Clinical Research Protocol

Standardized Treatment of Pulmonary Exacerbations II (STOP2)

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Approval :

PI or Sponsor Signature (Christopher Goss, MD MSc) — *Date* 11-2-2018

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PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing the Sponsor-Investigator with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: STOP2-IP-15

Protocol Title: Standardized Treatment of Pulmonary Exacerbations II (STOP2)

Protocol Date: November 2, 2018

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Investigator Signature *Date*

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Print Name and Title

Site #: _____

Site Name: _____

Address: _____

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LIST OF ABBREVIATIONS AND ACRONYMS

AE	adverse event
ANOVA	Analysis of variance
CF	cystic fibrosis
CFF	Cystic Fibrosis Foundation
CFFNPR	Cystic Fibrosis Foundation National Patient Registry
CFFT	Cystic Fibrosis Foundation Therapeutics
CFR	Code of Federal Regulations
CFRSD	Cystic Fibrosis Respiratory Symptoms Diary
CRISS	Chronic Respiratory Infection Symptom Score
CFTR	cystic fibrosis transmembrane conductance regulator
CRF	case report form
CRP	C-Reactive Protein
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
EDC	electronic data capture
ERR	Early Robust Response
FDA	Food and Drug Administration
$FEF_{25\%-75\%}$	forced expiratory flow
FEV_1	forced expiratory volume over one second
FVC	forced vital capacity
GCP	Good Clinical Practice
GLI	Global Lung Initiative
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
NERR	Non-Early Robust Response
PEx	pulmonary exacerbation
PFT	pulmonary function test
SAE	serious adverse experience
TDNCC	Therapeutics Development Network Coordinating Center

PROTOCOL SYNOPSIS

TITLE	Standardized Treatment of Pulmonary Exacerbations II (STOP2)
SPONSOR-INVESTIGATORS	Patrick Flume, MD Medical University of South Carolina Christopher H. Goss, MD MSc University of Washington
FUNDING ORGANIZATION	Cystic Fibrosis Foundation Therapeutics, Inc (CFFT)
NUMBER OF SITES	Approximately 60
RATIONALE	In patients with cystic fibrosis (CF) who are experiencing a pulmonary exacerbation, a strong desire among clinicians to reduce treatment durations (and reduce cost, inconvenience, and potential toxicities) is in conflict with belief that patients not responding robustly to treatment might benefit from extending treatment. An assessment taken after one week of treatment has been demonstrated to predict the overall response, especially for those with a robust improvement (Early Robust Response; ERR). These patients are often treated with shorter courses of intravenous (IV) antibiotics in clinical practice and will likely experience no additional benefit from an extended IV treatment. For those subjects who have a less robust early response to treatment, an extended treatment duration may be needed; however, the additional clinical benefit of such a prolonged course of IV antibiotic must outweigh potential risks of toxicity, treatment burden, and increased resource utilization.
STUDY DESIGN	This randomized, controlled, open-label study is designed to evaluate the efficacy and safety of differing durations of IV treatment, given in the hospital or at home for a pulmonary exacerbation in adult patients with CF. The study will assess the non-inferiority of 10 days versus 14 days treatment duration among ERR subjects and the superiority of 21 days versus 14 days treatment duration among the subjects who do not meet the definition of ERR (non-ERR; NERR) Subjects will undergo pulmonary function testing (spirometry) and complete a respiratory symptom score [Chronic Respiratory Infection Symptom Score (CRISS)] at initiation of IV treatment (Baseline/ Visit 1) and at Day 7-10 (Visit 2). At Visit 2, subjects will be allocated to groups ERR or NERR based on their initial clinical response as determined by the change in forced expiratory volume in 1 second (FEV_1; percent of predicted) and CRISS from Baseline and then randomized to an IV treatment duration (nested within group). ERR subjects [≥8% predicted improvement in FEV_1 from Baseline (Visit 1) to Visit 2 and CRISS reduction of ≥11 points from Baseline (Visit 1) to Visit 2] will be randomized 1:1 to either 10 days or 14 days total IV antibiotic treatment duration. Remaining (NERR)

	subjects will be randomized 1:1 to receive either 14 or 21 days total IV antibiotic treatment duration. All subjects will be evaluated again at Visit 3, 14 days following scheduled completion of IV antibiotic treatment.
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Dependent on the treatment arm, subjects will be on study from 24 to 35 days: ▪ Treatment prior to randomization: 7 – 10 days ▪ Treatment post-randomization: o ERR-10 subjects: 0 to 3 days = 10 days (±1 day) total IV treatment o ERR-14 subjects: 4 to 7 days = 14 days (±1 day) total IV treatment o NERR-14 subjects : 4 to 7 days = 14 days (±1 day) total IV treatment o NERR-21 subjects: 11 to 14 days = 21 days (±3 days) total IV treatment ▪ Follow-up: 14 days after end of scheduled IV antibiotic treatment (±2 days) The total duration of the study is expected to be approximately 42 months: 41 months for subject recruitment and 1 month for final subject follow-up.
PRIMARY OBJECTIVE	To evaluate the efficacy and safety of differing durations of IV antibiotic treatment for CF pulmonary exacerbations *ERR Group:* To determine if 10 days of IV antibiotic treatment (ERR-10) is as safe as and not clinically inferior (in terms of lung function response) to 14 days of IV antibiotic treatment (ERR-14) among subjects meeting the ERR threshold at Visit 2. *NERR Group:* To determine if 21 days of IV antibiotic treatment (NERR-21) is clinically superior (in terms of lung function response) and safe, compared to 14 days of IV antibiotic treatment (NERR-14) among subjects not meeting the ERR threshold at Visit 2.
SECONDARY OBJECTIVES	The secondary objectives are to: ▪ Evaluate efficacy of differing IV antibiotic treatment durations on other clinical outcomes such as weight, respiratory symptoms, and subsequent IV antibiotic treatments for pulmonary exacerbation. ▪ Determine the feasibility, uptake and adherence to a standardized protocol of antibiotic selection.

	Other objectives are to: ▪ Provide a study platform for ancillary studies of PEx treatment in adults with CF, including investigations into respiratory microbiome, health economics, and systemic inflammation. ▪ Establish a biorepository of CF serum and sputum samples before, during and after treatment for an adult PEx for use by the CF research community.
NUMBER OF SUBJECTS	Approximately 1330 screened to enroll a minimum of 310 completed ERR subjects and a minimum of 570 completed NERR subjects
SUBJECT SELECTION CRITERIA: **Inclusion Criteria**	Inclusion Criteria: 1. Male or female ≥18 years of age at Visit 1 2. Documentation of a CF diagnosis as evidenced by one or more clinical features consistent with the CF phenotype and one or more of the following criteria: ▪ Sweat chloride equal to or greater than 60 mEq/liter by quantitative pilocarpine iontophoresis test (QPIT) ▪ Two well-characterized mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene ▪ Abnormal nasal potential difference (change in NPD in response to a low chloride solution and isoproteronol of less than -5 mV) 3. Enrolled in the Cystic Fibrosis Foundation National Patient Registry (CFFNPR) prior to Visit 1 (US sites only) 4. At the time of Visit 1, there is a plan to initiate IV antibiotics for a pulmonary exacerbation 5. Performed spirometry at Visit 1 and Visit 2 and willing to perform spirometry at Visit 3 6. Completed the CRISS questionnaire at Visit 1 and Visit 2 and willing to complete the CFRSD questionnaire at Visit 3 7. Willing to adhere to a specific treatment duration determined by initial response to treatment and subsequent randomization 8. Willing to return for follow up Visit 3 9. Written informed consent obtained from the subject or subject's legal representative
SUBJECT SELECTION CRITERIA: **Exclusion Criteria**	Exclusion Criteria: 1. Previous randomization in this study 2. Treatment with IV antibiotics in the 6 weeks prior to Visit 1 3. Admission to the intensive care unit for current pulmonary exacerbation in the two weeks prior to Visit 2, unless admission was due to a desensitization protocol 4. Pneumothorax in the two weeks prior to Visit 2

	5. Primary diagnosis for current hospitalization is unrelated to worsening lower respiratory symptoms (e.g., pulmonary clean out, DIOS, sinusitis) 6. Massive hemoptysis defined as > 250 cc in a 24 hour period or 100 cc/day over 4 consecutive days occurring in the two weeks prior to Visit 2 7. Current pulmonary exacerbation thought to be due to allergic bronchopulmonary aspergillosis (ABPA) 8. At Visit 1, receiving ongoing treatment with a duration of more than 2 weeks with prednisone equivalent to >10mg/day 9. History of solid organ transplantation 10. Receiving antimicrobial therapy to treat non-tuberculous mycobacterium (e.g., *M. abscessus*, *M. avium* complex) in the two weeks prior to Visit 2
TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	Initial IV antibiotics will be selected by the treating physician using study-specific guidelines provided and taking into account prior sputum culture results, previous antibiotic intolerances, and known drug allergies.
CONTROL PRODUCT, DOSE AND ROUTE OF ADMINISTRATION	N/A
CONCOMMITANT MEDICATIONS	**Allowed Medications and Treatments** **Chronic Therapies** A stable therapeutic regimen between Baseline (Visit 1) and Visit 3 is the goal. Ongoing chronic treatment (>21 days prior to Visit 1) with Pulmozyme®, high dose ibuprofen, hypertonic saline, azithromycin, short and long bronchodilators, airway clearance, and FDA approved CFTR modulator therapy is allowed. Subjects that have been using any of these therapies chronically should be encouraged to continue them throughout the entire study period (through Visit 3). Any of these medications may be introduced between Visit 1 and Visit 3 if they are intended to remain as a chronic therapy. Chronic medications can be stopped if the clinician has determined that the therapy is either ineffective or doing harm. Continuation of ongoing chronic treatment (>21 days prior to screening) with inhaled or oral antibiotics is allowed according to the schedule below: ▪ If a subject is taking continuous inhaled or oral antibiotics, they may take them anytime between Visit 1 and 3. ▪ If a subject is taking cycled inhaled antibiotics, they may maintain their current on/off cycle, but ideally will not start a new cycle during the 14 days prior to Visit 3.

	Treatment of PEx Treatment with corticosteroids is allowed at the discretion of the treating clinician for the indication of the current PEx. However, the decision to use corticosteroids should be made prior to randomization at Visit 2 as this will be included as a randomization stratum. Subjects should perform maximally effective airway clearance therapies during the course of treatment for the PEx. These will be recommended by the treating clinician. **Following Completion of Treatment of PEx** Corticosteroids, if initiated during the treatment, should be weaned according to the clinician's usual practice. **Prohibited Medications and Treatments** No antibiotics (oral or inhaled) should be taken following the scheduled completion of the IV treatment of PEx until after Visit 3 except as noted in the Allowed Medications section. Investigational therapies are prohibited during the study.
PRIMARY ENDPOINT	Absolute change in percent predicted FEV_1 from initiation of IV treatment (Baseline/Visit 1) to two weeks after scheduled completion of IV antibiotic treatment (Visit 3).
SECONDARY ENDPOINTS	**Efficacy** ▪ Absolute change in CRISS from Visit 1 (Baseline) to Visit 3 ▪ Proportion of patients retreated for pulmonary exacerbation within 30 days following scheduled completion of IV antibiotics as collected in the CFFNPR ▪ Time (days) to next pulmonary exacerbation following scheduled completion of IV antibiotics as collected in the CFFNPR ▪ Relative change in FEV_1 (liters) from Visit 1 (Baseline) to Visit 3 ▪ Absolute change in weight (kg) from Visit 1 (Baseline) to Visit 3 **Safety** ▪ Incidence of adverse events, including clinically significant abnormal lab values ▪ Retreatment of pulmonary exacerbation prior to Visit 3 **Exploratory Endpoints** ▪ Baseline, treatment characteristics, and outcomes (via CFFNPR) of the un-randomized subjects by reason (e.g., ineligible, lost to follow-up) ▪ Baseline, treatment characteristics, and outcomes (via CFFNPR) of the randomized but lost to follow-up subjects ▪ Adherence to antibiotic selection protocol ▪ Adherence to randomization scheme

	▪ C-reactive protein at all visits and change from Visit 1 (Baseline) to Visit 2 and 3 ▪ Health related quality of life ▪ Direct and indirect medical costs ▪ Sputum microbiome
PLANNED INTERIM ANALYSIS	The Cystic Fibrosis Foundation Data Safety Monitoring Board (DSMB) will establish a Data Monitoring Committee (DMC) to review data relating to safety and efficacy, to conduct and review interim analyses, and to ensure the continued scientific validity and merit of the study. Serious adverse events will be monitored by the committee on an ongoing basis throughout the study. A pre-defined monitoring plan for feasibility, variance estimation, sample size adaptation, and study stopping rules will be formalized in conjunction with the DMC and will be in place prior to initiating the study. Feasibility will be closely monitored for the first 100 enrolled subjects to ensure adherence to antibiotic protocol, return for randomization, and adherence to randomized treatment duration. Each group (ERR and NERR) will have separate monitoring criteria and a decision to stop one may not be conditional on the other.
STATISTICS **Primary Analysis Plan**	The primary endpoint is absolute change in percent predicted FEV_1 from Visit 1 (Baseline) to two weeks after scheduled completion of IV antibiotics (Visit 3). The primary endpoint will be compared between treatment durations within ERR and NERR groups using Analysis of Variance (ANOVA) adjusted for dichotomous randomization strata: Visit 1 FEV_1, number of IV-treated exacerbations in prior year, location of IV administration by Visit 2, and use of systemic corticosteroids by Visit 2. The treatment effect for each group (ERR and NERR) (estimated via adjusted ANOVA least squares means) will be presented along with corresponding 95% confidence intervals. Observed treatment effect and the 95% CI will provide primary inference and evidence of non-inferiority, superiority, or lack thereof in both the ERR and NERR groups. *ERR Group:* The non-inferiority of ERR-10 versus ERR-14 will be tested against a 3.5% predicted non-inferiority margin with a two-sided 0.05 level of significance. *NERR Group:* The superiority of NERR-21 versus NERR-14 will be tested with a two-sided 0.05 level of significance. Further details will be provided in the Statistical Analysis Plan (SAP).
Rationale for Number of Subjects	*ERR Group:* A non-inferiority design to show that the change in FEV_1 between

	Visit 1 and Visit 3 in the ERR subjects who received 10 days of treatment (ERR-10) is no more than 3.5% predicted less than ERR subjects who received 14 days treatment (ERR-14) requires 310 subjects (155 per arm) who complete the study. STOP pilot data indicate a mean change (SD) in FEV_1 between Baseline and Day 28 in patients with an early response to be 12.5 % predicted, 95% CI [9.5, 15.6]. Assuming two-sided alpha =0.05, standard deviation =9.0% predicted and the true difference between two groups is zero, the ERR study has 93% power to detect a 3.5 % non-inferiority margin which preserves 72% of the treatment effect or 63% of the lower bound of treatment effect observed in the STOP pilot. *NERR Group:* A superiority design to show that the change in FEV_1 between Visit 1 and Visit 3 in NERR subjects who received 21 days treatment (NERR-21) is at least 2.5% predicted greater than NERR subjects who received 14 days treatment (NERR-14) requires 570 subjects (285 per arm) who complete the study. STOP pilot data indicate a mean change (SD) in FEV_1 between Baseline and Day 28 in patients without an early response to be 4.0% predicted, 95% CI [1.9, 6.1]. Assuming two-sided alpha =0.05 and standard deviation =9.0% predicted, the NERR study has 91% power to detect a 2.5% greater increase in FEV_1 among those treated with 21 days compared to 14 day IV antibiotic. Because this trial will enroll a slightly different patient population (including home IV, excluding patients who receive <7 days of IV antibiotics), a blinded, interim assessment of change in FEV_1 % predicted and variance (pooled) will be performed and expected sample size may be adjusted for either the ERR or NERR groups. Based on STOP pilot data, we anticipate 1:2 allocation of subjects into the ERR and NERR groups. To meet the enrollment goal of a minimum of 310 completed ERR subjects and a minimum of 570 completed NERR subjects), we will screen approximately 1330 subjects. Of these, we expect approximately 1236 subjects will be enrolled and randomized (assuming a conservative 7% drop-out rate between Visit 1 and Visit 2) and a minimum of 310 completed ERR subjects and a minimum of 570 completed NERR subjects (assuming an approximate 4% drop-out rate between Visit 2 and Visit 3).

1 BACKGROUND

Cystic fibrosis (CF), a life-shortening genetic disease, is marked by acute episodes during which symptoms of lung infection increase and lung function decreases, termed pulmonary exacerbations (PEx). PEx are associated with reduced health-related quality of life[1-3] accelerated pulmonary function decline[4] and decreased survival[5-8], and are commonly treated with antibiotics and supportive respiratory care. The incidence of PEx appears to be relatively constant over the life of a CF patient, but antibiotic treatments change as patient airway infections become more complex and lung disease advances.[9] In adolescents and adults, the proportions of PEx that are treated with intravenous (IV) antibiotics steadily increases.[9,10] There has been no consensus as to how long to treat PEx with IV antibiotics and treatment durations can range from days to weeks.[11] Cystic fibrosis consensus pulmonary guidelines for the treatment of PEx sponsored by the Cystic Fibrosis Foundation (CFF) in 2009[12] provided recommendations for PEx treatment and also identified key questions for which additional studies were needed, including whether there was an optimal duration of IV antibiotic treatment for CF pulmonary exacerbation.

2 STUDY RATIONALE

Clinical trials provide the strongest evidence for medical decisions and are relied upon for evidence-based treatment guidelines. Performing these trials can be expensive and burdensome; they typically require a specialized infrastructure that includes multiple sites with investigators and research coordinators, oversight providing intensive review of study protocols and study conduct, and development of rigorous data collection systems that require validation for accuracy. Because of the expense, many important questions may never be addressed. This is especially true for comparison of therapies within the context of comparative effectiveness research (CER) studies. These challenges are especially troublesome for those who treat patients with an orphan disease, such as CF. Because there are fewer patients, studies require an even greater number of sites, often driving up the expense. What are needed are innovative study designs that allow for greater flexibility, taking advantage of existing infrastructures to speed up the conduct of the trial and to reduce the overall cost.

An acute drop in pulmonary function is highly associated with the diagnosis and treatment of PEx[13] and treatment with IV antibiotics has been shown to result in improved lung function in CF patients experiencing PEx.[14] In 2011, 35.1% of patients of all ages followed in the Cystic Fibrosis Foundation National Patient Registry (CFFNPR, 9,516 patients) were treated at least once with IV antibiotics for PEx, with the median number of IV antibiotic treatment days per PEx varying greatly by CF care center, from 3 days to 24.2 days (CFF 2012).[15] Unfortunately, it has been estimated that as many as a quarter of patients with PEx treated with IV antibiotics fail to return to even 90% of the lung function they had prior to exacerbation.[16]

In 2011, the median duration of IV antibiotic treatment for PEx in the US was 13.5 days for children less than 18 years of age and 14.5 days for older patients.[15] There have been no objective studies of the effect of antibiotic treatment duration on patient response. For this reason, it is not known whether very short IV antibiotic treatment durations, apparently practiced in some US care centers,[15] are associated with incomplete patient responses. Similarly, if little additional benefit is realized beyond about 2 weeks of antibiotic treatment for PEx[11] (as has been suggested by VanDevanter et al), then IV antibiotic treatment regimens exceeding 14 days and received by

approximately half of US CF patients[15] may only serve to increase the risk of treatment-associated toxicity and burden without a corresponding improvement in health outcomes.

Identification of an optimal IV antibiotic treatment duration, if one exists, has the potential to improve overall PEx treatment outcomes and at the same time reduce toxicity and treatment burden associated with overtreatment for PEx.

Recently an observational pilot study of 220 CF subjects admitted to the hospital for treatment of a pulmonary exacerbation was conducted (STOP) to evaluate the variability of treatment durations and to identify the clinical outcome measures deemed most important to care-givers in determining treatment success. The design of the current STOP2 study has been informed by the first STOP study, the results of previous clinical trials and with input from both CF patients and clinicians obtained through surveys. Specifically, the proposed primary efficacy measures (changes in respiratory symptoms and spirometry) are known to change within 2-4 weeks (previous clinical trials and the observational STOP trial); furthermore, the survey data indicated that these two measures were the most important in defining treatment success to caregivers (spirometry) and patients (symptom resolution). In addition, these surveys indicated both a strong desire to reduce treatment duration (and reduce cost, inconvenience, and potential toxicities) and concern about whether subjects might be treated for too short of a period if they were not responding to treatment. The STOP2 trial will evaluate three different treatment durations (10, 14, and 21 days), but will utilize an early assessment of response after 7 to 10 days of treatment to determine whether to randomize a subject to a shorter or longer duration of treatment. In the observational STOP study, an assessment performed after one week of treatment was shown to predict the overall response, especially for those with a robust improvement (Early Robust Response; ERR) (STOP unpublished data); these patients are often treated with shorter courses of IV antibiotics in clinical practice. Subjects who are responding more slowly (Non-Early Robust Response; NERR) can be reassured they will not have early cessation of treatment, and that the treatment durations for subjects in the NERR groups are consistent with common practices.

For practical reasons, this study must be open-label as to the treatment durations; however, aggregate results will be blinded and tightly controlled until the end of the trial. Clinical care will be determined by the treating physician but will adhere to recommendations in the standardized protocol to assure patients are receiving optimal treatment and to reduce the variation in other treatment parameters.

2.1 Risk / Benefit Assessment

Treatment-Associated Risks:

This is an interventional study that will dictate the duration of IV antibiotics for the treatment of pulmonary exacerbation. There can be risks associated with the randomization as patients might be allocated to a duration of antibiotic therapy that may be too short or too long. The potential risk of an insufficient duration of antibiotics is an early relapse of the exacerbation, although surveys of CF clinicians reveal that a majority consider any new treatment for an exacerbation, at any time after the previous treatment, to be a new event rather than a relapse. The potential risks of an excess duration of antibiotics include unnecessary cost as well as the potential for injury attributed to the treatment, specifically drug toxicity (e.g., antibiotic-associated nephrotoxicity, ototoxicity, neurotoxicity, and/or vestibular toxicity, *C. difficile* colitis due to broad spectrum

antibiotic use) or a complication related to the indwelling IV catheter (e.g., thrombus). Clinicians are keenly aware of these potential complications as part of standard therapy and monitor these risks routinely. Generally, intravenous antibiotics used to treat acute pulmonary exacerbation in CF are all well tolerated, and CF patients have extensive experience receiving repeated courses of intravenous antibiotics for acute pulmonary exacerbation.

It is noted that the duration of antibiotics will be 10, 14 or 21 days, which are consistent with current durations used to treat patients (CFFNPR data). Of note, 50% of patients will be randomized to 14 days of IV antibiotics, which is the most frequently used duration (CFFNPR data) and the most frequently reported duration by CF clinicians (survey data , not published). In addition, the randomization is based upon the initial response to treatment such that the duration of antibiotics is even more likely to be consistent with current treatment practices [i.e., patients with a robust response will tend to get a shorter duration (10 vs 14 days) while those with a more sluggish response will tend to get a longer duration (14 vs. 21 days)]. This randomization allocation should mitigate the risks of inappropriately short or long durations as they will be tied to the initial patient response and are consistent with common practice among CF clinicians.

There are other potential risks associated with antibiotic usage including adverse effects that are non-toxic (e.g., nausea, diarrhea) as well as selection of pathogens that are resistant to the therapy chosen (i.e., resistant bacteria, fungi). It is noted that selection of resistant bacteria has been reported following standard of practice treatment of pulmonary exacerbations.[17] The study Data Safety Monitoring Board (DSMB) will follow drug-related adverse events closely in the clinical trial.

All other decisions regarding treatment of the pulmonary exacerbation (e.g., site of treatment, antibiotic selection, use of steroids) will be determined by the treating clinician. There is a required assessment between days 7 and 10, which may not be consistent with the current site practice, but the tests performed are consistent with standard practice to assess response to therapy (i.e., spirometry, symptom assessment); any additional studies performed by the site clinicians are at their discretion. For these reasons, there is little additional treatment-associated risk to patients based upon their participation in this study.

Risks of Study Procedures: All study procedures performed during the study are consistent with standard of clinical care and there are no perceived additional risks in regard to physical well-being. During the study, there will be additional blood draws. The risk of collecting blood includes soreness, bruising, mild pain, mild bleeding or infection at the site. There is also risk of fainting or light-headedness. Topical application of a numbing agent to reduce the pain from the blood draws will be allowed. This may cause mild skin discoloration or swelling that resolves in 1 to 2 hours. There is a small risk of wheezing, shortness of breath, and increased cough when performing spirometry.

Risks to Confidentiality: As with any research study, there is a potential risk of breach of individual patient confidentiality. Study personnel at each site will enter data from source documents into a protocol-specific electronic Case Report Form (CRF). Study subjects will not be identified by name in the study database or on any data capture screens, but will be identified by initials and a subject identification (ID) number unique to this study. Only authorized individuals will be able to link the study ID to the subject's name (site personnel at the individual sites, clinical site monitors, auditors).

Potential Benefits: As this is a randomized allocation to a treatment duration, there is no anticipation that patients will realize additional benefit beyond that associated with routine management of their pulmonary exacerbations. The anticipated overall benefit is definition of optimal treatment durations and standardized practice in the future.

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of this study is to evaluate the efficacy and safety of differing durations of IV antibiotic treatment for CF pulmonary exacerbations. Objectives for these two groups are as follows:

ERR Group: To determine if 10 days of IV antibiotic treatment (ERR-10) is as safe as and not clinically inferior (in terms of lung function) to 14 days of IV antibiotic treatment (ERR-14) among subjects meeting the ERR threshold at Visit 2.

NERR Group: To determine if 21 days of IV antibiotic treatment (NERR-21) is clinically superior (in terms of lung function) and safe, compared to 14 days of IV antibiotic treatment (NERR-14) among subjects not meeting the ERR threshold at Visit 2.

3.2 Secondary Objectives

The secondary objectives are to:

- Evaluate efficacy of differing IV antibiotic treatment durations on other clinical outcomes such as weight, respiratory symptoms, and subsequent IV antibiotic treatments for pulmonary exacerbation.
- Determine the feasibility, uptake and adherence to a standardized protocol of antibiotic selection.

3.3 Other Objectives

- Provide a study platform for ancillary studies of PEx treatment in adults with CF, including investigations into respiratory microbiome, health economics, and systemic inflammation.
- Establish a biorepository of CF serum and sputum samples before, during and after treatment for an adult PEx for use by the CF research community.

4 STUDY DESIGN

4.1 Study Overview

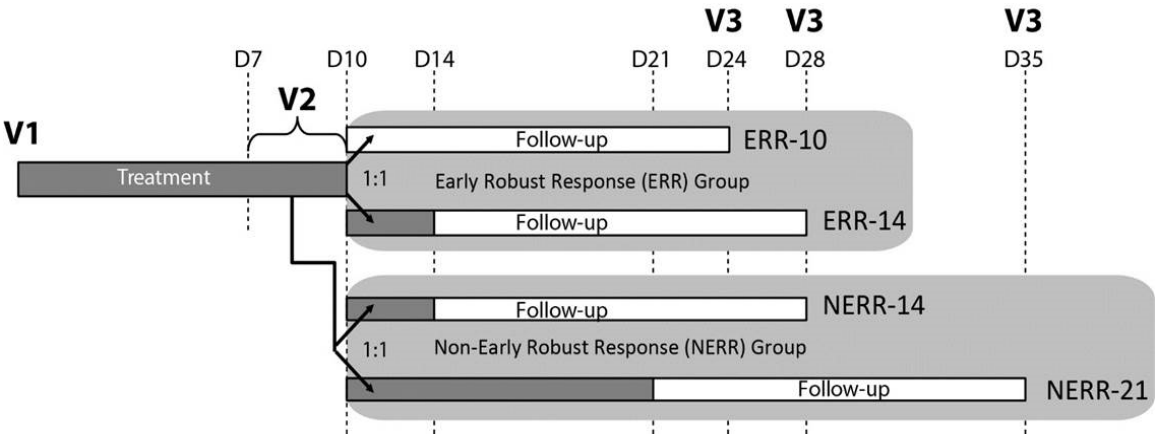
This randomized, controlled, open-label study is designed to evaluate the efficacy and safety of differing durations of IV treatment, given in the hospital or at home for a pulmonary exacerbation in adult patients with CF (Figure 1). Approximately 1330 subjects will be screened in an effort to enroll a minimum of 310 completed ERR subjects and a minimum of 570 completed NERR subjects.

The study will assess the non-inferiority of 10 days versus 14 days treatment duration among ERR subjects and the superiority of 21 days versus 14 days treatment duration among NERR subjects.

The duration of participation for each subject is dependent on the response group (ERR versus NERR) and randomization within group. Subjects will be on study anywhere from 24 to 35 days. Subjects will undergo pulmonary function testing (spirometry) and complete a respiratory symptom score (CRISS) at initiation of IV treatment (Baseline/Visit 1) and at Day 7-10 (Visit 2). At Visit 2, subjects will be allocated to groups ERR or NERR based on their initial clinical response as determined by the change in FEV_1 (percent of predicted) and CRISS from Baseline and then randomized to an IV treatment duration (nested within group). ERR subjects [those who have experienced ≥8% predicted improvement in FEV_1 from Baseline (Visit 1) to Visit 2 and CRISS reduction of ≥11 points from Baseline (Visit 1) to Visit 2] will be randomized 1:1 to either 10 days or 14 days total IV antibiotic treatment (ERR-10 and ERR-14 arms). NERR subjects (who have not experienced changes from Visit 1 that qualify them for the ERR group) will be randomized 1:1 to receive either 14 or 21 days total IV antibiotic treatment (NERR-14 and NERR-21 arms). All subjects will be evaluated again at Visit 3, 14 days following scheduled completion of IV antibiotic treatment (Figure 1).

Total duration of the study is expected to be approximately 42 months: 41 months for subject recruitment and 1 month for final subject follow-up.

Figure 1. STOP2 Study Schematic



5 CRITERIA FOR EVALUATION

5.1 Primary Endpoint

The primary endpoint in the study is a comparison in the absolute changes in percent predicted FEV_1 from initiation of IV antibiotic treatment at Visit 1 to two weeks after scheduled completion of IV antibiotic treatment (Visit 3).

5.2 Secondary Endpoints

Efficacy

- Absolute change in CRISS from Visit 1 (Baseline) to Visit 3
- Proportion of patients retreated for pulmonary exacerbation within 30 days following scheduled completion of IV antibiotics as collected in the CFFNPR

- Time (days) to next pulmonary exacerbation following scheduled completion of IV antibiotics as collected in the CFFNPR
- Relative change in FEV_1 (liters) from Visit 1 (Baseline) to Visit 3
- Absolute change in weight (kg) from Visit 1 (Baseline) to Visit 3

Safety

- Incidence of adverse events, including clinically significant abnormal lab values
- Retreatment of pulmonary exacerbation prior to Visit 3

5.3 Exploratory Endpoints

- Baseline, treatment characteristics, and outcomes (via CFFNPR) of the un-randomized subjects by reason (e.g., in-eligible, lost to follow-up)
- Baseline, treatment characteristics, and outcomes (via CFFNPR) of the randomized but lost to follow-up subjects
- Adherence to antibiotic selection protocol
- Adherence to randomization scheme
- C-reactive protein at all visits and change from Visit 1 (Baseline) to Visit 2 and 3
- Health related quality of life
- Direct and indirect medical costs
- Sputum microbiome

6 SUBJECT SELECTION

6.1 Study Population

Subjects with a diagnosis of CF who meet all of the inclusion and none of the exclusion criteria will be eligible for participation in this study.

6.2 Inclusion Criteria

1. Male or female ≥18 years of age at Visit 1
2. Documentation of a CF diagnosis as evidenced by one or more clinical features consistent with the CF phenotype and one or more of the following criteria:
   a. Sweat chloride equal to or greater than 60 mEq/liter by quantitative pilocarpine iontophoresis test (QPIT)
   b. Two well-characterized mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene
   c. Abnormal nasal potential difference (change in NPD in response to a low chloride solution and isoproteronol of less than -5 mV)
3. Enrolled in the Cystic Fibrosis Foundation National Patient Registry (CFFNPR) prior to Visit 1 (US sites only)
4. At the time of Visit 1, there is a plan to initiate intravenous (IV) antibiotics for a pulmonary exacerbation

5. Performed spirometry at Visit 1 and Visit 2 and willing to perform spirometry at Visit 3
6. Completed the CRISS questionnaire at Visit 1 and Visit 2 and willing to complete the CFRSD questionnaire at Visit 3
7. Willing to adhere to a specific treatment duration determined by initial response to treatment and subsequent randomization
8. Willing to return for follow up Visit 3
9. Written informed consent obtained from the subject or subject's legal representative

6.3 Exclusion Criteria

1. Previous randomization in this study
2. Treatment with IV antibiotics in the 6 weeks prior to Visit 1
3. Admission to the intensive care unit for current pulmonary exacerbation in the two weeks prior to Visit 2, unless admission was due to a desensitization protocol
4. Pneumothorax in the two weeks prior to Visit 2
5. Primary diagnosis for current hospitalization is unrelated to worsening lower respiratory symptoms (e.g., pulmonary clean out, DIOS, sinusitis)
6. Massive hemoptysis defined as > 250 cc in a 24 hour period or 100 cc/day over 4 consecutive days occurring in the two weeks prior to Visit 2
7. Current pulmonary exacerbation thought to be due to allergic bronchopulmonary aspergillosis (ABPA)
8. At Visit 1, receiving ongoing treatment with a duration of more than 2 weeks with prednisone equivalent to >10mg/day
9. History of solid organ transplantation
10. Receiving antimicrobial therapy to treat non-tuberculous mycobacterium (e.g., *M. abscessus*, *M. avium* complex) in the two weeks prior to Visit 2

6.4 Study Specific Tolerance for Inclusion/Exclusion Criteria

Subjects who fail to meet one or more of the inclusion criteria or who meet any of the exclusion criteria will not be enrolled in this study. Waivers of any of the above study entry criteria will not be granted.

6.5 Screen Fail Criteria

Any consented patient who is excluded from the study before randomization is considered a screen failure. All screen failures must be documented with the reason for the screen failure adequately stated. Screen failures can be re-screened for this study at a subsequent pulmonary exacerbation.

7 CONCURRENT MEDICATIONS

7.1 Allowed Medications and Treatments

7.1.1 Chronic Therapies

A stable therapeutic regimen between Baseline (Visit 1) and Visit 3 is the goal. Ongoing chronic treatment (>21 days prior to Visit 1) with Pulmozyme®, high dose ibuprofen, hypertonic saline, azithromycin, short and long bronchodilators, airway clearance, and FDA- approved CFTR modulator therapy is allowed. Subjects that have been using any of these therapies chronically should be encouraged to continue them throughout the entire study period (through Visit 3). Any of these medications may be introduced between Visit 1 and Visit 3 if they are intended to remain as a chronic therapy. Chronic medications can be stopped if the clinician has determined that the therapy is either ineffective or doing harm.

Continuation of ongoing chronic treatment (>21 days prior to screening) with inhaled or oral antibiotics is allowed according to the schedule below:

- If a subject is taking continuous inhaled or oral antibiotics, they may take them anytime between Visit 1 and 3.
- If a subject is taking cycled inhaled antibiotics, they may maintain their current on/off cycle, but ideally will not start a new cycle during the 14 days prior to Visit 3.

7.1.2 Treatment of PEx

Refer to Section 8.2 Antibiotic Selection for the study recommendations for antibiotic use.

Treatment with corticosteroids is allowed at the discretion of the treating clinician for the indication of the current PEx. However, the decision to use corticosteroids should be made prior to randomization at Visit 2 as this will be included as a randomization stratum.

Subjects should perform maximally effective airway clearance therapies during the course of treatment for the PEx. These will be recommended by the treating clinician.

7.1.3 Following Completion of Treatment of PEx

Corticosteroids, if initiated during the treatment, should be weaned according to the clinician's usual practice.

7.2 Prohibited Medications and Treatments

No antibiotics (oral or inhaled) should be taken following the scheduled completion of the IV treatment of PEx until after Visit 3 except as noted in Section 7.1.1 (above).

Investigational therapies are prohibited during the study. The combination modulator ivacaftor/tezacaftor or a triple combination therapy is not considered an investigational therapy and those subjects who are on an open label extension or an Expanded Access Program will be considered eligible for STOP2 as long as it is part of a stable regimen (i.e., >30 days of treatment).

8 STUDY TREATMENTS

8.1 Method of Assigning Subjects to Response Group and Treatment Arms

All eligible subjects will undergo pulmonary function testing (spirometry) and complete a respiratory symptom score (CRISS) at Baseline (Visit 1) and at Day 7-10 (Visit 2). At Visit 2, subjects will be allocated to either the ERR or NERR group based upon their initial clinical response as determined by the change from Baseline in FEV_1 (percent of predicted as determined by GLI equations) [18,19] and CRISS and then randomized to a treatment arm (duration nested within response group). The spirometry and CRISS measures must be present and entered into EDC for both Baseline (Visit 1) and Visit 2 for randomization to occur.

ERR subjects [≥8% predicted improvement in FEV_1 from Baseline (Visit 1) to Visit 2 and CRISS reduction of ≥11 points from Baseline (Visit 1) to Visit 2] will be randomized 1:1 to either 10 days (ERR-10) or 14 days (ERR-14) total IV antibiotic treatment duration while remaining subjects not meeting the ERR threshold will be randomized 1:1 to receive either 14 (NERR-14) or 21 (NERR-21) days total IV antibiotic treatment duration. A minimum of 310 subjects (155 per duration arm) will be allocated to the ERR group and a minimum of 570 subjects (285 per duration arm) to the NERR group. Randomization will occur by a predetermined scheme. Within each response group, subjects will be stratified by Visit 1 FEV_1 (FEV_1 < 50% of predicted versus ≥50% predicted), number of IV-treated exacerbations in prior year (0-1 versus 2+ in prior year), location of IV treatment by Visit 2 (exclusively home versus any hospital nights), and use of systemic corticosteroids by Visit 2.

Randomization will occur centrally using a web based randomization system linked to the electronic data capture (EDC) system. Only authorized site personnel are given access to the EDC system. Authorized site personnel will enter subject eligibility information as well as any information needed for randomization stratification. The system will provide the appropriate authorized site personnel with a randomization assignment for that subject that matches a specific treatment duration.

8.2 Antibiotic Selection

Initial IV antibiotics will be selected using study-specific guidelines provided and taking into account prior sputum culture results, previous antibiotic intolerances, and known drug allergies. Antibiotics may be changed at Visit 2 if presumed to be an insufficient response, sooner if there is a rapid decline, new intolerance or drug allergy. Such changes should still adhere to the study-specific guidelines and may represent newly identified pathogens in sputum cultures. If an antibiotic change is made due to insufficient response, the decision to change should be made prior to randomization at Visit 2.

Once the subject has completed the assigned IV antibiotic duration, no additional oral, inhaled, or IV antibiotics should be administered, except as specified in Section 7.1 above.

8.3 Treatment Location

The location of treatment (i.e., home vs. hospital) is at the discretion of the treating clinician. The patient may be treated entirely at home, entirely in the hospital, or any portion of treatment in the hospital with completion at home.

8.4 Measures of Treatment Compliance

Treatment compliance will be based on adherence to the study-specific antibiotic regimen and to the assigned duration of treatment. The site will record antibiotic use in the Concomitant Medications CRF and the IV Antibiotic Treatment CRF.

9 STUDY PROCEDURES AND GUIDELINES

The procedures described below will be performed at the visits noted in the Schedule of Events (Appendix 1) and in Section 10.

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization (if applicable) must be signed and dated by the subject or subject's legal representative. If appropriate, assent must also be obtained prior to conducting any study-related activities.

9.1 Clinical Assessments

9.1.1 Concomitant Medications

All concomitant medication and concurrent therapies will be documented as noted in the Schedule of Events. Dose, route, unit, frequency of administration, indication for administration, dates of medication, and administration in the hospital or at home will be recorded on the CRF.

9.1.2 Demographics and CFF Registry ID

Demographic information (date of birth, sex, race*)* will be recorded. CF Registry number will be recorded (US sites only).

9.1.3 Medical History

Relevant medical history, including history of current disease, other pertinent respiratory history, and information regarding underlying diseases will be recorded. Supplemental medical history will be collected from the CFFNPR, if applicable.

9.1.4 CF Diagnosis

Diagnosis date and CF diagnosis criteria will be recorded.

9.1.5 Physical Examination

A complete or abbreviated physical examination will be performed by a licensed professional (e.g., MD, NP, RN, PA) as noted in the Schedule of Events. The abbreviated exam includes respiratory, cardiovascular, and abdominal assessments.

After randomization, new clinically significant abnormal physical exam findings must be evaluated to determine if they should be documented as adverse events (AEs).

9.1.6 Weight and Height

Weight will be measured on the same scale if possible and recorded as noted in the Schedule of Events. Subjects may remain in clothes (without shoes). A standing height will be measured and recorded as noted in the Schedule of Events.

9.1.7 Spirometry

Spirometry will be performed as noted in the Schedule of Events and in accordance with the current American Thoracic Society recommendations for the performance and interpretation of tests. At Visit 1, repeat spirometry does not need to be performed if spirometry test results are available within the three days prior to Visit 1. If spirometry was performed more than 3 days prior to Visit 1, spirometry is required to be performed at Visit 1. If spirometry cannot be performed at Visit 1, it can be performed the next day.

Subjects who routinely use bronchodilators should use them consistently throughout the enrollment period. Standard guidelines are noted below as a reference:

- Subjects who routinely use short acting inhaled bronchodilators should use them 15 minutes to 2 hours prior to pulmonary function tests (PFTs) during study visits.
- Subjects who routinely use long acting bronchodilator agents should use them 15 minutes to 6 hours prior to PFTs during study visits.

Spirometry (FEV_1) will be centrally standardized to the Global Lung Initiative (GLI) percent predicted equations for response group allocation and analysis.

9.1.8 Subject Questionnaire: CFRSD©

Subjects will complete a CF-specific symptom diary called the CFRSD as noted in the Schedule of Events. This diary includes 16 questions and takes less than 5 minutes to complete. The CFRSD should be administered at the beginning of the visit.

9.1.9 Subject Questionnaire: CRISS©

Subjects will complete a CF-specific symptom diary called the CRISS as noted in the Schedule of Events. This diary includes 8 questions and takes less than 5 minutes to complete. The CRISS should be administered at the beginning of the visit.

9.1.10 Subject Questionnaire: EQ-5D-5L

Subjects will complete the EQ-5D-5L health questionnaire as noted in the Schedule of Events. The EQ-5D-5L is a standardized generic measure of health status developed by the EuroQol Group and used in clinical and pharmacoeconomic evaluations. It is a self-completed questionnaire with five (5) descriptive questions in the areas of mobility, self-care, usual activities, pain/discomfort and anxiety/depression and a visual analogue scale (EQ-VAS) that records the subject's self-rated health on a 20 cm vertical scale.

9.1.11 Adverse Events

Information regarding occurrence of AEs will be captured throughout each subject's study participation, starting at randomization and ending once the subject has terminated from the study. Duration (start and end dates), grade, seriousness, outcome, treatment, and relation to study treatment arm will be recorded on the CRF.

9.1.12 Signs and Symptoms Evaluation

At Visit 1, the presence of specific signs and symptoms will be assessed and documented.

9.1.13 Collection of Health Care Resource Use

Health care resource use will be documented throughout the trial as noted in the Schedule of Events. Inpatient hospitalization days, outpatient medical visits (primary care and specialists), and emergency department visits will be collected. Indirect costs including travel time to medical visits, caregiver time, and IV antibiotic treatment time at home will be collected as noted in the Schedule of Events. Job classification information for subjects and for their informal caregivers will also be collected as noted in the Schedule of Events.

9.1.14 CFFNPR Data Entry (US Sites Only)

For the hospitalization or home IV antibiotic treatment for the pulmonary exacerbation that triggers enrollment into this study, an episode must be completed in the CFFNPR.

9.2 Collection of Clinical Care Laboratory Results

9.2.1 Respiratory Cultures for CF Pathogens

Results from respiratory culture(s) used to determine care for the initial pulmonary exacerbation and any respiratory cultures performed as part of clinical care during the study will be recorded on the CRF.

9.2.2 Clinical Chemistry

Results for BUN and creatinine used to determine care for the initial pulmonary exacerbation and any BUN and creatinine tests performed as part of clinical care during the study will be recorded on the CRF.

Results for serum glucose performed as part of clinical care for the initial pulmonary exacerbation and during the study will be recorded on the CRF (if more than one is performed on a given day, only one test per day will be recorded).

9.3 Research Laboratory Measurements

9.3.1 Blood Collection for C-Reactive Protein (CRP) Testing

Blood will be obtained as noted in the Schedule of Events and sent to each site's clinical chemistry lab for determination of CRP.

9.3.2 Sputum for Microbiome Analysis

Expectorated sputum will be collected from subjects who are able to produce sputum as noted in the Schedule of Events. The samples collected will be stored frozen at -70 to -80ºC at the site and batch shipped as instructed by the Therapeutics Development Network Coordinating Center (TDNCC). Instructions for specimen collection, processing, storage and shipping of samples will be provided in the Study Laboratory Manual.

Subjects that are enrolled at study sites located in Canada will be excluded from the collection of sputum for microbiome analysis.

9.3.3 Specimens for Long-Term Biorepository Storage

Approximately 7.5 mL of blood for serum aliquots will be collected for the CFFT biorepository as noted in the Schedule of Events. The samples collected will be stored frozen at -70 to -80ºC at the site and batch shipped to the CFFT biorepository for long-term biorepository storage. Instructions for specimen collection, processing, storage and shipping of samples will be provided in the Study Laboratory Manual.

Any expectorated sputum remaining after microbiome analysis may be sent to the CFFT biorepository for long-term biorepository storage.

Subjects that are enrolled at study sites located in Canada will be excluded from the collection of serum specimens for long-term biorepository storage.

10 EVALUATIONS BY VISIT

Note: Day 1 is defined as the day IV antibiotics are initiated. Visit 1 procedures may occur up to three days prior to initiation of IV antibiotics (Day 1) or up to one calendar day after IV antibiotics are initiated.

10.1 Visit 1

1. Review the study with the subject (subject's legal representative) and obtain written informed consent and HIPAA authorization and assent, if appropriate.
2. Assign the subject a unique screening number.
3. Record demographics data and, for US sites, CFF Registry ID.
4. Record medical history, including a history of CF, diagnosis date, prior CF treatments and number of exacerbations in the previous year.
5. Record concomitant medications including current and planned systemic steroid use.
6. Confirm that the subject will begin treatment for the PEx following recommendations in the treatment protocol.
7. If a respiratory specimen for CF pathogens has been collected for clinical care, obtain results and record.
8. If Chemistry tests for BUN, creatinine and serum glucose have been collected for clinical care, obtain results and record.
9. Provide CRISS Self-Report to subject for completion.
10. Provide EQ-5D-5L to subject for completion.
11. Collect subject health care resource use information.
12. Perform a complete physical examination by a physician or designee.
13. Measure and record height and weight.
14. Perform and record spirometry if not performed within the past 3 days.
15. If able to expectorate sputum, collect expectorated sputum for microbiome.
16. Collect blood and test for CRP at site.

17. Collect blood and freeze serum for banking.
18. Complete Signs and Symptoms Assessment.
19. Schedule subject for Visit 2 to occur on Day 7 - 10 of IV antibiotics.

10.2 Visit 2 (Day 7-10 ±1 days)

1. Provide CRISS Self-Report to subject for completion.
2. Provide EQ-5D-5L to subject for completion.
3. Measure and record weight.
4. Perform and record spirometry.
5. Collect subject health care resource use information.
6. Record any respiratory microbiology results since Visit 1.
7. If Chemistry tests for BUN, creatinine and serum glucose have been collected for clinical care, obtain results and record.
8. Record changes to concomitant medications.
9. Perform abbreviated physical examination.
10. Re-confirm eligibility.
11. Enter required data into EDC for randomization (refer to CRF Completion Guidelines, includes CRISS and spirometry).
12. Randomize subject to treatment duration.
13. If able to expectorate, collect expectorated sputum for microbiome.
14. Collect blood and test for CRP at site.
15. Collect blood and freeze serum for banking.
16. Record any adverse events.
17. Schedule subject for Visit 3 dependent on treatment arm and to occur 2 weeks after scheduled completion of IV treatment.

10.3 Visit 3 (Follow-up 2 weeks after scheduled completion of IV treatment /Day 24 – 35 +/-2 days)

1. Provide CFRSD Self-Report to subject for completion.
2. Provide EQ-5D-5L to subject for completion.
3. Collect subject health care resource use information.
4. Record any respiratory microbiology results since Visit 1.
5. If Chemistry tests for BUN, creatinine and serum glucose have been collected for clinical care, obtain results and record.
6. Record any adverse events.

7. Record changes to concomitant medications.
8. Perform abbreviated physical examination.
9. Measure and record weight.
10. Perform and record spirometry.
11. If able to expectorate, collect expectorated sputum for microbiome.
12. Collect blood and test for CRP at site.
13. Collect blood and freeze serum for banking.

11 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

11.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject that is participating in this clinical investigation that is related to study participation (treatment arm assignment), study procedures, or any other significant AE as determined by the investigator.

AEs are defined as new or worsening of signs or symptoms, including clinically significant abnormal clinical laboratory values, that occur after randomization (Visit 2) until Visit 3.

An unexpected AE is one of a type not identified in nature, severity, or frequency or of greater severity or frequency than expected.

The Investigator will probe, via discussion with the subject, for the occurrence of AEs and record the information in the site's source documents. AEs will be recorded in the subject CRF.

AE Severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0, as modified for cystic fibrosis, should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. The modified criteria can be found in the Study Reference Binder. If the experience is not covered in the modified criteria, the guidelines shown in Table 1 below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 1. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Moderate (2)	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate Instrumental activities of daily living (e.g., preparing meals, using the telephone, managing money)
Severe (3)	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living (e.g., bathing, dressing, feeding self, using toilet, taking medications)

Life-threatening (4)	Life-threatening consequences; urgent intervention indicated
Death (5)	Death related to AE

AE Relationship to Treatment Arm Assignment

The relationship of an AE to the treatment arm assignment should be assessed using the following the guidelines in Table 2.

Table 2. AE Relationship to Treatment Arm Assignment

Relationship to Treatment	Comment
Definitely	An event that follows a reasonable temporal sequence from the clinical trial treatment arm assignment; that follows a known or expected response pattern to treatment arm assignment; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from the clinical trial treatment arm assignment; that follows a known or expected response pattern to treatment arm assignment; and that is not explained by any other reasonable hypothesis; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from the clinical trial treatment arm assignment; that follows a known or expected response pattern to treatment arm assignment; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the treatment arm assignment.

11.2 Serious Adverse Experiences (SAE)

An SAE is defined as any AE occurring that results in any of the following outcomes:

- death
- a life-threatening adverse experience
- inpatient hospitalization (excluding the initial enrollment hospitalization) or hospitalizations that occur after the initial enrollment and start of IV antibiotic treatment at home will be reported
- prolongation of existing hospitalization beyond the planned duration as indicated by randomization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

11.2.1 Serious Adverse Experience Reporting

Study sites will document all SAEs that occur (whether or not related to treatment arm assignment) on an SAE Report Form. The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed.

All SAE Report Forms will be reviewed by the site investigator and sent to the TDNCC within one business day of the site learning of the event. Sites will send the SAE report by either:

- Email (scanned copy) to: cfsaesfacsys@seattlechildrens.org
- TDNCC SAE Fax: (206) 985-3278

The site will notify the TDNCC of additional information or follow-up to an initial SAE Report as soon as relevant information is available. The TDNCC Medical Monitor may request additional information related to the SAE. Follow-up information is reported on an SAE Report Form.

In accordance with the standard operating procedures and policies of the local Institutional Review Board/Independent Ethics Committee (IRB/IEC), the site investigator will report SAEs to the IRB/IEC.

11.3 Medical Monitoring

The TDNCC Medical Monitoring Group should be contacted directly at this number to report medical concerns or questions regarding safety:

- (800) 341-0961

12 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

12.1 Early Withdrawal of Subjects from the Study

Early withdrawal of subjects may occur any time after the subject is randomized. All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice. This may include subjects who withdraw from study treatment early and who decline to continue to come in for remaining follow-up visits or it may include subjects who completed treatment and decline to come in for remaining follow up visits.

Reasonable attempts will be made by the investigator to provide a reason for early subject withdrawals. The reason for the subject's early withdrawal from the study will be specified in the subject's source documents.

Subjects who fail to adhere to treatment duration assignment are encouraged to complete all remaining study visits. Subjects should not be withdrawn for failure to adhere to treatment duration assignment.

12.2 Replacement of Subjects

Subjects who withdraw from the study will not be replaced.

13 PROTOCOL VIOLATIONS

A protocol violation occurs when the subject, investigator, or the Sponsor fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Use of a prohibited concomitant medication
- Failure to adhere to treatment duration assignment (within the pre-specified margins of acceptable durations)
- Failure to perform spirometry at each study visit

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by a Sponsor representative and the Investigator. A copy of the form will be filed in the site's regulatory binder and in the Sponsor's files. The site will report the violation to their IRB/IEC in accordance with their IRB/IEC reporting requirements.

14 DATA SAFETY MONITORING

The Cystic Fibrosis Foundation DSMB will establish a Data Monitoring Committee (DMC) to review data relating to safety and efficacy, to conduct and review interim analyses, and to ensure the continued scientific validity and merit of the study, according to the Cystic Fibrosis Foundation DSMB Operations Manual and a DMC Charter created for this protocol. Details regarding the timing and content of the interim reviews are included in Section 15.6, Interim Analysis below, the DMC Charter developed in conjunction with the DMC, and the Statistical Analysis Plan.

SAEs will be monitored by the committee on an ongoing basis throughout the study.

15 STATISTICAL METHODS AND CONSIDERATIONS

A detailed Statistical Analysis Plan (SAP) will be written that will describe all analyses that will be generated for this study. All analyses will be performed using SAS® (SAS Institute, Inc., Cary, NC, USA) or R (R Foundation for Statistical Computing, Vienna, Austria). The SAP will contain any modifications to the analysis plan described below.

15.1 Data Sets Analyzed

The primary NERR analyses will be performed using an intent-to-treat (ITT) population, which is defined as all subjects randomized at Visit 2. The analysis for NERR will be repeated in the per-protocol (PP) population, which is defined as subjects in the ITT population who have no protocol violations as defined in Section 13. The primary ERR analyses will be performed using PP population; the analysis will be repeated in the ITT population.

Subjects who fail to adhere to treatment duration assignment are encouraged to complete all remaining study visits and will remain in the analyses population according to ITT.

Handling of missing data will be outlined in the SAP, including sensitivity analyses.

15.2 Demographic and Baseline Characteristics

Treatment duration arms (ERR-10, ERR-14, NERR-14, NERR-21) within ERR and NERR groups will be described and compared with respect to Baseline demographic and clinical characteristics including age, sex, CFTR genotype, race, height, weight, and all randomization strata. For all analyses, Baseline clinical characteristics will be defined as measurements obtained at Visit 1.

15.3 Analysis of Primary Endpoint

The primary endpoint is absolute change in percent predicted FEV_1 from Visit 1 (Baseline) to two weeks after scheduled completion of IV antibiotics (Visit 3). The primary endpoint will be compared between treatment durations within ERR and NERR groups using Analysis of Variance (ANOVA) adjusted for dichotomous randomization strata: Visit 1 FEV_1 , number of IV-treated exacerbations in prior year, location of IV administration by Visit 2, and use of systemic corticosteroids by Visit 2.

The treatment effect for each group (ERR and NERR) (estimated via adjusted ANOVA least squares means) will be presented along with corresponding 95% confidence intervals. Observed treatment effect and the 95% CI will provide primary inference and evidence of non-inferiority, superiority, or lack thereof in both the ERR and NERR groups.

ERR Group: The non-inferiority of ERR-10 versus ERR-14 will be tested against a 3.5 % predicted non-inferiority margin with a two-sided 0.05 level of significance.

NERR Group: The superiority of NERR-21 versus NERR-14 will be tested with a two-sided 0.05 level of significance.

Further details will be provided in the SAP, which will be finalized before the clinical data lock for the study.

15.4 Analysis of Secondary Endpoints

Descriptive analyses and graphical displays will be used to summarize all secondary endpoints, including changes from baseline in continuous endpoints and rates over the follow-up period for event based endpoints. The ITT and PP populations will be used for all secondary analyses.

All reported SAEs and AEs will be coded using MedDRA and grouped by body system. (S)AEs will be tabulated by treatment durations within ERR and NERR groups using standard coding terms sorted by body system. The incidence of AEs (including emergent abnormal lab values collected for clinical care) in each treatment duration arm will be tabulated by seriousness, severity, and relationship to arm. If an AE is reported more than once during the study period for a given subject, the greatest severity and the worst-case relationship will be presented in tables. The number of (S)AEs will be summarized by treatment duration arms within ERR and NERR groups as follows: (i) The proportion of subjects with at least one (S)AE, (ii) The average number of (S)AEs per patient, and (iii) The rate of (S)AEs per patient month of follow-up. Histograms showing the frequency of the number of (S)AEs in each treatment duration arm will be included. Rates of (S)AEs by System Organ Class (SOC) will be presented by treatment duration arm. Poisson regression modeling will be used to derive rate ratios and 95% confidence

intervals for each SOC. The rate ratios will be compared using a two-sided 0.05 level test for Poisson count data.

Descriptive summaries of antibiotics received by patients will be presented by treatment duration arm within ERR and NERR groups. Proportion of patients retreated with IV antibiotics (as collected in the CFFNPR) for pulmonary exacerbation within 30 days following scheduled completion of IV antibiotic treatment will be summarized by treatment duration arm within ERR and NERR groups and differences in the proportion of subjects will be estimated and tested using a two-sided test of proportions. Time (days) to next exacerbation following scheduled completion of IV antibiotics will be presented using Kaplan-Meier survival estimation and compared between treatment durations within ERR and NERR groups using a Cox proportional hazards model with a test of the treatment effect at a two-sided significance level of 0.05. The hazard ratio and its 95% confidence interval will be presented. An additional secondary analysis may stratify by or adjust for the randomization strata.

Absolute change in CRISS, relative change in FEV_1 (liters), and absolute change in weight (kg) from Baseline (Visit 1) to two weeks after scheduled completion of IV antibiotics (Visit 3) will be summarized. Mean differences between treatment duration arms within ERR and NERR groups at each visit and corresponding 95% CIs will be presented. Changes from Baseline (Visit 1) to Visit 3 will be assessed using a two-sample, two-sided t-test and additional secondary analysis may adjust for the randomization strata.

15.5 Analysis of Exploratory Endpoints

The proportion of subjects discontinuing study before versus after randomization and before the end of assigned treatment duration will be tabulated by reason for discontinuation and by treatment duration arm, if randomized. Reason for discontinuations will be summarized. The screen failure reasons will be also summarized for all screening attempts. Characteristics of the un-randomized subjects by reason (e.g., lost to follow-up, missing FEV_1 or CRISS at Visit 2, patient withdrawal) will be summarized using descriptive characteristics. Similarly, the randomized but lost to follow-up subjects (no Visit 3) will be described. Comparison of these two groups with the randomized completed subjects will be performed for baseline characteristics, treatments and outcomes utilizing both the study data and the CFFNPR.

There will be descriptive summaries of adherence to antibiotic selection protocol and adherence to randomization scheme by response group (ERR and NERR), and treatment duration arm (ERR-10, ERR-14, NERR-14, and NERR-21).

Descriptive comparisons of the two cohorts treated for 14 days (ERR-14 and NERR-14) will be performed to characterize associations between early assessments of clinical response (at Visit 2) and after completion of treatment for a PEx (Visit 3).

Clinical lab CRP at each of the study visits and change in CRP from Baseline (Visit 1) will be summarized by response group (ERR and NERR) and by treatment duration arm (ERR-10, ERR-14, NERR-14, and NERR-21). Associations with CRP and change in CRP with clinical outcomes will be examined.

For all randomization arms (ERR-10, ERR-14, NERR-14, and NERR-21), quality of life and medical cost metrics will be collected for a comprehensive health economic analysis by Larry Kessler ScD, Professor and Chair, Dept. of Health Services, School of Public Health, University of Washington, Seattle according to the most recent guidance from the International Society for

Pharmacoeconomics and Outcomes Research Good Research Practices for Cost-Effectiveness Analysis Alongside Clinical Trials Task Force.

For all treatment duration arms (ERR-10, ERR-14, NERR-14, and NERR-21), the expectorated sputum will undergo analysis to describe and compare the respiratory microbiome by John Lipuma, MD, Professor of Pediatrics and Director of Pediatric Infectious Diseases, University of Michigan, Ann Arbor.

15.6 Interim Analysis

A pre-defined monitoring plan for feasibility, variance estimation, sample size adaptation, and study stopping rules will be formalized in conjunction with the DMC and will be in place prior to initiating the study. Feasibility will be closely monitored for the first 100 enrolled patients to ensure adherence to protocol, return for randomization, and adherence to randomized treatment duration arm.

Each treatment group (ERR and NERR) will have separate monitoring criteria and a decision to stop one may not be conditional on the other.

15.7 Sample Size

ERR Group:

A non-inferiority design to show that the change in FEV_1 between Visit 1 and Visit 3 in the ERR subjects who received 10 days of treatment (ERR-10) is no more than 3.5 % predicted less than ERR subjects who received 14 days treatment (ERR-14) requires 310 subjects (155 per arm) who complete the study. STOP pilot data indicate a mean change (SD) in FEV_1 between baseline and Day 28 in patients with an early response to be 12.5 % predicted, 95% CI [9.5, 15.6]. Assuming two-sided alpha =0.05, standard deviation =9.0% predicted and the true difference between two groups is zero, the ERR study has 93% power to detect a 3.5 % non-inferiority margin which preserves 72% of the treatment effect or 63% of the lower bound of treatment effect observed in the STOP pilot.

NERR Group:

A superiority design to show that the change in FEV_1 between Visit 1 and Visit 3 in NERR subjects who received 21 days treatment (NERR-21) is at least 2.5 % predicted greater than NERR subjects who received 14 days treatment (NERR-14) requires 570 subjects (285 per arm) who complete the study. STOP pilot data indicate a mean change (SD) in FEV_1 between baseline and Day 28 in patients without an early response to be 4.0 % predicted, 95% CI [1.9, 6.1]. Assuming two-sided alpha =0.05 and standard deviation =9.0% predicted, the NERR study has 91% power to detect a 2.5% or greater increase in FEV_1 among those treated with 21 days compared to 14 day IV antibiotic. A 2.5% improvement was chosen to represent a minimal clinically important difference in lung function to justify the additional burden and potential toxicity of 21 days of treatment versus 14. It is important to note that statistical significance can be shown at the end of the superiority NERR study with a smaller treatment effect than 2.5%.

Observed treatment effect (mean difference in absolute FEV_1 change) and the 95% CI will provide primary inference and evidence of non-inferiority, superiority, or lack thereof in both the ERR and NERR groups. Motivated to ensure conclusive results, this study was designed to provide sufficiently narrow 95% CIs at the end of the trial (ERR 95% CI half-width=2%;

NERR 95% CI half-width=1.5% when both SD=9%).

Because this trial will enroll a slightly different patient population (including home IV, excluding patients who receive <7 days of IV antibiotics), a blinded, interim assessment of change in FEV_1 % predicted and variance (pooled) will be performed and expected sample size may be adjusted for either the ERR or NERR groups.

Based on STOP pilot data, we anticipate 1:2 allocation of subjects into the ERR and NERR groups. To meet the enrollment goal of a minimum of 310 completed ERR subjects and a minimum of 570 completed NERR subjects, we will screen approximately 1330 subjects. Of these, we expect approximately 1236 subjects will be enrolled and randomized (assuming a conservative 7% drop-out rate between Visit 1 and Visit 2) and a minimum of 310 completed ERR subjects and a minimum of 570 completed NERR subjects (assuming an approximate 4% drop-out rate between Visit 2 and Visit 3).

16 DATA COLLECTION, RETENTION AND CLINICAL MONITORING

16.1 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject who signs informed consent.

Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic CRF when the information corresponding to that visit is available. Subjects will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee), but will be identified by a site number, subject number and, for US sites only, initials.

If a correction is required for a CRF, the time and date stamp tracks the person entering or updating CRF data and creates an electronic audit trail.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. A CD containing the CRF data will be provided to the site to be retained with the essential documents at the Investigator's site at the completion of the study.

16.2 Data Management Procedures

TDNCC utilizes Medidata Solutions, Inc. (Medidata) Rave for their EDC studies. The Medidata Rave EDC system is designed to be US Code of Federal Regulations (CFR) 21 Part 11 compliant, with a robust audit trail system and electronic signature capabilities. Study personnel at each site will enter data from a subject's visit onto electronic CRF screens via a web browser. Study subjects will not be identified by name in the study database or on any data capture screens, but will be identified by initials and a unique subject identification number. Only study personnel at the individual sites will be able to link the study ID to the subject's name. The Biostatistics and Clinical Data Management group of the TDNCC will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed. All procedures for the handling and analysis of data will be conducted using good computing practices for the handling and analysis of data for clinical trials.

16.3 Data Quality Control and Reporting

After data have been entered into the study database, data validation checks will be applied on a regular basis. Queries are entered, tracked, and resolved through the EDC system directly. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented in an audit trail.

16.4 Security and Archival of Data

The EDC system is hosted by Medidata; the data are stored at Medidata's primary data center in Houston, Texas, with fail-safe data centers in New Jersey. Data are regularly backed up by Medidata.

Medidata maintains 21 CFR Part 11-compliant electronic systems, with procedures in place to safeguard against unauthorized acquisition of data. Any authorized communication with the Medidata servers at the Houston Data Center is conducted via SSL (128-bit) encryption. Robust password procedures, consistent with 21 Part 11, are in place. Robust physical security procedures are in place at the Houston Data Center to prevent unauthorized personnel physical access to the server rooms. EDC account access is maintained and monitored by the Biostatistics and Clinical Data Management group of the TDNCC.

Other databases will be stored on Seattle Children's servers and are safeguarded against unauthorized access by established security procedures. Network accounts are password protected and maintained and monitored by the Seattle Children's Information Technology group. Data is backed up regularly according to the Information Services group's procedures.

Note that there is an intention to make biospecimens and associated data available to investigators for future exploration. The biospecimens will be collected under IRB/IEC approval, processed according to a rigorous standard operating procedure and stored at a central facility, with appropriate procedures to enable long term, stable storage. Researchers may apply, via a standardized process, for use of de-identified data and specimens for research purposes. Applications will undergo a scientific review process administered through CFFT. When applying for use of data or specimens, the applicant must agree to: (1) use the data and specimens only for research purposes and to not make any attempts to try to identify any individual subject; (2) securing the data and specimens using appropriate methods; and (3) destroy or return the data (and specimens) in accordance with the specimen/data use agreement after analyses are completed. Before data or specimens will be released to an investigator, documentation of IRB/IEC exemption or approval from their institution must be provided to the CFFT.

16.5 Availability and Retention of Investigational Records

The Investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB/IEC, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (e.g., patient files, signed informed consent forms, copies of CRFs, Essential Document and Study Reference Binders) must be kept secured for a period of one year

after database lock and accessible for 5 years following database lock. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted prior to removing study records for any reason.

16.6 Monitoring

By signing this protocol, the Investigator grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

16.7 Subject Confidentiality

In order to maintain subject confidentiality, only a site number, subject number, subject initials (US sites only) and subject's CFF patient registry number (US sites only) will identify all study subjects on CRFs and other documentation submitted to the Sponsor. Additional subject confidentiality issues (if applicable) are covered in the Clinical Study Agreement.

17 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996).

17.1 Protocol Amendments

Any amendment to the protocol will be written by the Sponsor. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs/IECs are notified within five working days.

17.2 Institutional Review Boards

The protocol and consent form will be reviewed and approved by the IRB/IEC of each participating center prior to study initiation. SAEs regardless of causality will be reported to the IRB/IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the Investigator will keep the IRB/IEC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC may need to fulfill its responsibilities (such as protocol, protocol amendments, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC. The IRB/IEC's written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB/IEC's unconditional approval statement will be transmitted by the Investigator to the Sponsor or

designee prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB/IEC; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

17.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form, assent (if applicable) and HIPAA authorization (if applicable) and provide the documents to the Sponsor or designee for approval prior to submission to the IRB/IEC. The consent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB/IEC. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations. The Investigator will send an IRB-approved copy of the Informed Consent Form to the Sponsor (or designee) for the study file.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB/IEC, assent from the subject will also be obtained. If a subject is unable to sign the informed consent form and the HIPAA authorization, a legal representative may sign for the subject. A copy of the signed consent form (and assent) will be given to the subject of the subject and the original will be maintained with the subject's records.

During the course of the study, if modifications are made to the consent form that impact the subject, the subject will be re-consented as described above.

17.4 Consent for Collection and Use of CFF Registry ID Number (US Sites Only)

To facilitate future evaluation of retrospective and prospective information from all patients who screen for this study, the subject's CFF Registry ID number will be collected. The CFFNPR collects data on all CF patients who consented to participate in the CFFNPR and who are followed at CFF-accredited care centers. The registry data includes information from clinical encounters, hospitalizations courses of antibiotics, and year-end surveys. Data also include microbiology results, spirometry results, CF genotype and other information such as survival.

17.5 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

17.6 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB/IEC review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
7. Ensure that an IRB/IEC that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
8. Promptly report to the IRB/IEC and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments).
9. Seek IRB/IEC approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

18 REFERENCES

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19 APPENDIX 1. SCHEDULE OF EVENTS

	Visit 1	**Visit 2**	**Visit 3** [1]
Event/Assessment	**Day 1** [4]	**Between Day 7 - 10 of IV Antibiotics** (±1 days)	**Between Day 24 - 35 2 wks after scheduled completion of IV treatment** (+/-2 days)
Informed Consent	X		
Medical History, Demographics, CF Diagnosis, CF Registry ID	X		
Collect subject health care resource use	X [2]	X [3]	X [3]
Concomitant Medication Review	X	X	X
Collect results of clinical care respiratory cultures for microbiology	X	➔	➔
Collect results of clinical care BUN, creatinine and serum glucose	X	➔	➔
Subject Questionnaire: CRISS	X	X	
Subject Questionnaire: CFRSD			X
Subject Questionnaire: EQ-5D-5L	X	X	X
Complete Physical Exam	X		
Abbreviated Physical Exam		X	X
Height	X		
Weight	X	X	X
Spirometry	X	X	X
Collect sputum for microbiome	X	X	X
Collect blood and test for CRP at site	X	X	X
Collect blood and freeze serum for banking	X	X	X
Complete Signs and Symptoms Assessment	X		
Allocation to group and Randomization to IV treatment duration		X	
Adverse Event Review		X	X

[1] Visit day will vary, dependent on group and duration arm

[2] Subject and care-giver job classifications

[3] Subject-reported travel time to visits, IV treatment times, caregiver care times, additional clinic visits. At Visit 3, only Health Care Resource Use information that was not previously collected or has changed since data was collected at Visit 2 will be collected.

[4] Day 1 is defined as the day that IV antibiotics are initiated. Visit 1 may occur up to three days prior to the initiation of IV antibiotics or up to 1 calendar day after IV antibiotics are initiated.