will be pooled from the published results from the studies conducted on the subjects with new onset of *PA* infection and similar TNS treatment duration and follow-up. {Gibson 2003, Proesmans 2013}. The proportion of subjects with *PA* eradication at 28 days post-treatment with TNS in Gibson 2003 is 6/8 (75%), while that based on estimates from KM curve in Proesmans 2013 is 18/23 (78%). The pooled proportion of subjects with successful *PA* eradication at 28 days post-treatment with TNS is estimated to be (6+18)/(8+23)=77%.

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7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using the MedDRA v24.1. System organ class (SOC), high-level term (HLT), and preferred term (PT) will be provided in the AE dataset.

7.1.2. Adverse Event Severity

Adverse events are graded by the investigator as Grade 1, 2, 3, 4 or 5 according to toxicity criteria specified in the protocol (Amendment 3). The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings. The missing category will be listed last in summary presentation.

7.1.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator selected "Related" on the AE CRF to the question of "Related to Study Treatment." Relatedness will always default to the investigator's choice, not that of the medical monitor. Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-subject data listings will show the relationship as missing.

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if the AEs met the definitions of SAEs that were specified in the study protocol. SAEs captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Global Patient Safety Department before data finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as 1 or both of the following:

- Any AEs with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug
- Any AEs leading to premature discontinuation of study drug.

7.1.5.2. Incomplete Dates

If the onset date of the AE is incomplete and the AE stop date is not prior to the first dosing date of study drug, then the month and year (or year alone if month is not recorded) of onset determine whether an AE is treatment emergent. The event is considered treatment emergent if both of the following 2 criteria are met:

- The AE onset is the same as or after the month and year (or year) of the first dosing date of study drug, and
- The AE onset date is the same as or before the month and year (or year) of the date corresponding to 30 days after the date of the last dose of study drug

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date later than the first dosing date of study drug, will be considered to be treatment emergent. In addition, an AE with the onset date missing and incomplete stop date with the same or later month and year (or year alone if month is not recorded) as the first dosing date of study drug will be considered treatment emergent.

7.1.6. Summaries of Adverse Events and Deaths

Treatment-emergent AEs will be summarized based on the Safety Analysis Set.

7.1.6.1. Summaries of AE incidence in Combined Severity Grade Subsets

A brief, high-level summary of the number and percentage of subjects who experienced at least 1 TEAE in the categories described below will be provided by treatment group. All deaths observed in the study will also be included in this summary.

The number and percentage of subjects who experienced at least 1 TEAE will be provided and summarized by SOC, HLT, PT, and treatment group. This summary will be provided for all subjects and by age (3 months to < 2 years, 2 to < 6 years, 6 to < 18 years).

For other AEs listed below, summaries will be provided by SOC, HLT, PT, and treatment group:

- TEAEs of Grade 3 or higher
- TE treatment-related AEs
- TE treatment-related AEs with Grade 3 or higher
- TE SAEs
- TE treatment-related SAEs
- TEAEs leading to premature discontinuation of study drug

- TE SAEs leading to hospitalization

Multiple events will be counted only once per subject in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC and HLT within each SOC (if applicable), and then by PT in descending order of total frequency within each SOC. For summaries by severity grade, the most severe grade will be used for those AEs that occurred more than once in an individual subject during the study.

In addition to the above summary tables, all TEAEs, TE SAEs, TE treatment-related AEs, and TE treatment-related SAEs will be summarized by PT only, in descending order of total frequency.

The AZLI exposure adjusted TEAE incidence rates will be presented by PT in descending order of overall rate.

In addition, data listings will be provided for the following:

- All AEs, indicating whether the event is treatment emergent
- All SAEs
- All Deaths
- All AEs of Grade 3 or higher
- All AEs leading to premature discontinuation of study drug

Summaries (number and percentage of subjects) of follow-up SAEs (by SOC, HLT, and PT) will also be provided using the safety analysis set. Follow-up SAEs are defined as those that start 30 days after the last dose of study drug and don't meet the definition of a treatment-emergent AE.

7.2. Laboratory Evaluations

Laboratory data collected at baseline will be analyzed and summarized. The analysis will be based on values reported in conventional units. When values are below the LOQ, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.7.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by treatment group for each baseline laboratory test specified in the study protocol

A baseline laboratory value will be defined as the last measurement obtained on or prior to the date/time of first dose of study drug. The mean, median, Q1, Q3, minimum, and maximum

values will be displayed to the reported number of digits; SD values will be displayed to the reported number of digits plus 1.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3.

7.2.2. Graded Laboratory Values

The Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 will be used to assign toxicity grades (0 to 4) to laboratory results for analysis. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1.

7.2.2.1. Summaries of Laboratory Abnormalities

A by-subject listing for abnormal laboratory test results will be provided by subject ID number for hematology, serum chemistry, and urinalysis. Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher will be included in the data listing, as appropriate.

7.3. Body Weight, Height, and Vital Signs

Descriptive statistics (sample size, mean, SD, median, Q1, Q3, minimum and maximum) will be provided by treatment group for body weight, height, BMI and vital signs (heart rate, systolic and diastolic blood pressure, body temperature, and respiratory rate) at baseline.

A baseline value will be defined as the last available value collected on or prior to the date/time of first dose of study drug. Body weight and vital signs measured at unscheduled visits will be included for the baseline value selection.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3. No formal statistical testing is planned.

A by-subject listing of vital signs will be provided by subject ID number at baseline and unscheduled visits in chronological order. Body weight, height, and BMI will be included in the vital signs listing.

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7.5. Prior and Concomitant Medications

Medications collected at screening and during the study will be coded using the current version of the World Health Organization (WHO) Drug dictionary.

7.5.1. Prior Medications

Prior medications are defined as any medications taken before a subject took the first study drug.

Prior medications will be summarized by Anatomical Therapeutic Chemical (ATC) drug class Level 2 and preferred name using the number and percentage of subjects for each treatment group and overall. A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of subjects who received that medication. The summary will be ordered alphabetically by ATC medical class and then by preferred term alphabetically within each ATC medical class.

For the purposes of analysis, any medication with a start date prior to the first dosing date of study drug will be included in the prior medication summary regardless of when the stop date is. If a partial start date is entered the medication will be considered prior unless the month and year (if day is missing) or year (if day and month are missing) of the start date are after the first dosing date. Medications with a completely missing start date will be included in the prior medication summary, unless otherwise specified.

Summaries will be based on the Safety Analysis Set. No formal statistical testing is planned.

7.5.2. Concomitant Medications

Concomitant medications are defined as medications taken while a subject took study drug. Use of concomitant medications will be summarized by ATC drug class Level 2 and preferred name using the number and percentage of subjects for each treatment group. A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of subjects who received that medication. The summary will be ordered alphabetically by ATC medical class and then by preferred term alphabetically within each ATC medical class.

For the purposes of analysis, any medications with a start date prior to or on the first dosing date of study drug and continued to be taken after the first dosing date, or started after the first dosing date but prior to or on the last dosing date of study drug will be considered concomitant medications. Medications started and stopped on the same day as the first dosing date or the last dosing date of study drug will also be considered concomitant. Medications with a stop date prior to the date of first dosing date of study drug or a start date after the last dosing date of study drug will be excluded from the concomitant medication summary. If a partial stop date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) prior to the date of first study drug administration will be excluded from the concomitant medication summary. If a partial start date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) after the study drug stop date will be excluded from the concomitant medication summary. Medications with completely missing start and stop dates will be included in the concomitant medication summary, unless otherwise specified. Summaries will be based on the Safety Analysis Set. No formal statistical testing is planned.

All prior and concomitant medications (other than per-protocol study drugs) will be provided in a by-subject listing sorted by subject ID number and administration date in chronological order.

7.6. Other Safety Measures

No additional safety measures are specified in the protocol.

7.7. Changes from Protocol-Specified Safety Analyses

Additional analyses describing impact of COVID-19 pandemic are described in the Section 4.4.4.

8. REFERENCES

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9. SOFTWARE

SAS® Software Version 9.4. SAS Institute Inc., Cary, NC, USA.

nQuery Advisor(R) Version 6.0. Statistical Solutions, Cork, Ireland.

10. SAP REVISION

Revision Date (DD MMM YYYY)	Section	Summary of Revision	Reason for Revision

11. APPENDIX 1 SCHEDULE OF ASSESSMENTS

	Screening[g]	Baseline (Day 1)[g]	Initial Eradication Phase				Follow-up culture Phase[k]		Other Visits	
Day/Week	**Day-13 to Day 1**	**Day 1[h]**	**Day 14/ Week 2**	**Day 29/ Week 4[h]**	**Week 6**	**Week 8**	**Weeks 16, 28, 40, 52, 64, 76, 88, 100**	**Week 112**		
Visit Windows			**± 1 day**	**± 1 day**	**± 3 day**	**± 3 day**	**± 14 day**	**± 14 day**		
Visit	**1**	**2**	**(Telephone contact)**	**3**	**4**	**5**	**6-13**	**14**	**ET**	**Unscheduled**
Written Informed Consent	X									
Inclusion/Exclusion Criteria	X	X[f]								
Subject Demographics	X									
Medical History	X									
Complete Physical Examination	X							X	X	
Modified Physical Examination		X		X	X	X	X			X
Body Weight, Height and Vital Signs	X									X
Hematology and Serum Chemistry	X[a]									
Blood for Biomarkers[i]	X									
Respiratory Sample for Microbiology[n]	X	X (pre-dose)		X	X	X	X	X	X	X
Nasal Swab for Microbiology		X (pre-dose)								
Urine Pregnancy Test[c]	X	X (pre-dose)		X		X			X[e]	X
Randomization		X								

	Screening[g]	Baseline (Day 1)[g]	Initial Eradication Phase				Follow-up culture Phase[k]		Other Visits	
Day/Week	**Day-13 to Day 1**	**Day 1[h]**	**Day 14/ Week 2**	**Day 29/ Week 4[h]**	**Week 6**	**Week 8**	**Weeks 16, 28, 40, 52, 64, 76, 88, 100**	**Week 112**		
Visit Windows			**± 1 day**	**± 1 day**	**± 3 day**	**± 3 day**	**± 14 day**	**± 14 day**		
Visit	**1**	**2**	**(Telephone contact)**	**3**	**4**	**5**	**6-13**	**14**	**ET**	**Unscheduled**
Instruct Subject on Study Drug Administration, Dosing, and Storage and on Proper Operation/Cleaning of Altera®		X								
Administer Study Treatment in Clinic		X								
Administer Study Treatment at Home, 3 times per day		X	X[l]							
Administer short-acting β2 agonist	X	X (pre[f] and post-dose)		X	X	X	X	X	X	X
CCI										
Clinical Observations for study drug-induced adverse events[b]		X (pre and post-dose)								
Dispense Study Treatment Kits, Sterilizer, Altera® Nebulizer System (eBase & handset, mask if applicable), and Dosing Log		X								

	Screening[g]	Baseline (Day 1)[g]	Initial Eradication Phase				Follow-up culture Phase[k]		Other Visits	
Day/Week	**Day-13 to Day 1**	**Day 1[h]**	**Day 14/ Week 2**	**Day 29/ Week 4[h]**	**Week 6**	**Week 8**	**Weeks 16, 28, 40, 52, 64, 76, 88, 100**	**Week 112**		
Visit Windows			**± 1 day**	**± 1 day**	**± 3 day**	**± 3 day**	**± 14 day**	**± 14 day**		
Visit	**1**	**2**	**(Telephone contact)**	**3**	**4**	**5**	**6-13**	**14**	**ET**	**Unscheduled**
Collect device system components (eBase Unit, Handset and Mask if applicable), Used and Unused Drug Vials, and Dosing Log				X					X[j]	
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X
Adverse Events[m]	X	X	X	X	X	X	X	X	X	X

PA= Pseudomonas aeruginosa, OP= Oropharyngeal, [redacted]
AZLI= Aztreonam for Inhalation Solution.

a Hematology and serum chemistry only needed at screening if there are no labs available within the previous 12 months to assess eligibility
b For subjects 3 months of age to <6 years of age and subjects 6 years of age and older who cannot reliably perform spirometry assessments - chest auscultation, respiratory rate, and oxygen saturation
c All females of childbearing potential, if result is positive confirm with a serum pregnancy test
[redacted]
e If ET visit occurs within 30 days of the last dose of study drug
[redacted]
g These visits may be combined and performed on the same day
h Fungal culture (for *Aspergillus spp*) analysis from respiratory sample only on Day 1 and Day 29
i Anti-*PA* Antibodies (only needed at screening if there are no results available within the previous 24 months)
j If ET visit occurs before Day 29
k These visits (not including Week 112 or the ET visit) can be performed at home by specialist CF nurses if this is standard of care at the clinic and appropriate respiratory samples can be obtained and processed
l Subjects should be contacted via telephone on Day 14 to assess whether they have had any adverse events or taken any concomitant medications and instruct subject/parent to switch to second carton of study drug treatment on Day 15
m During Follow-up Culture phase, only those AE/SAEs related to protocol mandated procedures should be reported to Gilead PVE. Also, AEs/SAEs related to Cayston treatment in the re-treatment phase must be collected and reported to Gilead PVE.
n If the subject is not able to expectorate sputum at a study visit, alternative methods of lower respiratory tract specimen collection may be performed as per local standard of care (eg induced sputum, cough swab, nasopharyngeal aspiration, laryngeal suction). If a lower respiratory specimen cannot be obtained, an oropharyngeal (throat) swab may be taken

12. APPENDIX 2 DETERMINING MISSING AND VIRTUAL VISITS DUE TO COVID-19

This appendix describes the clinical trial site collection of COVID-19 data pertaining to missed/virtual visits and the data processing algorithm that will be used to determine which visits are missing and which visits are virtual.

12.1. Data Collection

A COVID-19 supplement to the eCRF Completion Guidelines (CCG) was provided by Clinical Data Management to instruct clinical trial sites with data entry expectations pertaining to scenarios related to the COVID-19 pandemic. If a visit was missed, sites were instructed to enter "Visit missed due to COVID-19" and if an in-person visit was conducted virtually, sites were instructed to enter "Virtual visit due to COVID-19".

12.2. Determination of Missed and Virtual Visits

Natural Language Processing (NLP) will be used to search the CRF comment fields to identify instances of "COVID-19", "Virtual", or synonyms (see Table 12-1). The search terms will be maintained in a global lookup table and can be modified to tune the NLP model. Any comments with COVID-19 search terms, "Missed visit" or "Virtual visit will be assigned as follows:

i. If COVID-19 terms are identified through NLP and the visit date is missing, then result is "Missed Visit"
ii. If COVID-19 and Virtual terms are identified through NLP for a visit, then result is "Virtual Visit". When there are multiple records for the same subject and the same visit, if one record could be categorized as "Virtual Visit", all records associated with this subject and this visit will be categorized as "Virtual Visit"
iii. Otherwise result is missing

Table 12-1. Example Search Terms for "COVID-19" and "Virtual" Used to Identify Missed/Virtual Visits.

Search Terms for "COVID-19"	Search Terms for "Virtual"
COVID19	VIRTUAL
CORONA	TELEMED
CORONAVIRUS	TELEHEALTH
PANDEMIC	TELEPHONE
OUTBREAK	REMOTE
CRISIS	TELEMEDICINE
LOCKDOWN	TELECONSULTATION
QUARANTINE	TELEPHONICALLY
SHELTER	PHONE
	HOME VISIT
	ZOOM
	SKYPE

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Biostatistics eSigned	04-Dec-2021 18:06:24
PPD	Clinical Research eSigned	05-Dec-2021 04:40:54