GILEAD

CLINICAL STUDY PROTOCOL

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
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA, 94404
IND Number:	064402
EudraCT Number:	2016-002749-42
Clinical Trials.gov Identifier:	NCT03219164
Indication:	For the treatment of new onset respiratory tract *Pseudomonas aeruginosa* infection/colonization
Protocol ID:	GS-US-205-1850
Gilead Study Director and Medical Monitor:	Name: PPD Telephone: PPD Mobile: PPD Fax PPD E-mail: PPD
Protocol Version/Date:	Original: 11 November 2016 Amendment 1: 31 March 2017 Amendment 2: 06 November 2017 Amendment 3: 15 April 2020

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PROTOCOL SYNOPSIS

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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
IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	064402 2016-002749-42 NCT03219164
Study Centers Planned:	Approximately 85 sites globally.
Objectives:	The primary objective of this study is to evaluate the safety and efficacy of a 14-day course vs a 28-day course of AZLI 75 mg three times a day (TID) in subjects with new onset *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 2009} over a 108-week post-treatment follow-up period CCI [redacted]

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. 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: For the purpose of this protocol, 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).
Number of Subjects Planned:	Approximately 140 randomized subjects.
Target Population:	Pediatric subjects age 3 months to less than 18 years with CF and newly detected *PA* respiratory tract colonization/infection.
Duration of Treatment:	Subjects will receive either AZLI 75 mg administered TID for 28 days or AZLI 75 mg administered TID for 14 days followed by PTM TID for 14 days. Study treatment will be administered in a blinded fashion. Subjects will be followed through Week 8 for safety and recurrence of *PA,* and through Week 112 for additional comparative analyses. Subjects with *PA* recurrence after study drug treatment will be re-treated at the Investigators' discretion. All subjects will be followed for *PA* recurrence during the Initial Eradication and Follow-Up Culture Phases. Total study duration is 112 weeks.
Diagnosis and Main Eligibility Criteria:	**Main Inclusion Criteria:** • Male or female aged 3 months to less than 18 years • Diagnosis of CF as determined by the 2008 CF Consensus Conference criteria: Sweat chloride level ≥ 60 mEq/L by quantitative pilocarpine iontophoresis; or a genotype with 2 identifiable mutations consistent with CF; or an abnormal nasal transepithelial potential difference (NPD), and 1 or more clinical features consistent with CF • 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) • $FEV_1 \geq 80\%$ predicted (for subjects ≥ 6 years of age who can reliably perform spirometry assessments) • Clinically stable with no evidence of acute significant respiratory symptoms that would require administration of IV antipseudomonal antibiotics, oxygen supplementation, or hospitalization

Main Exclusion Criteria:

- Use of IV or inhaled antipseudomonal antibiotics within 2 years of Screening
- Use of oral antipseudomonal antibiotics for a respiratory event within 30 days of study entry (Screening visit)
- History of intolerance to inhaled short acting β2 agonists
- History of lung transplantation
- Current requirement for daily continuous oxygen supplementation or requirement of more than 2 L/minute at night
- Hospitalization for a respiratory event within 30 days prior to Screening
- Changes in bronchodilator, corticosteroid, dornase alfa, or hypertonic saline medications within 7 days prior to Screening
- Significant changes (per investigators discretion) in physiotherapy technique or schedule within 7 days prior to Screening
- Abnormal renal or hepatic function results at most recent test within the previous 12 months, defined as

  AST or ALT >5 times upper limit of normal (ULN), or

  Serum creatinine > 2 times ULN for age
- Presence of a condition or abnormality that would compromise the subject's safety or the quality of the study data, in the opinion of the Investigator
- Known hypersensitivity to aztreonam, its metabolites, or formulation excipients in AZLI
- Respiratory cultures performed within 24 months prior to Screening that are positive for ANY *Burkholderia spp.* or Non-tuberculous Mycobacteria (NTM)

Study Procedures/ Frequency:

Study visits for all subjects will occur at Screening, Day 1, Day 29, and Weeks 6, 8, 16, 28, 40, 52, 64, 76, 88, 100, and 112. Special consideration for the pediatric study population will be maintained for all study procedures throughout the study (refer to Section 6.2). Study procedures to be performed are as follows:

Complete Physical Exam: Screening and at Week 112 or the Early Termination (ET) visit

Body Weight, Height and Vital Signs: Screening

Blood Draw for Serum Chemistry and Hematology: Screening (if not available within previous 12 months to assess eligibility)

	Blood Draw for Antipseudomonal Antibodies: Screening (if not available within previous 24 months) *Respiratory Sample Collection for Microbiology:* All study visits. If the subject is not able to spontaneously expectorate sputum at a study visit, alternative methods of lower respiratory tract specimen collection may be performed as per the site's 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, although this will limit microbiology testing. *Nasal swab for Bacteria and Virus Detection:* Day 1 *Spirometry (for subjects ≥ 6 years old who can reliably perform spirometry assessments):* Screening, Day 1 (pre- and post-dose), and every subsequent visit *Clinical Observations for study drug-induced adverse events (for subjects < 6 years old and subjects 6 years of age and older who cannot reliably perform spirometry assessments):* Including chest auscultation, respiratory rate, and oxygen saturation: Day 1 pre- and post-dose
Test Product, Dose, and Mode of Administration:	Subjects will receive either AZLI 75 mg administered TID for 28 days or AZLI 75 mg administered TID for 14 days followed by PTM for 14 days. Both treatment regimens to be delivered via the PARI Altera® Nebulizer System for 28 days. For the purpose of this protocol, AZLI and PTM are both considered "study drug treatment". Study drug treatment is recommended to be administered to subjects aged: • < 2 years via the SmartMask® Baby, • 2 to < 6 years via the SmartMask Kids®, and • ≥ 6 years via the nebulizer mouthpiece Investigator has the discretion to select the appropriate mask or mouthpiece for each subject in order to optimize fit and delivery. Subjects should be instructed to administer a bronchodilator (BD) prior to taking each dose of study drug (see Section 5.4).
Reference Therapy, Dose, and Mode of Administration:	PTM administered TID using the same administration procedure as for AZLI.

Criteria for Evaluation:	Respiratory tract cultures positive or negative for *PA* following a 14-or 28-day course of AZLI.
Safety:	Safety endpoints will include adverse events (AEs), airway reactivity (study drug-induced bronchospasm) as determined by post-dose spirometry or clinical observations.
Efficacy:	The primary objective of this study is to evaluate the proportion of subjects with *PA* eradication for each treatment group through 28 days following the end of AZLI treatment. During the Initial Eradication phase, *PA* cultures will be monitored at all study visits through 28 days after cessation of study drug treatment; microbiological cultures will be obtained at Screening, Day 1, Day 29, and Weeks 6 and 8. Secondary objectives include the evaluations of the time to recurrence of *PA* from primary eradication over the 108-week post-treatment follow-up period. Primary eradication is defined as all *PA*-negative cultures through 28 days post AZLI treatment. Cultures will be obtained at week 16 and then at 12-week intervals during the follow-up time frame.
Statistical Methods:	The Evaluable Analysis Set will include all randomized subjects who complete the AZLI treatment with at least 75% compliance and do not use any anti-*PA* antibiotics while on study treatment with AZLI. Missing *PA* culture data will be adjudicated before data unblinding based on available *PA* culture results. The Safety Analysis Set will include all randomized subjects who receive at least 1 dose of study drug. Primary analysis of the primary endpoint is the test of noninferiority of 14-day treatment compared to 28-day treatment with AZLI based on the Evaluable Analysis Set. The proportion of subjects with primary *PA* eradication defined as all *PA*-negative tests through 28 days post-AZLI treatment for each treatment group (Week 6 for subjects in 14-day treatment group and Week 8 for subjects in 28-day group) and the difference between treatment groups will be presented with 2-sided 95% confidence intervals (CI). The unblinded primary analysis of the primary endpoint will be conducted after all evaluable subjects have completed Study Week 8, or Study Week 16 if Week 8 culture data are missing, or are early terminated, and the data have been cleaned and finalized for the analysis. Noninferiority of the 14-day treatment regimen will be claimed if the 1-sided 97.5% lower confidence limit of the treatment difference

	in the proportion of *PA*-negative subjects through 28 days post-treatment is above the noninferiority margin of -20%. Safety will be assessed by AEs and airway reactivity (study drug induced bronchospasm) as determined by post-dose spirometry or clinical observations. Safety data will be summarized by descriptive statistics. **Sample Size:** 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%. Assuming a non-evaluable rate of 5% to 7%, up to 140 subjects will be enrolled to obtain 130 evaluable subjects for the efficacy analyses.

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATS	American Thoracic Society
AZLI	aztreonam for inhalation solution
BAL	bronchoalveolar lavage
BD	bronchodilator
BID	twice a day
BMI	body mass index
BUN	blood urea nitrogen
CF	cystic fibrosis
COVID-19	coronavirus disease 2019
CRF	case report form
CI	confidence interval
CRO	clinical research organization
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DMC	data monitoring committee
eCRF	electronic case report form
EDC	electronic data capture
ET	Early Termination
FDA	Food and Drug Administration
FEF	forced expiratory flow
FEV	forced expiratory volume
FVC	forced vital capacity
GCP	Good Clinical Practice
HEENT	head, ears, eyes, nose and throat
IB	investigator brochure
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IEC	independent ethics committee
IRB	institutional review board
IV	intravenous
IWRS	interactive web response system
MIC	minimum inhibitory concentrations
MRSA	methicillin-resistant *S. aureus*
MSSA	methicillin-sensitive *S.aureus*
MT	mid-turbinate

NTM	non-tuberculous mycobacteria
OP	oropharyngeal
PA	*Pseudomonas aeruginosa*
PIP	pediatric investigation plan
PTM	placebo to match
PVE	Pharmacovigilance & Epidemiology (formerly Drug Safety and Public Health [DSPH])
SADR	serious adverse drug reaction
SAE	serious adverse event
SAP	statistical analysis plan
SmPC/PI	summary of product characteristics/product information
SOP	standard operating procedures
SUSAR	suspected unexpected serious adverse reaction
TID	three times a day
TNS	tobramycin nebulizer solution
ULN	upper limit of normal
vs	versus

1. INTRODUCTION

1.1. Background

Cystic fibrosis (CF) affects an estimated 100,000 people worldwide. {Cystic Fibrosis Worldwide 2016} In Europe, approximately 29,000 people are estimated to have CF.{McCormick 2010} In the United States (US), similar numbers of individuals are affected. {Cystic Fibrosis Foundation 2015} CF is the most common life-shortening genetic disorder in Caucasians. The incidence in European Caucasians is estimated at 1 case per 2500 live births. Approximately 66% of European patients are conservatively estimated to be children (< 18 years of age); however, estimates can vary widely and McCormick J et al. reported 56% are pediatric patients.{European Lung Foundation 2007, McCormick 2010} Average life expectancy across Europe ranges from the early 30s to approximately 40 years of age.{Cystic Fibrosis Trust 2007, Cystic Fibrosis Worldwide 2016, European Lung Foundation 2007, Vaincre la Mucoviscidose 2006} In the US in 2014, the median age of death for CF patients was 29.1 years and approximately 5% of these deaths occurred in pediatric patients < 18 years old. The median predicted survival age in the US in 2014 was 39.3 years. {Cystic Fibrosis Foundation 2015} However, throughout many areas of the world life expectancy for patients with CF varies greatly depending on access to care. {Cystic Fibrosis Worldwide 2016}.

CF is an autosomal recessive disease characterized by a defective CF transmembrane receptor gene, resulting in abnormal ion transport across cell membranes. The viscous airway secretions in CF patients provide an environment for chronic bacterial infection that leads to progressive, obstructive pulmonary disease. CF patients are particularly susceptible to pulmonary infections with organisms such as *Pseudomonas aeruginosa (PA)*, *Staphylococcus aureus*, *Achromobacter species (spp.)*, *Burkholderia spp.*, *Stenotrophomonas maltophilia*, and *Haemophilus influenzae*. Acquisition of specific pathogens, namely *PA* and *Burkholderia spp*., can significantly alter the clinical course of the patient with CF.{Courtney 2004, Treggiari 2007} Infected patients experience progressive obstruction of the airways and loss of lung function that is due in large part to the inflammatory response to chronic bacterial infection. Loss of pulmonary function is the primary cause of death in patients with CF.{Cystic Fibrosis Foundation 2015, European Lung Foundation 2007} In 2014, 84% of all deaths were due to respiratory failure or complications of lung transplantation, the only definitive therapy for end-stage CF lung disease. {Cystic Fibrosis Foundation 2015}.

The most significant bacterial pathogen associated with CF pulmonary disease is *PA*. {Gibson 2003a} *PA* infection is a significant predictor of mortality and has also been associated with higher rates of pulmonary function decline.{Henry 1992, Pamukcu 1995} Relative lung function, expressed as the percentage of Forced Expiration Volume in 1 second (FEV_1) predicted, is the strongest clinical predictor of mortality in CF. Patients with an FEV_1 below 30% of their predicted value have a 2-year mortality rate greater than 50%. Corey et al. showed that patients who died earlier in life had experienced significantly higher rates of lung function decline than longer lived patients. {Corey 1997, Kerem 1992}.

Lung function is better in the pediatric CF population compared to adult CF patients. {Cystic Fibrosis Foundation 2008, Wiedemann 2001}In US CF patients < 18 years, approximately 65% have normal or mildly impaired lung function ($FEV_1 \geq 70\%$), 30% have moderate lung function impairment (FEV_1 40%-69%), and 5% have severe lung function impairment ($FEV_1 < 40\%$). Median FEV_1 % predicted remains normal from age 6 to 12 and progressively declines in adolescents. Further declines in FEV_1 are observed in adults.

In general, pediatric CF patients have a lower incidence of *PA* airway infection compared to adults. In the European Union (EU), approximate prevalences are 24% in 0 to 4 year olds, 25% in 5 to 9 year olds, 40% in 10 to 14 year olds, and 50% in 15 to 19 year olds. In the US, approximate prevalences are 20% in children <6 years old; 25% in 6 to 10 year olds; 40% in 11 to 17 year olds, and 60-75% in ≥18 year olds {Cystic Fibrosis Foundation 2015}. These *PA* infection rates have been decreasing over the past decade, with the greatest decline seen in adolescents.

Initial infection with *PA* can occur at any age in the CF population. Some patients may avoid *PA* infection until the third decade of life, while others experience chronic *PA* infection within the first decade of life. While *PA* has been detected in infants < 1 year of age, this is a relatively rare occurrence. In a bronchoscopy study of newly diagnosed CF infants < 6 months of age, 0 out of 46 subjects had a positive respiratory culture for *PA*.{Ho 1998} Reported incidences of *PA* in CF infants at 1 year of age, as documented by bronchoalveolar lavage fluid cultures, ranged from 6%, to 18%.{Abman 1991, Burns 2001}.

Initial infection with *PA*, prior to the development of chronic infection, has been characterized as a window of opportunity for *PA* eradication. Early and aggressive antibiotic treatment of initial *PA* infection in young patients with CF has been observed to improve pulmonary function and delay the onset of chronic *PA* infection, thus increasing survival. {Doring 2004, Frederiksen 1996} Multiple *PA* eradication studies have been published subsequently, utilizing a variety of treatment regimens, including inhaled, inhaled plus oral, and IV antibiotics. Despite differing study designs, definitions of eradication and follow-up times, similar rates of *PA* eradication have been reported. {Schelstraete 2013}.

Eradication of *PA* at initial detection is now a treatment strategy used by most CF centers. {Zemanick 2010} Recently published guidelines by the Cystic Fibrosis Foundation (CFF) strongly recommend inhaled antibiotic therapy for new onset *PA* infection. Inhaled tobramycin is the CFF recommended treatment, however, no inhaled antibiotic has a labeled indication for treatment of new onset *PA* infection in CF patients. {Mogayzel 2014}.

1.2. Aztreonam for Inhalation Solution (AZLI)

1.2.1. General Information

Gilead Sciences, Inc. (Gilead) has developed aztreonam for inhalation solution (AZLI), a lyophilized formulation of the monobactam antibiotic aztreonam, for the treatment of CF patients with *PA* infection. AZLI is specifically designed for inhalation therapy with lysine as an excipient. AZLI was first approved for marketing under the trade name Cayston® in Canada on 11 September 2009 for use in CF patients with chronic pulmonary *PA* infections and is currently approved in 36 countries, including the United States, Canada, Australia, Switzerland, and the European Union.

Although the spectrum of activity of aztreonam is similar to that of tobramycin and gentamicin, {Brewer 1991} because the mechanism of action of monobactams is different than that of the aminoglycosides treatment with AZLI provides clinicians with an additional option to avoid bacterial resistance. Furthermore, aztreonam has been shown to have activity against aminoglycoside-resistant CF pathogens. {Shawar 1999} Finally, extensive clinical use of parenteral aztreonam has demonstrated a safety profile, which lacks the toxic effects (both acute and cumulative) characteristic of the aminoglycosides, and unlike other members of the beta-lactam class, aztreonam is rarely immunogenic. {Adkinson 1990, Adkinson 1984, Brewer 1991, Saxon 1984, Saxon 1985}.

AZLI is a reconstituted product that consists of the sterile lyophilized powder of aztreonam (75 mg aztreonam and 52.5 mg lysine monohydrate) mixed with 1 mL of sterile, 0.17% w/v saline diluent immediately prior to aerosolization. In clinical trials, AZLI is delivered using the Investigational eFlow® Nebulizer System (nebulizer) manufactured by PARI. The eFlow is a single-patient, multi-use device that uses a vibrating perforated membrane to generate an aerosol with a relatively mono-dispersed particle spectrum (the average mass median diameter is 3.5 µm with a geometric standard deviation of approximately 1.6), which is well suited for lower airway drug deposition. {Newman 1985} Previous studies indicate that the eFlow is capable of rapid delivery of AZLI to the lungs taking only 2 to 3 minutes.

For further information on AZLI, refer to the current Investigator's Brochure (IB) for AZLI and Summary of Product Characteristics/Product Information (SmPC/PI).

1.2.2. Preclinical Pharmacology and Toxicology

Extensive preclinical pharmacology and toxicology studies of AZLI have been conducted to identify local and systemic adverse effects associated with AZLI administration.
These individual preclinical studies are discussed in detail in the IB. To date, no clinically relevant adverse effects have been reported in any of these studies.

1.2.3. Clinical Trials of AZLI

Results of completed trials can be found in the AZLI IB.

1.3. Rationale for This Study

Initial acquisition of *PA* typically involves nonmucoid strains that are generally susceptible to antipseudomonal antibiotics. Studies of various antibiotic regimens have demonstrated the ability to eradicate early *PA* infection and maintain a significant infection-free interval. {Frederiksen 1997, Gibson 2007, Ratjen 2001, Ratjen 2009, Valerius 1991, Wiesemann 1998} Consensus treatment guidelines recommend early and aggressive attempts to eradicate recently acquired *PA*, in order to prevent the establishment of chronic infection and the associated progressive decline in lung function. {Mogayzel 2014}.

Existing treatments authorized for pediatrics are not satisfactory and alternative methods with an improved expected benefit-risk balance are needed. Despite the currently available inhaled antibiotics (TNS and colistin, which are not labeled for the treatment of initial *PA* infection) pediatric CF patients continue to suffer significant morbidity and mortality due to *PA* airway infection.

AZLI is a monobactam with a different mechanism of action than aminoglycoside antibiotics. AZLI has demonstrated significant reductions in *PA* sputum density in CF patients with chronic *PA* infection. This potent antibacterial effect justifies additional study of AZLI for eradication of initial *PA* infection in pediatric patients 3 months to less than 18 years.

In GS-US-205-0162, a single-arm, open-label Phase 2 study of AZLI in CF pediatric subjects with new onset *PA* infection {Freiberg 2013, Tiddens 2015}, 105 pediatric subjects aged 3 months to < 18 years (24 subjects aged 3 months to < 2 years; 25 subjects aged 2 to < 6 years; 56 subjects aged 6 to < 18 years) with CF and documented initial/new onset *PA* infection /colonization received Cayston 75 mg 3 times a day for a single course of 28 days.

Of the 101 evaluable subjects, 89.1% (n = 90) were free of *PA* at the end of treatment (Day 28) and 75.2% (n = 76) were free of *PA* 1 month after the end of treatment (Day 56). Of the 79 subjects evaluable for the primary endpoint, 58.2% were *PA* culture negative at all post-treatment time points through 6 months following end of treatment. These eradication rates are consistent with success rates reported in the literature for various antibiotic regimens, including other inhaled antibiotics studied for eradication.

The current study will address key issues in the management of pediatric CF subjects with new onset *PA* infection:

1) The primary comparison of 14 days vs 28 days of AZLI treatment will provide evidence that a shorter AZLI regimen is effective as an initial treatment for *PA* eradication, which has significant implications for treatment adherence in young subjects.

2) A re-treatment phase for *PA* culture positive patients during the follow-up period will provide insights into the treatment of patients with primary eradication treatment failure; this long-term follow-up period will provide natural history data on the management strategies aimed at maintaining patients free of chronic *PA* infection.

This study is required as part of an approved Pediatric Investigation Plan (PIP) for AZLI in the EU (EMEA-000827-PIP01-09-M04). The AZLI PIP was originally approved in October 2010; a modification was subsequently approved on 29 January 2016.

1.4. Risk/Benefit Assessment for the Study

Chronic *PA* infection has devastating consequences for CF patients, in terms of persistent pulmonary symptoms, frequent acute pulmonary exacerbations often requiring hospitalization and treatment with IV antibiotics, and progressive lung function decline ultimately leading to lung transplantation and/or death. Prior to the establishment of chronic infection, there is an opportunity to eradicate new onset *PA* infection with inhaled anti-pseudomonal antibiotic treatment, with the goal of delaying the onset of chronic *PA* infection. This can preserve lung function, reduce symptom progression, and prolong survival.

The *PA* eradication rates in Study GS-US-205-0162 {Tiddens 2015} have demonstrated the ability of a 28-day treatment course of AZLI to eradicate new onset *PA* infection, with rates comparable to other regimens of inhaled antibiotics. The adverse events reported for AZLI-treated subjects in this study are similar to the safety profile documented for pediatric subjects with chronic *PA* infection.

Previous studies have shown that AZLI is well tolerated in the pediatric population age 6 to 17 years old. Delivery time of 2-3 minutes via the Investigational eFlow® Nebulizer System (eFlow nebulizer) should enhance compliance, particularly in the pediatric population.

The risk of a shorter (14-day) treatment course compared to the standard 28-day course is a sub-optimal rate of *PA* eradication. This risk of eradication failure in this study is obviated (in both treatment arms) by the frequency of repeat culturing to detect eradication failure and the re-treatment with additional antibiotics per the investigators' discretion, which is the standard of care in clinical practice. However, if the 2 treatment arms are shown to be similar in the ability to eradicate new onset *PA*, this will support shorter treatment duration for initial eradication treatment with AZLI, and will be of benefit to pediatric CF patients (and parents/caregivers) in terms of reduced treatment burden and improved adherence to this treatment regimen.

1.5. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice, and all applicable regulatory requirements.

2. OBJECTIVES

The primary objective of this study is to evaluate the safety and efficacy of a 14-day course vs a 28-day course of AZLI 75 mg three times a day (TID) in subjects with new onset *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) twice daily (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 2009} over a 108-week post-treatment follow-up period

CCI

[redacted]

[redacted]

3. STUDY DESIGN

3.1. Endpoints

The primary endpoint of this study 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

The secondary 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 for a sub-group of subjects matching the population in the TNS ELITE Study over a 108-week post-treatment follow-up period

CCI [redacted]

3.2. 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 to 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/Baseline (Day 1), Day 29, Weeks 6, 8, 16, and at 12-week intervals thereafter through Study 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 PTM TID. Note: For the purpose of this protocol, 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 after that for 112 weeks total study duration.

Re-Treatment Phase:

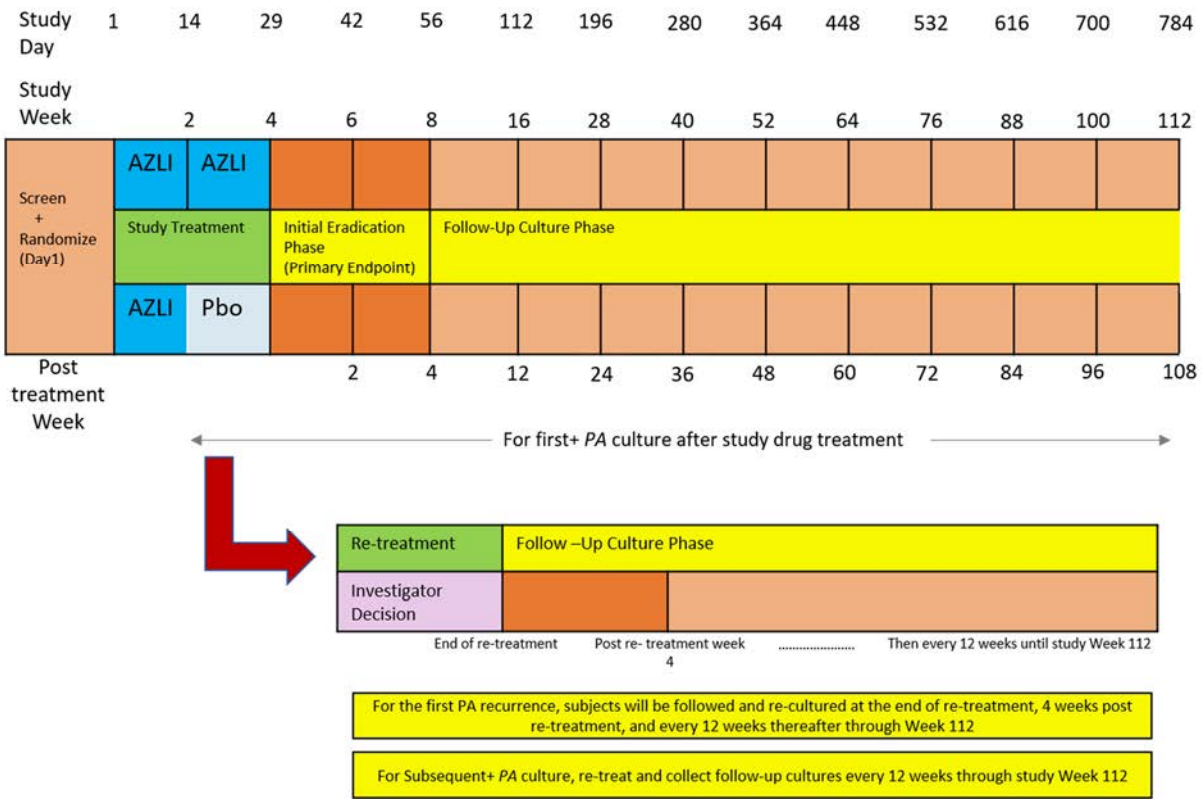
Subjects with *PA* recurrence after study drug treatment should be re-treated with a standard of care antipseudomonal antibiotic regimen at the discretion of the Investigator. A non-exclusive list of re-treatment regimen options include:

- 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).

Figure 3-1. Study Schema:



3.3. Study Treatments

Subjects will be randomized at Day 1 and receive either AZLI 75 mg administered TID 28 days or AZLI 75 mg administered TID for 14 days followed by PTM TID for 14 days. Both treatment regimens to be delivered via the PARI Altera® Nebulizer System for 28 days. For the purpose of this protocol, AZLI and PTM will both be considered "study drug treatment".

Study drug treatment is recommended to be administered to subjects aged:

- < 2 years via the SmartMask® Baby,
- 2 to < 6 years via the SmartMask Kids®, and
- ≥ 6 years via the nebulizer mouthpiece

The Investigator has the discretion to select the appropriate mask or mouthpiece for each subject in order to optimize fit and delivery. If the Investigator feels subjects over the age of 6 years are not ready to use the Altera® standard nebulizer mouthpiece, they may use a SmartMask for drug delivery. Additionally, if subjects under the age of 6 years are able to demonstrate the ability to use a mouthpiece, it is recommended they use the Altera® standard nebulizer mouthpiece for optimal drug delivery.

AZLI and PTM will be packaged separately in 14-day dosing cartons. On Day 1 all subjects will receive two cartons: Carton 1 and Carton 2.

Carton 1 contains the product required for administration on Day 1 to 14. Carton 1 only contains AZLI 75mg TID.

At Day 14 subjects will start Carton 2 which contains the vials required for administration on Days 15 to 28. Carton 2 will contain either blinded AZLI 75 mg TID or PTM TID.
Subject treatment allocation for Carton 2 will be determined by randomization on Day 1.

Use of non-study antipseudomonal antibiotics is prohibited during the 28-day treatment period. Subjects who violate this criterion will be withdrawn from the study. These subjects will come for an Early Termination (ET) visit and be followed for 30 days and/or until all ongoing adverse events resolve. Subjects who do not violate the criteria of Evaluable Analysis Set will be included in the primary efficacy analysis. If at any time after the 28-day treatment period the physician determines that a subject requires antipseudomonal antibiotics, the subject will not be withdrawn from the study but an unscheduled visit will be scheduled to document treatment.

3.4. Duration of Treatment

Randomized subjects will complete 28 days of daily dosing. Subjects will have their final visit 108 weeks after the last dose. The total study duration is 112 weeks.

3.5. Discontinuation Criteria

For discontinuation criteria refer to Section 6.8.

3.6. Source Data

The subject identification number and randomization number captured by the interactive web response system (IWRS) are considered source data. All other information entered into the electronic data capture (EDC) requires source documentation to be available for verification.

3.7. Biomarker Testing

3.7.1. Biomarker Samples to Address the Study Objectives:

Blood and respiratory samples (sputum and swabs) will be collected in this study and these samples may be used to evaluate the association of exploratory systemic and/or tissue specific biomarkers with study drug response, including efficacy and/or adverse events as well as to increase knowledge and understanding of the biology of CF or related diseases or the validation of a companion diagnostic for AZLI. The specific analyses will include, but will not be limited to, antipseudomonal antibodies. *PA*-specific antibody titers will be obtained at Screening if no results are available within 24 months. Because biomarker science is a rapidly evolving area of investigation, and adverse events in particular are difficult to predict, it is not possible to specify prospectively all tests that will be done on the specimens provided. The testing outlined below is based upon the current state of scientific knowledge. It may be modified during or after the end of the study to remove tests no longer indicated and/or to add new more applicable tests. Any future testing must be approved by local authorities as applicable according to specific local regulations.

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4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 140 subjects will be enrolled in this study.

4.2. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study:

1) Male or female aged 3 months to less than 18 years at screening

2) Diagnosis of CF as determined by the 2008 CF Consensus Conference criteria {Farrell 2008}:

   sweat chloride level ≥ 60 mEq/L by quantitative pilocarpine iontophoresis;

   or a genotype with 2 identifiable mutations consistent with CF;

   or an abnormal nasal transepithelial potential difference (NPD), and 1 or more clinical features consistent with CF

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)

4) $FEV_1 \geq 80\%$ predicted (for subjects ≥ 6 years of age who can reliably perform spirometry assessments)

5) Clinically stable with no evidence of acute significant respiratory symptoms that would require administration of IV antipseudomonal antibiotics, oxygen supplementation, or hospitalization

6) A negative serum pregnancy test is required for female subjects of child bearing potential who have a positive urine pregnancy test at screening

7) Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 3

8) Lactating females must agree to discontinue nursing before administration of study drug

9) Subjects and/or parent/guardian must be able to give written informed consent prior to study related procedures

4.3. Exclusion Criteria

Subjects who meet *any* of the following exclusion criteria are not to be enrolled in this study.

1) Use of IV or inhaled antipseudomonal antibiotics within 2 years of Screening

2) Use of oral antipseudomonal antibiotics for a respiratory event within 30 days of study entry (Screening visit)

3) History of intolerance to inhaled short acting β2 agonists

4) History of lung transplantation

5) Administration of any investigational drug or device within 28 days prior to Screening

6) Concurrent use of oral corticosteroids in doses exceeding the equivalent of 10 mg prednisone per day or 20 mg prednisone every other day

7) Current requirement for daily continuous oxygen supplementation or requirement of more than 2 L/minute at night

8) Hospitalization for a respiratory event within 30 days prior to Screening

9) Changes in bronchodilator, corticosteroid, dornase alfa, or hypertonic saline medications within 7 days prior to Screening

10) Significant changes (per investigators discretion) in physiotherapy technique or schedule within 7 days prior to Screening

11) Abnormal hepatic or renal function results at most recent test within the previous 12 months, defined as

    AST or ALT >5 times upper limit of normal (ULN), or

    Serum creatinine > 2 times ULN for age

12) Presence of a condition or abnormality that would, in the opinion of the Investigator, compromise the subject's safety or the quality of the study data

13) Known hypersensitivity to aztreonam, its metabolites, or formulation excipients present in AZLI

14) Respiratory cultures performed within 2 years prior to Screening that are positive for ANY *Burkholderia spp.* or NTM

4.4. Screen Failure Criteria and Rescreening

Any consented subject who is excluded from the study before enrollment at Baseline (Day 1) visit is considered a screen failure. Subjects may only be re-screened once for study eligibility. The re-screen may not occur on the same day as the initial screening visit. All screen failures must be documented with the reason for the screen failure stated as noted below:

- Subject failed to meet all of the study inclusion criteria or met any of the exclusion criteria prior to randomization (Day 1)
- Subject withdrew consent
- Other (specify)

4.5. Randomization Criteria

Any enrolled subject that has remained clinically stable is eligible for randomization to study drug if the following criteria are met:

- Has not received antipseudomonal antibiotics for a respiratory event within 30 days of study entry (Screening visit) and through Baseline (Day 1) visit
- Has not received any IV or inhaled antipseudomonal antibiotics within 2 years of study entry (Screening visit) and through Baseline (Day 1) visit
- Has not developed a condition requiring hospitalization or other change in clinical status which, in the opinion of the Investigator, precludes the subject's ability to continue participation in the study

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding and Treatment Codes

An IWRS will be employed to manage subject randomization and enrollment, shipping of study drug, and dispensing of study drug.

During the randomized phase subjects and all personnel directly involved in the conduct of the study will be blinded to treatment assignment. Specified personnel may be unblinded based on their study role. Study drug will be dispensed by the study pharmacist, or designee, in a blinded fashion to the subjects. Individuals in Clinical Packaging & Labeling or Clinical Supply Management who have an Unblinded Inventory Manager role in the IWRS system for purposes of study drug inventory management will remain unblinded. Individuals in Pharmacovigilance & Epidemiology (PVE) responsible for safety signal detection, IND safety reporting and/or expedited reporting of suspected unexpected serious adverse reactions (SUSARs) may be unblinded to individual case data and/or group level summaries. External (ie, contract research organizations) Biostatisticians and Programmers will be unblinded for data monitoring committee (DMC). Regulatory Quality and Compliance personnel in Research and Development may also be unblinded for purposes of supporting Quality Assurance activities and/or Regulatory Agency inspections.

5.1.1. Planned Primary Endpoint Unblinding

In order to assess the primary efficacy endpoint for regulatory planning purposes and/or submission, Gilead personnel will be unblinded to subject-level treatment codes after all subjects have completed Week 8, or Week 16 if Week 8 visit culture data are missing, or are early terminated and the data have been cleaned and finalized for the analysis. Unblinded treatment-level summaries may be shared externally. Unblinding procedures for analyses will be followed as specified in Gilead SOPs. Investigators, site personnel, and subjects will remain blinded to subject-level treatment codes until the completion of the study.

5.1.2. Procedures for Breaking Treatment Codes

In the event of a medical emergency where breaking the blind is required to provide medical care to the subject, the Investigator may obtain treatment assignment directly from the IWRS system for that subject. Gilead recommends but does not require that the Investigator contact the Gilead medical monitor before breaking the blind. Treatment assignment should remain blinded unless that knowledge is necessary to determine subject emergency medical care. The rationale for unblinding must be clearly explained in source documentation and on the case report form/electronic case report form (CRF/eCRF), along with the date on which the treatment assignment was obtained. The Investigator is requested to contact the Gilead medical monitor promptly in case of any treatment unblinding.

Blinding of study treatment is critical to the integrity of this clinical trial and therefore, if a subject's treatment assignment is disclosed to the Investigator, the subject will have study treatment discontinued. All subjects will be followed until study completion unless consent to do so is specifically withdrawn by the subject.

Gilead PVE may independently unblind cases for expedited reporting of suspected unexpected serious adverse reactions (SUSARs).

5.2. Description and Handling of Study Drug

5.2.1. Reconstitution

Study drug must be reconstituted using the supplied diluent by the subject or the subject's caregiver. Adequate supplies of study drug and diluent will be provided to the subject at baseline. Detailed instructions for reconstitution are available in Study Drug Information Booklet. Once constituted, it should be used immediately.

5.2.2. Formulation

5.2.2.1. AZLI Formulation:

AZLI will be supplied as vials of sterile lyophilized powder containing 75 mg aztreonam as aztreonam lysine. Diluent for AZLI will be supplied in ampules, each of which contains 1 mL of sterile 0.17% w/v sodium chloride solution. When the diluent is added to the lyophilized powder, the final product is 75 mg/ml of aztreonam with a pH of 4.5 to 6.0.

5.2.2.2. Placebo to Match (PTM):

The PTM will be supplied as vials of lyophilized sterile powder containing lactose monohydrate and sodium chloride and will be identical in physical appearance to AZLI vials. Diluent for PTM is the same as for AZLI and will be supplied in ampules, each of which contains 1 mL of sterile 0.17% w/v sodium chloride solution.

5.2.3. Packaging and Labeling

AZLI and PTM will be supplied in 2 mL amber glass vials with a siliconized rubber stopper and an over-seal cap closure.

Study drug will be packaged in two 14-day dosing cartons. Carton 1 contains AZLI (42 vials) required for administration on Day 1 to 14. Carton 2 will contain either AZLI (42 vials) or PTM (42 vials) required for administration on Days 15 to 28. Carton 1 and Carton 2 will both be given to subjects after randomization on Day 1. In each carton there will be 6 additional vials of study drug treatment in case administration of the study drug is compromised for any reason (eg, spillage of vial contents prior to nebulizer use). Adequate diluent will be provided in a separate carton for 28 days of study drug treatment.

Study drugs to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the United States Food and Drug Administration (FDA), EU Guideline to Good Manufacturing Practice – Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.2.4. Storage and Handling

AZLI or PTM should be stored at 2°C to 8°C (36°F to 46°F). Storage conditions are specified on the label. Until dispensed to the subjects, all study drug should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability and proper identification, study drug (s) should not be stored in a container other than the container in which they were supplied.

Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling.

5.3. Dosage and Administration of Study Drug

Subjects will receive either AZLI 75 mg administered TID for 28 days or AZLI 75 mg administered TID for 14 days followed by PTM administered TID for 14 days. Both treatment regimens will be delivered via the PARI Altera® Nebulizer System provided to each subject.

Subjects, and/or the subject's caregiver, should be instructed to administer a bronchodilator prior to taking each dose of study drug (see Section 5.4). For subjects taking multiple inhaled therapies, the recommended order of administration is as follows: bronchodilator, mucolytics, and lastly, study drug.

The first dose of study drug will be administered in the clinic during the Baseline (Day 1) visit. After the first dose, subjects will administer study drug (in the morning, afternoon, and evening/night) at home. Doses are to be taken a minimum of 4 hours apart. If a dose is missed, all daily doses should be taken as long as they are at least 4 hours apart.

5.4. Bronchodilator Use

All subjects, and/or the subject's caregiver, should be instructed to refrain from using short-acting inhaled Bronchodilators (BDs; such as albuterol) within 4 hours prior to each study visit (unless used for rescue).

At Baseline (Day 1) visit, subjects should administer a short-acting BD in the clinic 15 to 30 minutes prior to spirometry and within 1 hour prior to in-clinic study drug administration. Subjects should also be instructed to administer their routine short-acting BD prior to each study drug dose at home.

Subjects who do not routinely use BDs should be prescribed an appropriate BD by the Investigator for use during the study drug treatment periods. This BD use should be recorded on the Concomitant Medications and Therapies eCRF.

Subjects who routinely use either short-acting and/or long acting inhaled BDs should adhere to the following guidelines for at-home use:

- If a subject normally administers a long-acting inhaled BD twice daily, the subject, and/or the subject's caregiver, will be advised to ensure that a long-acting BD has been used at least 30 minutes before treatment and no more than 12 hours prior to study drug administration at home, or
- If a subject normally administers a long-acting inhaled BD once daily, the subject, and/or the subject's caregiver, will be advised to ensure that the long-acting BD has been used at least 30 minutes before treatment and no more than 24 hours prior to study drug administration at home, or
- If a subject does not normally administer a long-acting inhaled BD, the subject, and/or the subject's caregiver, will be instructed to administer a short-acting inhaled BD at least 15 minutes before treatment and no more than 4 hours prior to study drug administration at home.

All subjects who normally use a BD should continue their use as prescribed, however, subjects should be instructed to refrain from using a short-acting inhaled BD within 4 hours of each study visit (unless used for rescue), and from using a long-acting inhaled BD within 12 hours of each study visit if the BD is used twice daily, or within 24 hours of each study visit if the BD is used once daily. If a subject has taken a BD treatment within 4 hours (short-acting) or 12 hours (long-acting) of a study visit, this should be noted in the CRF and no BD should be given at that study visit.

If part of their regularly prescribed therapy, subjects may be permitted to use a combination of long-acting and short-acting BDs during the study.

5.5. Prior and Concomitant Medications

Concomitant medications are any prescription medications, over-the-counter preparations, or therapies used by the subject between Screening and Week 112 or early termination.

Use of concomitant medication or treatment required for the clinical management of subjects will be at the Investigator's discretion.

Use of hypertonic saline therapy is permitted. Subjects must be on a stable chronic regimen from Screening to Day 29 (no changes in or initiation of regimen).

At Screening, concomitant medications and therapies including airway clearance techniques will be recorded. All antibiotics given in the past 24 months prior to screening should be recorded. All medications, indications for use, dose (amount, dose units, frequency, and route of administration), and dates of administration must be recorded. At subsequent visits, subjects will be questioned about any changes in their medications or concomitant therapy.

5.5.1. Prohibited Concomitant Medications

Use of concomitant medications or treatments required for the clinical management of subjects will be at the Investigator's discretion unless otherwise specified here or in the exclusion criteria:

- Concurrent use of oral antipseudomonal antibiotics for a respiratory event or any IV or inhaled antibiotics for any indication (excluding chronic, stable treatment with a macrolide) is prohibited from Screening to Day 28. Use of these specific types of antibiotics during this period will require study withdrawal and conduct of an ET Visit, as described in Section 3.3.
- Changes in chronic bronchodilator, corticosteroid, azithromycin, or bronchial hygiene therapy are prohibited within 28 days of Baseline.
- The use of any investigational drug or device other than those designated in this study is prohibited within 28 days prior to Baseline and through Day 56. Subjects who complete study drug treatment and follow-up cultures for the primary endpoint (through Day 56) are allowed to participate in other investigational drug trials. The one restriction is entry into another inhaled antibiotic trial unless, and until, the first positive post-treatment culture for *PA* is obtained. (This is to preserve the *PA* culture-negative study population for the time to *PA* recurrence endpoint).

5.5.2. Allowed Concomitant Medications

After Day 29, Investigators may prescribe non-study antibiotics to any subject who is experiencing worsening respiratory signs and/or symptoms, or for a positive *PA* respiratory culture. It should be noted that the use of non-study antipseudomonal antibiotics is prohibited during the 28-day study drug treatment phase. Subjects requiring treatment with additional antipseudomonal antibiotics during the study drug treatment phase will be withdrawn from the study, as described in Section 3.3. In the event of worsening respiratory symptoms between study visits, the subject should return to the clinic for an Unscheduled Visit in order to be evaluated for treatment with non-study antibiotics. In addition to completing the Unscheduled Visit procedures, the prescribing physician must record the subject's specific worsening respiratory symptoms in source documents and then in the eCRF. If necessary for appropriate management of the subject, and for timely treatment with antibiotics, this visit can be conducted over the phone. If the subject will be withdrawn from the study, the Early Termination Visit should be scheduled as soon as possible following the call.

If the requirement for non-study antibiotics is identified during a regular scheduled study visit, the specific respiratory symptoms indicating need for antibiotics must be documented as described above. In either case, the subject will be allowed to continue study participation.

5.6. Devices

5.6.1. PARI Altera® Nebulizer System

The Altera® Nebulizer System (manufactured by PARI GmbH, Starnberg, Germany) will be used to deliver study drug. The Altera® Nebulizer System consists of an eBase controller unit

and the Altera® Nebulizer Handset to deliver the study drug. Gilead Sciences will supply a nebulizer system for each eligible subject. The nebulizer is to be used by the subject for the administration of study drug only.

AZLI or PTM is recommended to be administered to subjects aged:

- < 2 years via the SmartMask® Baby,
- 2 to < 6 years via the SmartMask Kids®, and
- ≥ 6 years via the nebulizer mouthpiece

The Investigator has the discretion to select the appropriate mask or mouthpiece for each subject in order to optimize fit and delivery.

The Investigator, study coordinator, or research nurse will instruct the subject and/or parent/guardian on use of the nebulizer and breathing technique prior to the first dose. Nebulizer accessories for use in the trial and instructions for use, cleaning, and disinfecting will be supplied to each subject.

At the Baseline visit, subjects and/or subjects' parent/guardian should:

- Read the Altera® instructions for use
- Be instructed by the study coordinator on how to breathe with the Altera®
- Demonstrate to the study coordinator that he/she can disassemble, clean, sterilize, and reassemble the Altera®

A functionality test is performed on the Altera® prior to each subject's first dose to ensure that the unit was not damaged during shipment.

5.7. Study Drug and Device Accountability

The Investigator is responsible for ensuring adequate accountability of all used and unused study drug vials, diluent ampules, nebulizers, and masks. This includes acknowledgement of receipt of each shipment of study drug, nebulizers, handsets, and masks (quantity and condition). All used and unused study drug, solvent/diluent ampules, nebulizers, sterilizers, and masks dispensed to subjects must be returned to the site.

Study drug and device accountability records will be provided to each study site to:

- Record the date received and quantity of study drug kits
- Record the date, subject number, subject initials, and the study drug kit number dispensed
- Record the date, quantity of used and unused study drug returned, and the initials of the person recording the information.

5.7.1. Study Drug and Device Return or Disposal

Where possible, study drug (and diluent) and devices (Altera® nebulizers, sterilizers and masks) will be destroyed at the site. If the site has appropriate Standard Operating Procedures (SOPs) for study drug and device destruction, the site may destroy used study drug and devices (empty vials, ampules, and nebulizers) and unused study drug supplies in accordance with the SOPs, after the monitor has completed study drug and device accountability. If the site does not have acceptable procedures in place for study drug and device destruction, arrangements will be made between the site and Gilead (or Gilead's representative) for return of study drug and study drug supplies.

At the start of the study, the study monitor will evaluate each study center's disposal procedures and provide instruction for return or destruction of unused study drug and study drug supplies. If unused study drug and study drug supplies will be destroyed on site, a copy of the site's SOP for study drug destruction will be obtained for central files.

If study drug is destroyed on site, the Investigator must maintain accurate records for all study drug vials destroyed. Records must show how the identification and quantity of each unit destroyed, the method of destruction, and person who disposed of the study drug. All study drug records must be submitted to Gilead at the end of the study. Upon study completion, a copy of the study drug and device accountability forms must be filed at the site. Another copy will be returned to Gilead.

6. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form and described in the text that follows. Additional information is provided in the study procedures manual.

The Investigator must document any deviation from protocol procedures and notify the sponsor or contract research organization (CRO). Missed visits/procedures due to the coronavirus disease 2019 (COVID-19) pandemic will be documented as deviation from the protocol due to the COVID-19 pandemic.

6.1. Subject Enrollment and Treatment Assignment

It is the responsibility of the Investigator to ensure that subjects are eligible to participate in the study prior to randomization/enrollment and throughout the study.

Once consent has been obtained, all screening tests and procedures have been assessed, and study eligibility has been confirmed, eligible subjects will be randomized to study treatment as described in Section 3.3.

The study center will not be activated and allowed to Screen subjects until:

- The Institutional Review Board (IRB) or Ethics Committee (EC) have reviewed and approved the study and the informed consent document
- All required regulatory documents have been submitted to and approved by Gilead or the CRO
- A master services agreement and/or study agreement is executed
- The site initiation meeting has been conducted by the Gilead clinical monitor (or designee). The initiation meeting will include a review of the protocol, the IB, and the Investigator's responsibilities

6.2. Study Assessments

This study consists of a minimum of 13 scheduled visits with total study duration of 112 weeks.

The study procedures to be conducted for each subject enrolled in the study are described in the following sections. In addition, Table 6-1 presents the study procedures in tabular form.

Refer to the lab manual for information on collection and shipment of all required study samples.

Care must be taken by the Investigator to minimize any possible pain and distress that subjects may experience as a result of study participation. Additionally, whenever possible the Investigator should take action to try to ensure the comfort of subjects. The degree of burden to

subjects in this trial has been evaluated and is not significantly more than that involved in routine CF care and treatment. The level of anticipated risk to minors is minimal; however, Investigators should attempt to reduce subject discomfort whenever possible. The following study procedures may have a potential for risk of discomfort, distress, or embarrassment: blood sampling, sputum sampling, nasal sampling, pulmonary function testing, physical exams, and collections of body weight and/or height. Methods to reduce discomfort from blood sample collection include the use of numbing cream prior to venipuncture to lessen the discomfort of the subject.

If the subject is not able to spontaneously expectorate sputum at a study visit, alternative methods of lower respiratory tract specimen collection may be performed as per the site's 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, although this will limit microbiology testing. A mid-turbinate (MT) swab will be used to collect a nasal sample and is less invasive than a nasal oropharyngeal swab.

The following considerations are suggested in order to minimize distress and anticipation of pain:

- Investigators are advised to provide an age appropriate explanation to the child of all study procedures involved in this trial
- Whenever possible, separation of the child from the parent/legal representative should be avoided, or if this is not possible, a member of the study team should accompany the child to provide reassurance
- Prior to the child's participation, the parent/legal representative and the child will be informed of which procedures are related to the study, and which are part of the child's routine CF care

The frequency of study visits and the study procedures monitoring safety ensure that a pediatric subject's level of risk, and burden will be closely monitored during his or her participation in the trial. Additional visits may occur if needed, at the discretion of the Investigator.

Overall, Investigators must continually monitor the risk for potential distress and suffering during a child's participation. During the follow-up culture phase study visits may be scheduled to coincide with routine quarterly clinic visits, so as to not be overly burdensome to the subjects/families.

Follow-up visits (from Week 16 to Week 100 and not including Week 112 or the ET visit) can be performed at home by qualified CF specialist nurses if this is standard of care at the clinic and appropriate cultures can be obtained and processed.

Table 6-1. Study Procedures Table

	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, CCI [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

CCI [redacted]

e If ET visit occurs within 30 days of the last dose of study drug

CCI [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

6.3. Pretreatment Assessments

6.3.1. Screening Visit

Subjects will be screened before randomization to determine eligibility for participation in the study. Invasive study procedures such as blood draws should be done at the end of the study visit. The following will be performed and documented at screening:

- Obtain written Informed Consent
- Obtain demographics and medical history
- Ask subject and/or parent/caregiver about their concomitant medications
- Obtain vital signs, including weight and height
- Perform a complete physical examination
- Obtain urine sample for pregnancy test (female subjects of child bearing potential only). If result is positive confirm with a serum pregnancy test
- Administer short-acting β2 agonist
- [redacted]
- Obtain respiratory sample for microbiology
- Obtain blood samples for hematology, serum chemistry if no results available in past 12 months
- Obtain blood sample for biomarkers if no *PA* antibody titer data are available in past 24 months
- Assess subject eligibility per Inclusion/Exclusion criteria
- Assess subject for adverse events (all AEs/SAEs related to protocol mandated procedures to be reported)

6.3.2. Day 1 Assessments

Subjects will have 14 days from the time of screening to complete Day 1. It is acceptable for the Screening visit and Day 1 to occur on the same day. In this case, the Study procedures performed at Screening will not need to be repeated.

At Day 1, after the subject's eligibility for the study has been confirmed, the subject will be randomized into the study to receive one of two study dosing regimens.

Prior to Treatment with Study Drug

The following will be performed and documented at Day 1 prior to dosing:

- Assess subject eligibility per Inclusion/Exclusion criteria
- Ask subject and/or parent/caregiver about any new or changes to existing concomitant medications
- Perform a modified physical exam
- Obtain urine sample for pregnancy test (female subjects of child bearing potential only)
- Obtain respiratory sample for microbiology
- Obtain nasal swab sample for microbiology
- Randomize subject in IWRS

Treatment with Study Drug

- Dispense Study treatment kits, Altera® Nebulizer System (eBase and Altera® handset, mask if applicable), sterilizer and dosing log
- Instruct subject on study drug administration, dosing, and storage and on proper operation/cleaning of Altera® nebulizer
- Perform nebulizer functionality test
- Administer short-acting β2 agonist
- [redacted]
- Perform clinical observation (for subjects 3 months of age to <6 years of age and subjects 6 years of age and older who can't reliably perform spirometry assessments, including: chest auscultation, respiratory rate, and oxygen saturation)
- Administer study drug in the presence of the investigator, study nurse, or research coordinator; delivery of this dose will be timed

Post Study Drug Procedures

- Assess and document any AEs occurring since drug administration (all AEs/SAEs regardless of cause or relationship to be reported).
- Administer short-acting β2 agonist

[redacted]

- Perform clinical observation (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, including: chest auscultation, respiratory rate, and oxygen saturation) at least 30 minutes post-dose (or until investigator feels it is safe to discharge the subject) to ascertain whether the subject experiencing acute bronchospasm, and/or allergic response

[redacted]

6.3.3. Randomization

Subjects will be randomly allocated to a dosing group in a blinded fashion according to a pre-specified randomization scheme prepared by an independent statistician. Upon qualification for the study, subjects will be randomized using a computerized IWRS system.

The IWRS system will provide kit numbers so that Study Treatment Kits can be dispensed.

6.4. Initial Eradication Phase

6.4.1. Day 14

Subjects should be contacted via telephone on Day 14 to assess whether they have had any adverse events (All AEs/SAEs regardless of cause or relationship to be reported) or taken any concomitant medications and instruct subject/parent to switch to second carton of study drug treatment on Day 15. A visit to the study center may be substituted for a telephone contact, per the subjects and Investigator's discretion.

6.4.2. Day 29/Week 4

Following the completion of study treatment subjects will return to the site for their Day 29 visits. The following assessments will be completed (Invasive study procedures such as blood draws should be performed at the end of the study visit):

- Collect used and unused drug vials, Altera® Nebulizer System (eBase and Altera® handset/mask if applicable), sterilizer and dosing log from subject
- Ask subject and/or parent/caregiver about any new or changes to existing concomitant medications
- Perform a modified physical exam
- Obtain urine sample for pregnancy test (female subjects of child bearing potential only)
- Administer short-acting β2 agonist

[redacted]

- Obtain respiratory sample for microbiology
- Assess subjects for adverse events (All AEs/SAEs regardless of cause or relationship to be reported)

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[redacted]

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6.5.1.

[redacted]

- Assess subject for adverse events (only AE/SAEs related to protocol-mandated procedures must be collected and reported to Gilead PVE. Also, AEs/SAEs related to Cayston treatment in the re-treatment phase must be collected and reported to Gilead PVE)

6.5.2. Week 112/End of Study

The end of this trial is defined as the date of the last study visit of the last study subject. Subjects that continue through their Week 112 study visit will have the following end of study assessments completed.

- Ask subject and/or parent/caregiver about any new or changes to existing concomitant medications
- Perform a complete physical exam
- Administer short-acting β2 agonist
- [redacted]
- Obtain respiratory sample for microbiology
- Assess subject for adverse events (only AE/SAEs related to protocol-mandated procedures must be collected and reported to Gilead PVE. Also, AEs related to Cayston treatment in the re-treatment phase must be collected and reported to Gilead PVE)

6.6. Assessments for Premature Discontinuation from Study

If a subject discontinues study dosing (for example, as a result of an AE), every attempt should be made to keep the subject in the study and continue to perform the required study-related follow-up and procedures (see Section 6.8, Criteria for Discontinuation of Study Treatment). If this is not possible or acceptable to the subject or Investigator, the subject may be withdrawn from the study and an ET visit is to be scheduled immediately. In addition, an ET visit is required if subjects withdraw their consent from participation. The following assessments will be completed at an ET visit. Invasive study procedures such as blood draws should be performed at the end of the visit.

- Collect used and unused drug vials, Altera® Nebulizer System (eBase and Altera® handset, mask if applicable), and dosing log from subject (if ET visit is prior to Day 29 visit)
- Ask subject and/or parent/caregiver about any new or changes to existing concomitant medications
- Perform a complete physical exam
- Obtain urine sample for pregnancy test if ET visit is within 30 days of last dose of study drug (female subjects of child bearing potential only)
- Administer short-acting β2 agonist

[redacted]

- Obtain respiratory sample for microbiology
- Assess subject for adverse events (see Section 7.3 to identify which AEs are required to be reported)

6.7. Unscheduled Visits

If subjects come to the study center outside of their study visit schedule for any reason related to their participation in GS-US-205-1850 it will be considered an unscheduled study visit and the following assessments will be completed.

- Ask subject and/or parent/caregiver about any new or changes to existing concomitant medications
- Obtain vital signs, including weight and height
- Perform a modified physical exam
- Obtain urine sample for pregnancy test (female subjects of child bearing potential only)
- Administer short-acting β2 agonist

[redacted]

- Obtain respiratory sample for microbiology
- Assess subject for adverse events (see Section 7.3 to identify which AEs are required to be reported)

6.8. Criteria for Discontinuation of Study Treatment

Study medication may be discontinued in the following instances:

- Use of a non-study antipseudomonal antibiotic during the 28-day treatment period.
- Intercurrent illness that would, in the judgment of the Investigator, affect assessments of clinical status to a significant degree.
- Unacceptable toxicity, or toxicity that, in the judgment of the Investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest
- Subject request to discontinue for any reason
- Subject noncompliance with visit schedule, study drug dosing or procedures
- Pregnancy during the treatment period
- Discontinuation of the study at the request of Gilead, a regulatory agency or an IRB/IEC

6.9. Details of Scheduled Assessments

6.9.1. Medical History

The subject's medical history will be documented at Screening. The medical history should include significant diagnoses of acute and chronic medical conditions, including prior surgeries, co-morbid diseases, and allergies (β-lactams, in particular). The subject's CF disease history, including any CF-related conditions (eg, CF lung disease, CF-related malabsorption, CF-related liver disease) and previously performed CF-related procedures, will be recorded. The subject's *PA* infection history, including the number of previous *PA* infections, number of cultures taken and sampling methods in the previous 2 years will also be recorded.

6.9.2. Physical Examination/Modified Physical Examination, Vital Signs, and Height and Weight Measurements

A complete physical examination will be conducted by an Investigator (a medical doctor listed on FDA Form 1572) at Screening and Week 112 or the ET visit. At all other visits, modified physical examinations will include head, ears, eyes, nose and throat (HEENT), respiratory, cardiovascular, and any other relevant organ systems based on AEs or clinical symptoms. Any changes since the previous visit will be assessed. Worsening of any pre-existing physical finding (since Screening) should be evaluated for significance and recorded as an AE in the AE eCRF, if appropriate.

Vital signs (heart rate, diastolic and systolic blood pressure, temperature, and respiratory rate) will be recorded at Screening. Heart rate and respiratory rate will be conducted for a full minute. Blood pressure will be assessed after the subject has been seated/reclined for 5 minutes. Height (length for infants) will be measured to the nearest 0.1 cm (or in). Weight will be reported to the nearest 0.1 kg (or lb).

6.9.3. Clinical Observation

For all subjects < 6 years of age and subjects 6 years of age and older who cannot reliably perform spirometry assessments, clinical observation will be conducted by a qualified Investigator (either a licensed nurse practitioner or physician listed on FDA Form 1572) prior to drug administration on Day 1 and 30 minutes post drug administration to evaluate for evidence of drug-related bronchospasm. Clinical observation will include auscultation of the chest, and measurement of respiratory rate and oxygen saturation to ascertain whether the subject is experiencing acute bronchospasm, and/or allergic response. Worsening of any pre-study drug administration finding should be evaluated for significance and recorded as an AE in the AE eCRF, if appropriate. Repeat evaluations should be performed until the Investigator considers it safe to discharge the subject.

6.9.4. Samples for Laboratory Tests

Blood, respiratory samples, nasal swab, and urine samples will be collected during scheduled visits and at the Investigator's discretion during unscheduled visits. Urine pregnancy tests will be performed for females of child bearing potential. All clinical laboratory tests will be sent to the central laboratory specified in the study manual. In addition, respiratory samples collected outside of the study as standard of care may be sent to a local laboratory.

6.9.4.1. Hematology

The following hematological assessments will be performed if there are no labs available within the previous 12 months: hemoglobin (Hb), total red blood cell count (RBC), hematocrit (Hct), mean cell hemoglobin (MCH), mean cell volume (MCV), mean cell hemoglobin concentration (MCHC), white blood cell count (WBC) with differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), and platelets.

6.9.4.2. Serum Chemistry

The following serum chemistry assessments will be performed if there are no labs available within the previous 12 months: blood urea nitrogen (BUN), AST, ALT, total protein, bilirubin, gamma glutamyl transferase (GGT), calcium, sodium, potassium, chloride, glucose, creatinine, and bicarbonate.

A blood draw will be taken at Screening for antipseudomonal antibody testing if there are no results available within the previous 24 months.

6.9.4.3. Respiratory Sampling

Sputum or OP

Microbiological assessments will include qualitative and quantitative culture for *PA*, *Burkholderia* spp., *S. aureus* (methicillin-resistant *S. aureus* [MRSA] and methicillin-sensitive *S. aureus* [MSSA]), *S. maltophilia*, *Achromobacter spp*., *Haemophilus influenza*, and *Aspergillus spp*. At Day 1 and Day 29, a separate fungal culture will be performed to analyze the presence of *Aspergillus spp*.

Minimum inhibitory concentrations (MIC) of aztreonam and other antibiotics for *PA* will be determined at each visit. All phenotypically unique *PA* isolates from each subject at all visits will be genotyped when Day 1 isolates are available for comparison.

A minimum of 0.5 ml of sputum should be collected in a sterile specimen container.

If the subject is not able to spontaneously expectorate sputum at a study visit, alternative methods of lower respiratory tract specimen collection may be performed as per the site's 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, although this will limit microbiology testing.

Note: every effort should be made to obtain an expectorated sputum sample. Detailed instructions on processing and shipment of microbiology sputum samples are provided in the Laboratory Manual.

Many participating sites will also collect and analyze respiratory PA samples outside of the study as standard of care. The local laboratory culture data from these samples will be captured in the eCRF. Local laboratory culture data may be used for analysis purposes.

At the conclusion of this study bacterial isolates collected from sputum may be retained in storage by the sponsor for an indefinite period for additional microbiology testing.

Note: microbiology samples should be collected at least 4 hours after study drug or inhaled antibiotic dosing.

Nasal Swab

Upper respiratory microbiological assessment will include qualitative molecular detection for bacteria and virus using the Biofire testing panel. A mid-turbinate (MT) swab will be used to sample the inferior mid-turbinate region of 1 nostril. The MT swab should be placed in storage media immediately and stored frozen. Detailed instructions on collecting, storing and shipping of upper respiratory microbiology samples are provided in the Laboratory Manual.

6.9.5. Pregnancy Test

A urine pregnancy test will be performed on all female subjects of child bearing potential. If the urine pregnancy test is positive, the subject will be notified and a confirmatory serum pregnancy test will be performed. If the confirmatory serum pregnancy test is positive, the subject will be discontinued from the study drug. Pregnancies that occur after the end of treatment visit but within 30 days of the last dose of study drug should be reported as specified in Section 7.7.2.1.

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7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events, Adverse Reactions, and Serious Adverse Events

7.1.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical study subject administered a medicinal product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include pre- or post-treatment complications that occur as a result of protocol specified procedures, lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an adverse event and must be reported
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.7.1)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history CRF.

Preexisting events or conditions that increase in severity or change in nature after the consent form is signed or as a consequence of participation in the clinical study will also be considered AEs.

7.1.2. Serious Adverse Events

A **serious adverse event** (SAE) is defined as an event that, at any dose, results in the following:

- Death

- Life-threatening (Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)

- In-patient hospitalization or prolongation of existing hospitalization

- Persistent or significant disability/incapacity

- A congenital anomaly/birth defect

- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

7.2. Assessment of Adverse Events and Serious Adverse Events

The Investigator or qualified subinvestigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study drugs and Procedures

The Investigator or qualified subinvestigator is responsible for assessing the relationship to study drug therapy using clinical judgment and the following considerations:

- **No**: Evidence exists that the adverse event has an etiology other than the study drug. For SAEs, an alternative causality must be provided (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).

- **Yes**: There is reasonable possibility that the event may have been caused by the investigational medicinal product.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse event reporting.

The relationship to study procedures (eg, invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the adverse event has an etiology other than the study procedure.

- **Yes:** The adverse event occurred as a result of protocol procedures, (eg, venipuncture).

7.3. Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events

Requirements for collection prior to study drug initiation:

After informed consent, but prior to initiation of study medication, the following types of events should be reported on the case report form (CRF/eCRF): all SAEs and adverse events related to protocol-mandated procedures.

Adverse Events:

Following initiation of study medication, collect all AEs, regardless of cause or relationship, until 4 weeks after last administration of study drug. AEs must be reported to the CRF/eCRF database as instructed.

During the Follow-up culture phase (Through Week 112), AEs related to protocol-mandated procedures must be collected and reported to Gilead PVE. Also, AEs related to Cayston treatment in the re-treatment phase must be collected and reported to Gilead PVE.

All AEs should be followed up until resolution or until the adverse event is stable, if possible. Gilead may request that certain AEs be followed beyond the protocol defined follow up period.

Serious Adverse Events:

All SAEs and deaths, regardless of cause or relationship, that occurs after the subject first consents to participate in the study (i.e., signing the informed consent) until 4 weeks after study drug treatment must be reported to the CRF/eCRF database and Gilead PVE as instructed. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed. During the follow-up culture phase (through week 112), SAEs related to protocol mandated procedures must be collected and reported to Gilead PVE.

Investigators are not obligated to actively seek SAEs after the protocol defined follow up period; however, if the Investigator learns of any SAEs that occur after study participation has concluded and the event is deemed relevant to the use of study drug, he/she should promptly document and report the event to Gilead PVE.

During the Re-Treatment Phase if the subject is treated with Cayston and the investigator learns of any SAEs that are related to Cayston treatment a 'Post Marketing Adverse Event Report Form' must be completed. This report can be sent via email PPD or fax PPD to PVE within 24 hours of becoming aware of such information.

- All AEs and SAEs will be recorded in the eCRF database within the timelines outlined in the eCRF completion guideline.

Electronic Serious Adverse Event (eSAE) Reporting Process

- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead PVE within 24 hours of the Investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.
- If for any reason it is not possible to record the SAE information electronically, i.e., the eCRF database is not functioning (i.e. cannot be accessed or is not available), record the SAE on the paper serious adverse event reporting form and submit within 24 hours of the investigator's knowledge of the event to Gilead PVE:

  Fax: PPD

  E-mail: PPD
- As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF Database according to instructions in the eCRF completion guidelines.
- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.
- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.
- Additional information may be requested to ensure the timely completion of accurate safety reports.
- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's CRF/eCRF and the event description section of the SAE form.

7.4. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs, serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the Investigator's brochure or relevant local label as applicable.

All Investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study drug. The Investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

7.5. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to study drug interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (i.e. decreased hemoglobin).

For AEs or SAEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality, see Section 7.6.

Adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). Severity should be recorded and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, which can be found at: http://evs.nci.nih.gov/ftp1/CTCAE/ and listed under the following file name: "*CTCAE 4.03 2010-0614 QuickReference 8.5x11.pdf*."

7.6. Toxicity Management

- All clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in Appendix 2.
- Grade 3 and 4 clinically significant laboratory abnormalities should be confirmed by repeat testing within 3 calendar days of receipt of results and before investigational medicinal product discontinuation, unless such a delay is not consistent with good medical practice.
- When restarting investigational medicinal product following resolution of the adverse event, the investigational medicinal product should be restarted at full dose or modified dose that is dependent upon discussion with the Gilead Sciences Medical Monitor.
- Any recurrence of the investigational medicinal product-related Grade 3 or 4 clinical or clinically significant laboratory adverse event following dose interruption mandates permanent discontinuation of investigational medicinal product.
- Any questions regarding toxicity management should be directed to the Gilead Sciences Medical Monitor (North America) and the PPD Medical Monitor (Europe).

7.7. Special Situations Reports

7.7.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, product complaints for investigational medicinal product and/or medical device (as applicable) with associated adverse events, and pregnancy reports regardless of an associated AE, and AE in an infant after exposure from breastfeeding.

Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, subject, or consumer.

Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a subject.

Misuse is defined as any intentional and inappropriate use of a medicinal product that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the Investigator has reason to suspect that the subject has taken the additional dose(s).

Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.

Occupational exposure is defined as exposure to a medicinal product as a result of one's professional or non-professional occupation.

7.7.2. Instructions for Reporting Special Situations

7.7.2.1. Instructions for Reporting Pregnancies

The Investigator should report pregnancies in female study subjects that are identified after initiation of study medication and throughout the study, including the post study drug follow-up period, to Gilead PVE using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

Refer to Section 7.3 and the CRF/eCRF completion guidelines for full instructions on the mechanism of pregnancy reporting.

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons.

Any premature termination of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Sections 7.1.1 and 7.1.2. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead PVE.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported Gilead PVE using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PVE. Gilead PVE contact information is as follows: Email:PPD and Fax: PPD.

Pregnancies of female partners of male study subjects exposed to Gilead or other study drugs must also be reported and relevant information should be submitted to Gilead PVE using the pregnancy and pregnancy outcome forms within 24 hours. Monitoring of the subject should continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PVE, fax number PPD or email PPD.

Refer to Appendix 3 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.7.2.2. Reporting Other Special Situations

All other special situation reports must be reported on the special situations report form and forwarded to Gilead PVE within 24 hours of the Investigator becoming aware of the situation. These reports must consist of situations that involve study drug and/or Gilead concomitant medications, but do not apply to non-Gilead concomitant medications.

Special situations involving non-Gilead concomitant medications does not need to be reported on the special situations report form; however, for special situations that result in AEs due to a non-Gilead concomitant medication, the AE should be reported on the AE form.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as “misuse,” but may be more appropriately documented as a protocol deviation.

Refer to Section 7.3 and the CRF/eCRF completion guidelines for full instructions on the mechanism of special situations reporting.

All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time using the AE CRF/eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objective of this study is to evaluate the safety and efficacy of a 14-day course vs a 28-day course of AZLI 75 mg TID in subjects with new onset *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 TNS 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 2009} over a 108-week post-treatment follow-up period

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8.1.2. Primary Endpoint

The primary endpoint of this study is:

- The proportion of subjects with *PA*-negative cultures through 28 days post-treatment in the 14-day treatment group vs the 28-day treatment group.

8.1.3. Secondary Endpoint

Secondary endpoints are:

- Time from primary eradication to *PA* recurrence over the 108-week post-treatment follow-up period. The primary eradication is achieved when all available cultures at 14 and 28 days post AZLI treatment are *PA* negative
- 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 over the 108-week post-treatment follow-up period for a sub-group of subjects matching the population in the TNS ELITE Study over a 108-week post-treatment follow-up period.

CCI . CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.2. Planned Analyses

8.2.1. Primary Analysis

The unblinded primary analysis of the primary endpoint will be conducted after all evaluable subjects have completed Study Week 8, or Study Week 16 if Week 8 culture data are missing, or are early terminated, and the data have been cleaned and finalized for the analysis.

The primary analysis will be tested with a -20% noninferiority margin at a 1-sided significance level of 0.025. This analysis of the primary endpoint will serve as the final analysis for this endpoint.

Additional unblinded analyses on secondary endpoint Week 8 and safety data may also be conducted, depending on data availability.

8.2.2. Final Analysis

The unblinded final analysis will be performed after all subjects have completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized. Final analysis will include analyses of data for secondary endpoints that depends on study completion and analysis on safety data collected during study follow-up phase.

8.3. Analysis Conventions

8.3.1. Analysis Sets

8.3.1.1. Efficacy

The primary analysis set for the efficacy analysis is the Evaluable Analysis Set that will include all randomized subjects who complete AZLI treatment with at least 75% compliance, and do not use any anti-*PA* antibiotics while on study treatment with AZLI. Missing *PA* culture data will be adjudicated before data unblinding based on available *PA* culture results.

The Intent-to-treat (ITT) Analysis Set will include 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. 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 2009}. The detailed criteria for subject's inclusion in the ELITE study matching analysis set will be provided in the Statistical Analysis Plan (SAP).

8.3.1.2. Safety

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

All data collected on or after the start of treatment and up to 4 weeks after the last dose of study drug will be included in the safety summaries.

8.3.1.3. Biomarkers

The Biomarker Analysis Set includes all subjects who were randomized and have received at least 1 dose of the study drug and for whom biomarker data are available. Subjects will be analyzed according to the treatment they actually receive.

8.4. Data Handling Conventions

No imputations will be made for missing baseline data unless otherwise specified.

8.5. Demographic Data and Baseline Characteristics

Demographic and baseline measurements will be summarized using standard descriptive methods.

Demographic summaries will include sex, race/ethnicity, and age.

Baseline characteristics will include a summary of body weight, height, BMI, anti-*PA* antibodies, MIC for *PA* isolates, and spirometry measurements (where applicable).

8.6. Efficacy Analysis

8.6.1. Primary Analysis

Primary analysis of the primary endpoint is the test of noninferiority of the 14-day AZLI course compared to the 28-day AZLI course based on the Evaluable Analysis Set.

The proportion of subjects *PA*-negative through 28 days post-treatment (Day 42 for subjects in the 14-day treatment group and Day 56 for subjects in the 28-day group) for each treatment group and the difference between treatment groups will be presented with 2-sided 95% confidence intervals (CI).

Noninferiority 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 noninferiority margin of -20%.

To evaluate the impact of the treatment regimens on the treatment effect, the primary efficacy analysis will be repeated using the ITT analysis set.

Descriptive summaries of *PA* eradication over 28 days post-treatment will be provided by age subgroups (3 months to < 2 years, 2 years to < 6 years, 6 to 17 years).

The effect of baseline characteristics that include clinical and laboratory parameters collected prior to start of study treatment on the success or failure of primary *PA* eradication will be explored using the appropriate statistical methodology.

The unblinded primary analysis of the primary endpoint will be conducted after all evaluable subjects have completed Study Week 8, or Study Week 16 if Week 8 culture data are missing, or are early terminated, and the data have been cleaned and finalized for the analysis.

8.6.2. Secondary Analyses

The median time to *PA* recurrence after the primary eradication over the 108-week post-treatment period will be assessed using Kaplan-Meier method. The median time and 95% CIs will be presented based on the Evaluable Analysis Set. Additional summaries of time to *PA* recurrence will be provided by age subgroups (3 months to < 2 years, 2 years to < 6 years, 6 to 17 years).

The proportion of subjects with *PA*-negative cultures during 28 days post-treatment period in the 14-day course group will be presented with 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 2003b, Proesmans 2013}. The pooled proportion of subjects with successful *PA* eradication at 28 days post-treatment with TNS is estimated to be 77%. Details of the estimation will be provided in the SAP.

The median time to *PA* recurrence and 95% CI will be presented for ELITE-matching analysis set and compared descriptively with the published result from ELITE Study.

8.7. Safety Analysis

All safety data collected on or after the date that study drug was first dispensed up to the date of last dose of study drug plus 30 days will be summarized by treatment group (according to the study drug received). All data including the pretreatment and treatment-free follow-up period will be presented in the data listings.

8.7.1. Extent of Exposure

A subject's extent of exposure to study drug data will be generated from the study drug administration record. Exposure and level of adherence will be summarized by treatment group.

8.7.2. Adverse Events

Clinical and laboratory adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class (SOC), High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Term (PT), and Lower-Level Term (LLT) will be attached to the clinical database.

Events will be summarized on the basis of the date of onset for the event. A treatment-emergent adverse event will be defined as any adverse event that begins on or after the date of first dose of study drug up to the date of last dose of study drug plus 30 days or leading to premature discontinuation of study treatment.

Summaries (number and percentage of subjects) of treatment-emergent adverse events (by SOC, and PT) will be provided by treatment group.

8.7.3. Laboratory Evaluations

Selected laboratory parameters will be summarized using only observed data, without imputation for missing data. Observed values and change from baseline at all scheduled time points will be summarized.

Graded laboratory abnormalities will be defined using the grading scheme in Appendix 3.

Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least one toxicity grade from baseline at any time post baseline up to and including the date of last dose of study drug plus 30 days, will be summarized by treatment group. If baseline data are missing, then any graded abnormality (i.e., at least a Grade 1) will be considered treatment emergent.

Laboratory abnormalities that occur before the first dose of study drug or after the subject has been discontinued from treatment for at least 30 days will be included in a data listing.

8.7.4. Other Safety Evaluations

Airway reactivity will be assessed by spirometry and clinical observation at 30 minutes post treatment.

Vital signs will be summarized using descriptive statistics (n, mean, standard deviation, median, Q1, Q3, minimum, and maximum).

8.8. Biomarker Analysis

PA-specific antibody titers will be obtained at Screening (if there is no historical data available within 24 months). Categorical results of anti-*PA* IgG antibody titer will be presented by the highest titer result and by individual antigen.

8.9. Sample Size

A maximum feasible sample size of 130 evaluable subjects (65 subjects per arm) will provide 75% power to show that the treatment with AZLI for 14 days is not inferior to 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%. The -20% noninferiority margin preserves at least 65% of the comparator arm treatment effect, where treatment effect is calculated as the difference in *PA* eradication rates between AZLI for 28 days (from Study GS-US-205-0162) and the historical control placebo {Gibson 2003b, Wiesemann 1998}. With a nonevaluable rate of 5%-7%, up to 140 subjects will be enrolled to reach 130 evaluable.

Data Monitoring Committee

An external multidisciplinary data monitoring committee (DMC) will review the progress of the study, perform interim reviews of safety data and provide recommendation to Gilead whether the nature, frequency, and severity of adverse effects associated with study treatment warrant the early termination of the study, whether the study should continue as planned, or whether the study should continue with modifications. The DMC may also provide recommendations as needed regarding study design.

The DMC's specific activities will be defined by a mutually agreed charter, which will define the DMC's membership, conduct and meeting schedule.

While the DMC will be asked to advise Gilead regarding future conduct of the study, including possible early study termination, Gilead retains final decision-making authority on all aspects of the study.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with ICH E6(R2) addendum to its guideline for GCP and applicable laws and regulations.

9.1.2. Financial Disclosure

The investigator and subinvestigators will provide prompt and accurate documentation of their financial interest or arrangements with Gilead, or proprietary interests in the investigational drug during the course of a clinical study. This documentation must be provided prior to the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last subject completes the protocol-defined activities.

9.1.3. Institutional Review Board/Independent Ethics Committee Review and Approval

The investigator (or Gilead as appropriate according to local regulations) will submit this protocol, informed consent form, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC. The investigator will not begin any study subject activities until approval from the IRB/IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC any modifications made to the protocol or any accompanying material to be provided to the subject after initial IRB/IEC approval, with the exception of those necessary to reduce immediate risk to study subjects.

9.1.4. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study before undertaking any study-related procedures. The investigator must use the most current IRB- or IEC-approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IRB or IEC or local requirements. The consent form will inform subjects about genomic testing and/or planned sample retention. In addition to the study-specific informed consent to be signed by each subject participating in the study, subjects will be required to document agreement to provide additional samples or to allow the use of the remainder of their already collected specimens for optional

future research, in accordance with applicable regulations. In addition to the study-specific informed consent to be signed by each subject participating in the study, subjects will be required to document agreement to provide additional samples for optional genomic research. The results of the tests done on the samples will not be given to the subject or the investigator.

9.1.5. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code and any other unique identifier(s) as allowed by local law (such as year of birth) will be recorded on any form or biological sample submitted to Gilead, or laboratory. Laboratory specimens must be labelled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions . NOTE: The investigator must keep a screening log with details for all subjects screened and enrolled in the study, in accordance with the site procedures and regulations. Subject data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Gilead, including but not limited to the investigator's brochure, this protocol, CRF/eCRF, the study drug, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.6. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 2 categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, paper or electronic completed subject CRFs, and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each subject:

- Subject identification;
- Documentation that subject meets eligibility criteria, ie, medical history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);

- Documentation of the reason(s) a consented subject is not enrolled
- Participation in study (including study number);
- Study discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol-specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end dates (including dose regimen) of study drug, including dates of dispensing and return;
- Record of all adverse events and other safety parameters (start and end dates, and including causality and severity), and documentation that adequate medical care has been provided for any adverse event
- Concomitant medication (including start and end dates, dose if relevant; dose changes);
- Date of study completion and reason for early discontinuation, if it occurs.

All clinical study documents must be retained by the investigator until at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, United States, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the subject, appropriate copies should be made for storage away from the site.

9.1.7. Case Report Forms

For each subject consented, an eCRF casebook will be completed by an authorized study staff member whose training for this function is completed in the EDC system. The eCRF casebook will only capture the data required per the protocol schedule of events and procedures.
The Inclusion/Exclusion Criteria and Enrollment eCRFs should be completed only after all data

related to eligibility have been received. Data entry should be performed in accordance with the CRF Completion Guidelines (CCGs) provided by the Sponsor. Subsequent to data entry, a study monitor will perform source data verification (SDV) within the EDC system. System-generated or manual queries will be issued in the EDC system as data discrepancies are identified by the monitor or Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site investigator or site coordinator or other designee is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (e.g., data entry error). Original entries as well as any changes to data fields will be stored in the audit trail of the system. At a minimum, prior to any interim time points or database lock (as instructed by Gilead), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. At the conclusion of the study, Gilead will provide the site investigator with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.6.

9.1.8. Investigator Inspections

The investigator will make available all source documents and other records for this study to Gilead's appointed study monitors, to IRBs/IECs, or to regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Gilead. The investigator must submit all protocol modifications to the IRB/IEC in accordance with local requirements and receive documented approval before modifications can be implemented.

9.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency. Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met: The results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years.

The investigator will submit to Gilead any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation. No such communication, presentation, or publication will include Gilead's confidential information (see Section 9.1.5).

The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol, eg, attendance at Investigator Meetings. If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to Federal and State agencies any expenses paid or reimbursed for such services, including any clinical study payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

The monitor is responsible for routine review of the CRF/eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries in the CRF/eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Gilead medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

Both Gilead and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the subjects, appropriate regulatory authority, IRBs, and ECs . In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

10. REFERENCES

Abman SH, Ogle JW, Harbeck RJ, Butler-Simon N, Hammond KB, Accurso FJ. Early bacteriologic, immunologic, and clinical courses of young infants with cystic fibrosis identified by neonatal screening. J Pediatr 1991;119 (2):211-7.

Adkinson NF, Jr. Immunogenicity and cross-allergenicity of aztreonam. Am J Med 1990;88 (3C):12S-5S; discussion 38S-42S.

Adkinson NF, Jr., Swabb EA, Sugerman AA. Immunology of the monobactam aztreonam. Antimicrob Agents Chemother 1984;25 (1):93-7.

Brewer NS, Hellinger WC. The monobactams. Mayo Clin Proc 1991;66 (11):1152-7.

Burns JL, Gibson RL, McNamara S, Yim D, Emerson J, Rosenfeld M, et al. Longitudinal assessment of Pseudomonas aeruginosa in young children with cystic fibrosis. J Infect Dis 2001;183 (3):444-52.

Corey M, Edwards L, Levison H, Knowles M. Longitudinal analysis of pulmonary function decline in patients with cystic fibrosis. J Pediatr 1997;131 (6):809-14.

Courtney JM, Dunbar KEA, McDowell A, Moore JE, Warke TJ, Stevenson M, et al. Clinical outcome of *Burkholderia cepacia* complex infection in cystic fibrosis adults. J Cyst Fibros 2004;3 (2):93-8.

Cystic Fibrosis Foundation. Patient Registry 2006 Annual Data Report. The Foundation 2008.

Cystic Fibrosis Foundation. Cystic Fibrosis Foundation Patient Registry 2014 Annual Data Report. 2015.

About cystic fibrosis. webpage www.cftrust.org.uk. Accessed July 30, 2007.

Cystic Fibrosis Worldwide. Cystic Fibrosis Worldwide Annual report 2015. Available at: https://cfww.derekgrimes.com/. Accessed 23 June. 2016.

Doring G, Hoiby N. Early intervention and prevention of lung disease in cystic fibrosis: a European consensus. J Cyst Fibros 2004;3 (2):67-91.

Cystic fibrosis. website http://www.european-lung-foundation.org. Accessed July 30, 2007.

Farrell PM, Rosenstein BJ, White TB, Accurso FJ, Castellani C, Cutting GR, et al. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation consensus report. J Pediatr 2008;153 (2):S4-S14.

Frederiksen B, Koch C, Hoiby N. Antibiotic treatment of initial colonization with Pseudomonas aeruginosa postpones chronic infection and prevents deterioration of pulmonary function in cystic fibrosis. Pediatr Pulmonol 1997;23 (5):330-5.

Frederiksen B, Lanng S, Koch C, Høiby N. Improved survival in the Danish Center-treated cystic fibrosis patients: results of aggressive treatment. Pediatr Pulmonol 1996;21 (3):153-8.

Freiberg MS, Chang CC, Kuller LH, Skanderson M, Lowy E, Kraemer KL, et al. HIV Infection and the Risk of Acute Myocardial Infarction. JAMA internal medicine 2013;173 (8):1-19.

Gibson RL, Burns JL, Ramsey BW. Pathophysiology and management of pulmonary infections in cystic fibrosis. Am J Respir Crit Care Med 2003a;168 (8):918-51.

Gibson RL, Emerson J, Mayer-Hamblett N, Burns JL, McNamara S, Accurso FJ, et al. Duration of treatment effect after tobramycin solution for inhalation in young children with cystic fibrosis. Pediatr Pulmonol 2007;42 (7):610-23.

Gibson RL, Emerson J, McNamara S, Burns JL, Rosenfeld M, Yunker A, et al. Significant microbiological effect of inhaled tobramycin in young children with cystic fibrosis. Am J Respir Crit Care Med. 2003b;167 (6):841-9.

Henry RL, Mellis CM, Petrovic L. Mucoid *Pseudomonas aeruginosa* is a marker of poor survival in cystic fibrosis. Pediatr Pulmonol 1992;12 (3):158-61.

Ho PL, Chan KN, Ip MS, Lam WK, Ho CS, Yuen KY, et al. The effect of Pseudomonas aeruginosa infection on clinical parameters in steady-state bronchiectasis. Chest 1998;114 (6):1594-8.

Kerem E, Reisman J, Corey M, Canny GJ, Levison H. Prediction of mortality in patients with cystic fibrosis. N Engl J Med 1992;326 (18):1187-91.

McCormick J, Mehta G, Olesen HV, Viviani L, Macek M, Jr., Mehta A. Comparative demographics of the European cystic fibrosis population: a cross-sectional database analysis. Lancet 2010;375 (9719):1007-13.

Mogayzel PJ, Naureckas ET, Robinson KA, Brady C, Guill M, Lahiri T, et al. Cystic Fibrosis Foundation Pulmonary Guideline. Pharmacologic Approaches to Prevention and Eradication of Initial Pseudomonas Aeruginosa Infection. Annals of the American Thoracic Society 2014;11 (10):1640-50.

Newman SP. Aerosol deposition considerations in inhalation therapy. Chest 1985;88 (2 Suppl):152S-60S.

Pamukcu A, Bush A, Buchdahl R. Effects of *Pseudomonas aeruginosa* colonization on lung function and anthropometric variables in children with cystic fibrosis. Pediatr Pulmonol 1995;19 (1):10-5.

Proesmans M, Vermeulen F, Boulanger L, Verhaegen J, De Boeck K. Comparison of two treatment regimens for eradication of Pseudomonas aeruginosa infection in children with cystic fibrosis. J Cyst Fibros 2013;12 (1):29-34.

Ratjen F, Doring G, Nikolaizik WH. Effect of inhaled tobramycin on early Pseudomonas aeruginosa colonisation in patients with cystic fibrosis. Lancet 2001;358 (9286):983-4.

Ratjen F, Munck A, Kho P, Angyalosi G. Treatment of early Pseudomonas aeruginosa infection in patients with cystic fibrosis: the ELITE trial. Thorax 2009;65 (4):286-91.

Saxon A, Hassner A, Swabb EA, Wheeler B, Adkinson NF, Jr. Lack of cross-reactivity between aztreonam , a monobactam antibiotic, and penicillin in penicillin-allergic subjects. J Infect Dis 1984;149 (1):16-22.

Saxon A, Swabb EA, Adkinson NF, Jr. Investigation into the immunologic cross-reactivity of aztreonam with other beta-lactam antibiotics. Am J Med 1985;78 (2A):19-26.

Schelstraete P, Haerynck F, Van daele S, Deseyne S, De Baets F. Eradication therapy for Pseudomonas aeruginosa colonization episodes in cystic fibrosis patients not chronically colonized by P. aeruginosa. J Cyst Fibros 2013;12 (1):1-8.

Shawar RM, MacLeod DL, Garber RL, Burns JL, Stapp JR, Clausen CR, et al. Activities of tobramycin and six other antibiotics against *Pseudomonas aeruginosa* isolates from patients with cystic fibrosis. Antimicrob Agents Chemother 1999;43 (12):2877-80.

Tiddens HA, De Boeck K, Clancy JP, Fayon M, H GMA, Bresnik M, et al. Open label study of inhaled aztreonam for Pseudomonas eradication in children with cystic fibrosis: The ALPINE study. J Cyst Fibros 2015;14 (1):111-9.

Treggiari MM, Rosenfeld M, Retsch-Bogart G, Gibson R, Ramsey B. Approach to eradication of initial *Pseudomonas aeruginosa* infection in children with cystic fibrosis. Pediatr Pulmonol 2007;42 (9):751-6.

Vaincre la Mucoviscidose, Institut national d'études démographiques. The French National Cystic Fibrosis Observatory (ONM): Report on 2004 Data. ONM 2006.

Valerius NH, Koch C, Hoiby N. Prevention of chronic Pseudomonas aeruginosa colonisation in cystic fibrosis by early treatment. Lancet 1991;338 (8769):725-6.

Wiedemann B, Steinkamp G, Sens B, Stern M. The German cystic fibrosis quality assurance project: clinical features in children and adults. Eur Respir J 2001;17 (6):1187-94.

Wiesemann HG, Steinkamp G, Ratjen F, Bauernfeind A, Przyklenk B, Doring G, et al. Placebo-controlled, double-blind, randomized study of aerosolized tobramycin for early treatment of Pseudomonas aeruginosa colonization in cystic fibrosis. Pediatr Pulmonol 1998;25 (2):88-92.

Zemanick ET, Harris JK, Conway S, Konstan MW, Marshall B, Quittner AL, et al. Measuring and improving respiratory outcomes in cystic fibrosis lung disease: opportunities and challenges to therapy. J Cyst Fibros 2010;9 (1):1-16.

11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
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STUDY ACKNOWLEDGEMENT

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.

AMENDMENT 3 PROTOCOL- 15 APRIL 2020

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

PPD

Name (Printed)
Author

PPD

Signature

17 April 2020

Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

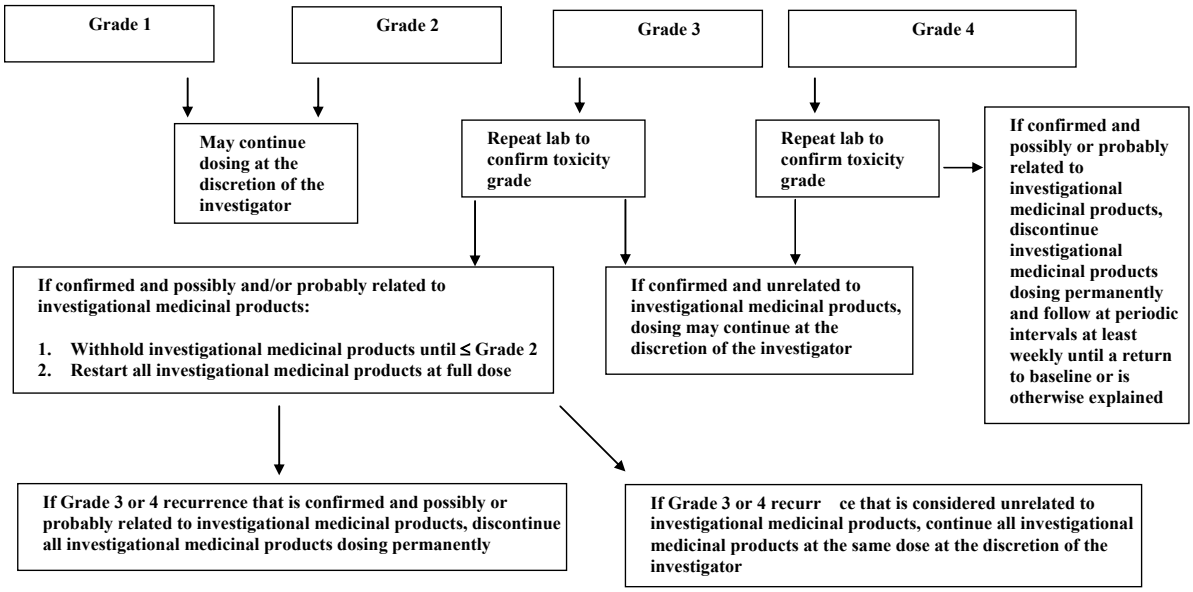
Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Management of Clinical and Laboratory Adverse Events



Appendix 3. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a Definition of Childbearing Potential

For the purposes of this study, a female born subject is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming post-menopausal, unless permanently sterile or with medically documented ovarian failure.

b Definition of Male Fertility

For the purposes of this study, a male born subject is considered fertile after the initiation of puberty unless permanently sterile by bilateral orchidectomy or has medical documentation of permanent male infertility.

2) Contraception Requirements for Female Subjects

a Study Drug Effects on Pregnancy and Hormonal Contraception

Non-clinical toxicity studies of aztreonam have demonstrated no adverse effect on fertility or embryo-fetal development. However, there are no clinical studies of AZLI in pregnant women. Data from clinical pharmacokinetic interaction studies of aztreonam have demonstrated that there is no reduction in the clinical efficacy of hormonal contraception. Please refer to the latest version of the Investigator's brochure for additional information and to the SmPC/PI.

b Contraception Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires using at least an acceptable effective contraceptive measure. They must have a negative serum pregnancy test at Screening and a negative pregnancy test on the Baseline/Day 1 visit prior to randomization. In the event of a delayed menstrual period (over one month between menstruations), a pregnancy test must be performed to rule out pregnancy. This is true even for women of childbearing potential with infrequent or irregular periods. They must also agree to one of the following from Screening until after the last dose of study drug.

- Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the subject's preferred and usual lifestyle.

Or

- Consistent and correct use of 1 of the following methods of birth control listed below.

  Intrauterine device (IUD) with a failure rate of <1% per year

  Intrauterine hormone-releasing system (IUS) with a failure rate of <1% per year

  Tubal sterilization

Essure micro-insert system (provided confirmation of success 3 months after procedure)

Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure)

Barrier methods (one female barrier and one male barrier must be used in combination)

- Female barriers (diaphragm with spermicide, cervical cap with spermicide, sponge with spermicide)
- Male barriers (male condom, with or without spermicide)

Hormonal methods

- Oral contraceptives (either combined or progesterone only)
- Injectable progesterone
- Implants of levonorgestrel
- Transdermal contraceptive patch
- Contraceptive vaginal ring

Female subjects must also refrain from egg donation and in vitro fertilization during treatment and until after the last dose of study drug.

3) Contraception Requirements for Male Subjects

During the study, male subjects with female partners of childbearing potential should use condoms when engaging in intercourse of reproductive potential.

4) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM). Female condom and male condom should not be used together.

5) Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the Investigator if they become pregnant at any time during the study, or if they become pregnant within 4 weeks of last study drug dose. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the Investigator and discontinue study drug immediately. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.7.2.1.