STOP-2

FINAL REPORT

PROTOCOL NUMBER:	STOP2-IP-15
PROTOCOL TITLE:	Standardized Treatment of Pulmonary Exacerbations II (STOP 2)
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FUNDING AGENCIES:	Cystic Fibrosis Foundation Therapeutics, Inc (CFFT)
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1. Overview

1.1 Study Rationale and Design

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 an early 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 (although this has never been objectively studied). Patients who have a less robust early response to treatment often receive extended treatments in a belief that better overall responses are attained. Although the additional clinical benefit of prolonged courses of IV antibiotics should outweigh potential risks of toxicity, treatment burden, and increased resource utilization, these relationships have also never been objectively tested.

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 of treatment among ERR subjects and the superiority of 21 days versus 14 days treatment duration among the subjects who do not meet the ERR definition(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 their change in forced expiratory volume in 1 second (FEV_1; percent of predicted) and CRISS from Baseline and then subsequently 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. Dependent on the treatment arm, subjects will be on study from 24 to 35 days.

The primary objective of this study is 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 EER threshold at Visit 2.

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. Interim DSMB Reviews

1.2 Data Monitoring Committee Reviews

Oversight for this trial will be performed by the Cystic Fibrosis Foundation (CFF) Data Safety Monitoring Board (DSMB; Chair, Wayne Morgan, MD). A Data Monitoring Committee (DMC) has been selected by the Associate Chair Dr. Richard Simon to specifically monitor this trial according to the DMC Charter. The DMC consists of at least two physicians experienced in treating patients with CF and a biostatistician. The DMC is responsible for safeguarding the interests of study participants, assessing the safety and efficacy of study procedures, and for monitoring the overall conduct of the study.

The Table below outlines reporting schedule, content, and participation throughout the study.

Content of Reporting	Semi-Annual (no meeting)	Initial 10% Enrollment (teleconference)	Initial 20% Enrollment (as needed) (teleconference)	Comprehensive 50% Enrollment (teleconference)	Comprehensive 75% Enrollment (teleconference)
Enrollment/Feasibility (Pooled)	--	--	--	**O**	**O**
Enrollment/Feasibility (by Duration Arm)	**C**	**O**	**O**	**C**	**C**
Abbreviated Safety Summaries (by Duration Arm)	**C**	**C**	**C**	**C**	**C**
Comprehensive Efficacy Interim (by Duration Arm)	--	--	--	**C**	**C**

O - OPEN report for DMC, Study Biostatisticians, Study manager, and Sponsor-Investigators

C - CLOSED report for DMC and Study Biostatisticians only

Abbreviated summary reports tabulating SAEs by treatment duration arm will be reported to the DSMB on semi-annual basis starting after the first patient is randomized. There will be one initial interim report at approximately 10% of enrollment, followed by a second identical report at 20% of enrollment, if deemed necessary. The initial interim report will focus on feasibility, adherence to protocol, return for randomization, and adherence to randomized treatment duration arm. An unblinded, open review by treatment duration arm with the DMC and the Sponsor-Investigators of Sections 1-3 and Appendix A of this document will take place. The safety data summarized by treatment duration group will be presented in the closed section of the DMC meeting (Sections 4-5), as outlined in the table above.

Comprehensive interim reports including efficacy endpoints and formal statistical monitoring will be generated after approximately 50% and 75% of subjects have been randomized. The contents of these reports are outlined in the table above and will be comprised of both an open (pooled enrollment) and a closed report (feasibility, safety, and efficacy by treatment duration arm).

1.3 Report Generation

The final statistical report will describe and justify any deviations from the original statistical plan described herein. Analyses will be performed using SAS 9.4 software or most current version of R. No adjustments for multiple comparisons will be made. Any analyses requiring CFFNPR data will be performed after the study close-out. The timing of these analyses will depend on availability of the Registry data containing relevant study participant information. Any tables or figures requiring such data are noted with an asterisk in the table and figure shells that follow. All programs used to produce this report will be documented, tested, and archived and all tables, figures and listings will be validated before considered final.

1.4 Definition of the Analysis Populations

Enrollment and screening summaries will be generated using all screened participants. All compliance and safety analyses will be performed using an intent-to-treat (ITT) population, defined as all subjects randomized at Visit 2. The ITT population will also be used to generate all NERR primary efficacy analyses. The primary ERR analyses will be performed using per-protocol population (PP), defined as subjects in the ITT population who have no protocol violations.

2. Results

2.1 Enrollment and Screen Failures

The cumulative enrollment of participants randomized into the study is graphically summarized. The number of participants screened, eligible, randomized, withdrawn, and completing the study is summarized by treatment duration arm and site within ERR and NERR groups.

The un-randomized participants are categorized as screen failures, those discontinuing the study before randomization, or eligible but not randomized. Reasons for screen failures, study discontinuations, and decision to not randomize are given. The screen failure reasons are summarized for all screening attempts.

Participants who are deemed eligible at Visit 1 but are not assessed at Visit 2 are further summarized by age group, admission FEV_1, and IV antibiotic location (home vs hospital).

Participant disposition figure detailing enrollment, treatment allocation, follow-up, and analyses populations is provided.

2.2 Withdrawals, Treatment Duration Compliance, and Prohibited Antibiotic Utilization

The number of participants who withdrew early from the study is tabulated by treatment duration arm within ERR and NERR groups. The reason for withdrawal is also listed. Withdrawals are further summarized by age group, admission FEV1, and IV antibiotic location (home vs hospital).

Treatment duration adherence is summarized descriptively by treatment duration arm within ERR and NERR groups. Also included are descriptive summaries of prohibited antibiotic use and unplanned use of corticosteroids.

2.2 Demographics and Baseline Characteristics

Treatment duration arms within ERR and NERR groups are 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 are defined as measurements obtained at Visit 1.

2.3 Adverse Events

All reported SAEs and AEs are coded using MedDRA and grouped by body system. (S)AEs are 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 is 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 is presented in tables. The number of (S)AEs is 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 week of follow-up. Histograms showing the frequency of the number of (S)AEs in each treatment duration arm are included. Rates of (S)AEs by System Organ Class (SOC) are presented by treatment duration arm. Poisson regression modeling is used to derive rate ratios and 95% confidence intervals for each SOC. The rate ratios is compared using a two-sided 0.05 level test for Poisson count data.

2.4 Other Safety Measures

Summaries of proportions of participants experiencing any elevated and clinically significant BUN or creatinine findings between Visit 1 and Visit 3 are provided.

Also summarized are proportions of participants retreated with IV antibiotics. Retreatment is defined as any additional IV antibiotics administered 3 or more days after the stop date of the initial IV antibiotic treatment for pulmonary exacerbation and prior to Visit 3 (e.g. rescue treatment or treatment of the new pulmonary exacerbation).

2.5 Summary of Primary Efficacy Endpoint

The primary endpoint is the 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 is 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) is presented along with corresponding 95% confidence intervals. Observed treatment effect and the 95% CI provide primary inference and evidence of non-inferiority, superiority, or lack thereof in both the ERR and NERR groups.

ERR Group (PP population): The non-inferiority of ERR-10 versus ERR-14 is tested against a 3.5 % predicted non-inferiority margin with a one-sided 0.025 level of significance.

NERR Group (ITT population): The superiority of NERR-21 versus NERR-14 is tested with a two-sided 0.05 level of significance.

The primary analysis for ERR is repeated in the ITT population, and the primary analysis for NERR is repeated in the PP population.

2.6 Summary of Antibiotics and Other Medications

Descriptive summaries of antibiotics received by participants are presented by treatment duration arm within ERR and NERR groups. Also summarized is the use of steroids or airway clearance any time during the study. 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 is summarized by treatment duration arm within ERR and NERR groups and differences in the proportion of subjects are estimated and tested using a two-sided test of proportions.

2.7 Time to Next Pulmonary Exacerbation

Time (days) to next exacerbation following scheduled completion of IV antibiotics is 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 are presented. Additionally, results from a model adjusted for randomization strata are shown. Also performed are exploratory analyses testing proportion of time spent receiving home IVs and the timing of corticosteroid initiation.

2.8 Summary of CRISS

Absolute change in CRISS from Baseline (Visit 1) to two weeks after scheduled completion of IV antibiotics (Visit 3) is summarized. Mean differences between treatment duration arms within ERR and NERR groups at each visit and corresponding 95% CIs are presented. Changes from Baseline (Visit 1) to Visit 3 are assessed using a two-sample, two-sided t-test. Additionally, an ANOVA model adjusted for randomization strata is used to compare the change in CRISS between treatment duration arms within ERR and NERR groups. Also summarized is the proportion of participants who experienced a clinically meaningful reduction in CRISS of 11 or more units.

2.9 Summary of Spirometry Results

Absolute and relative changes in spirometry measures from Baseline (Visit 1) to each post-baseline visit are summarized. Mean differences between treatment duration arms within ERR and NERR groups at each visit and corresponding 95% CIs are presented. Changes from Baseline (Visit 1) to Visit 3 are assessed using a two-sample, two-sided t-test. Additionally, an ANOVA model adjusted for randomization strata is used to compare the relative change in FEV_1 (L) between treatment duration arms within ERR and NERR groups.

2.10 Summary of Anthropometric Measures

Absolute changes in weight (kg) and BMI from Baseline (Visit 1) to each post-baseline visit are summarized. Mean differences between treatment duration arms within ERR and NERR groups at each visit and corresponding 95% CIs are presented. Changes from Baseline (Visit 1) to Visit 3 are assessed using a two-sample, two-sided t-test. Additionally, an ANOVA model adjusted for randomization strata is used to compare the change in weight (kg) between treatment duration arms within ERR and NERR groups.

2.11 Summary of CRP Results

Clinical lab CRP at each of the study visits and change in CRP from Baseline (Visit 1) are summarized by response group (ERR and NERR) and by treatment duration arm. Associations between Baseline (Visit 1) CRP and change in CRP with clinical outcomes (e.g. baseline values and changes in spirometry, weight, and CRISS) are summarized. Further, clinical baseline characteristics and outcomes are summarized by CRP response.

2.12 Randomized Completers, Randomized Lost to Follow-up, and Un-Randomized Participants

Baseline characteristics of the un-randomized subjects are summarized descriptively. Similarly, the randomized but lost to follow-up subjects (no Visit 3) are described. Comparisons of these two groups with the randomized completed subjects are performed for baseline characteristics, treatments and outcomes utilizing both the study data and the CFFNPR.

2.13 ERR-14 and NERR-14 Participants

Descriptive comparisons of the two cohorts treated for 14 days (ERR-14 and NERR-14) are performed to characterize associations between early assessments of clinical response (at Visit 2) and after completion of treatment for a PEx (Visit 3). Comparisons of these two groups are performed for baseline characteristics, treatments and outcomes utilizing both the study data and the CFFNPR.

2.14 Study Impact on PEx Treatment Duration

Summarized are distributions of pulmonary exacerbation treatment durations (as collected in the CFFNPR) observed at the STOP2 study centers during the conduct of this study and after the study completion (Month, Year through Month, Year). Also shown are distributions of pulmonary treatment durations observed at a select non-STOP2 CF centers during the same time frames.

2.15 Appendix A

Listing 1 shows protocol violations and exceptions and Listing 2 provides SAE narratives from the clinical tracking spreadsheet.