SIMPLIFY
Master
Statistical Analysis Plan
for the
Final and Interim Statistical Reports

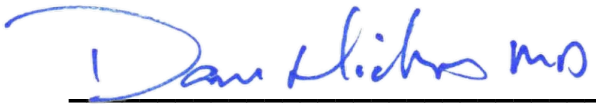
PROTOCOL NUMBER:	SIMPLIFY-IP-19
PROTOCOL TITLE:	A Master Protocol to Test the Impact of Discontinuing Chronic Therapies in People with Cystic Fibrosis on Highly Effective CFTR Modulator Therapy (SIMPLIFY)
PRINCIPAL INVESTIGATORS:	Dave Nichols, MD University of Washington/Seattle Children's Nicole Mayer-Hamblett, PhD University of Washington/Seattle Children's Alex Gifford, MD Dartmouth-Hitchcock Medical Center
FUNDING AGENCIES:	Cystic Fibrosis Foundation, Inc. (CFF)
PREPARED BY:	CF Therapeutics Development Network Coordinating Center: Nicole Mayer-Hamblett, PhD Katherine Odem-Davis, PhD Michelle Skalland, MS Renee Russell, MS
RELEASE DATE:	July 6, 2020
NCT NUMBER:	Screening: NCT04378153 Dnase Trial: NCT0635047 Hypertonic Saline Trial: NCT06350461

PREFACE

The Statistical Analysis Plan (SAP) as outlined in this document was drafted and approved prior to the completion of the first comprehensive Data Monitoring Committee (DMC) interim report, with approval by sponsor investigators on July 10, 2020 and a corresponding interim report template sent to the DMC on August 13, 2020. Modifications to the SAP following that review are documented in Summary of Changes to the Approved SAP table (page 4). The SAP contains all modifications and updates to the planned analyses that were outlined in the original study protocol. This plan details all *a priori* specified analyses that will be performed upon completion of the randomized phase of the study (through Week 6), with detailed specifications for all tables, figures, and statistical models. Details of analysis of the mucociliary clearance (MCC) sub-study data and additional exploratory analyses will be detailed elsewhere.

Signature Page

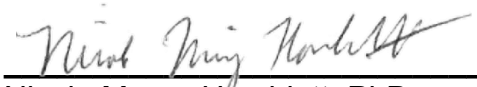
Analysis plan approved by:



06 July 2020

Dave Nichols, MD
Principal Investigator
University of Washington/Seattle Children's

Date



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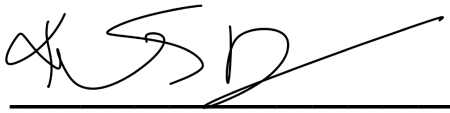

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Summary of Changes from Approved SAP

The following table summarizes changes from the original, approved statistical analysis plan and/or study protocol. A brief description of the change, addition or deletion is provided as well as the rationale for each change and date the change was identified. Minor wording or formatting changes or inclusion of clarifying language or footnotes are not included in this table.

Section or Exhibit Number	Description of Change	Rationale for Change	Date of Change
Section 1.2 DMC Interim Analysis	Included 12% loss of follow-up to enrollment projections for DMC interim reports	Clarification	9/2021
Section 2.4: Analysis Populations	Added #7 to PPA definition: excluding enrolled but ineligible participants	Some participants were determined to be ineligible after enrollment constituting a protocol violation – this was unexpected and therefore not prespecified	3/2021
Section 2.4: Analysis Populations	Extended the missing data imputation method used for the primary endpoint for use in key secondary endpoints (CRISS, CFQ-R and LCI)	Aligns with sensitivity analysis for the primary endpoint	3/2021
Section 3.2.4 Adverse Event results and Table 4.10	Proportion of participants with temporary or permanent therapy modifications was a prespecified safety endpoint in the protocol. Here it is described specifically as therapy modifications occurring due to an adverse event.	Clarification	3/2021
Section 3.2.7 Spirometry results, Table 7.2 and Figure 7.3	The subgroup analyses for the primary endpoint are further specified.	The primary endpoint repeated among subgroups was an originally specified analysis, but the specific subgroups were not defined in the original SAP. The specific subgroups were pre-specified in the SIMPLIFY study design paper [1].	1/2021
Section 3.2.13 Lower Lung Function (LLF) Cohort	Added descriptions of analysis to be performed among the LLF cohort for the interim and final analysis	Enrollment in the LLF cohort was contingent on DMC approval after review of safety data. A subset of the analyses specified in the SAP were identified for inclusion in a LLF specific report.	9/2021
Table E.3.2, 2.1 Summary of Baseline Characteristics	Added baseline indicator of chronic systemic steroid use	Oversight	3/2021
Table 3.1 Summary of Withdrawals	Increased maximum withdrawal date (loss to follow-up) from 49 to 60 days	A loss to follow-up of 60 days aligned better with the study follow-up period and allowed ample time for research coordinator contact effort	3/2021
Table 4.11 Respiratory Adverse Event Overview	Added a table summarizing respiratory adverse events by baseline FEV % predicted category	Requested by the Data Monitoring Committee	3/2021
Tables 6.1, 6.2, 7.4, 9.2, 9.4, 9.6, 11.3 Results from ANOVA Model for Change in FEV, QOL measures, LCI	Clarified that the LS mean estimates were calculated using weighting based on observed frequencies of randomization factors (footnote 3)	Type of LS mean estimates was not specified in the original SAP	1/2021
Figure 7.4 Mean Relative Change in FEV1 (Liters) Over Time	Previously included both relative and absolute change. Removed absolute change.	Descriptive summaries of relative change are included. The relative change figure was removed as it was determined to be redundant.	1/2021
Figure 9.1 Change in CRISS Score over Time	Minimum clinically important difference (MCID) is included with reference	Added for interpretation context	1/2021
Figure 9.2 Change in CFQ-R Respiratory Domain over Time	Minimum clinically important difference (MCID) is included with reference	Added for interpretation context	1/2021
Figure 9.4 Distribution of Impact of Changing Daily Therapies Scores	Specified as an exploratory outcome from the protocol originally not included in the SAP	Oversight	1/2022
Table 9.7 Summary of Impact of Changing Daily Therapies Score	Specified as an exploratory outcome from the protocol originally not included in the SAP	Oversight	1/2022
Figure 10.1 and Table 10.1 Summary of Weight Percentile	The original SAP included weight summaries in kg only, added weight percentile	Oversight	3/2021
Figure 10.3 and Table 10.3 Summary of BMI Percentile	The original SAP included BMI summaries in kg/m^2 only, added BMI	Oversight	3/2021

	percentile		
Tables 11.2 and 11.3 LCI summaries	Multiple breath washout endpoint changed from LCI 5 to LCI 2.5	LCI 5 was mistakenly included as the endpoint for the multiple breath washout procedure. After discussion with MBW experts, LCI 2.5 was identified as the appropriate and standard endpoint [2]	1/2021
Table 11.3 Results from ANOVA Model for Change in LCI (2.5)	Specified that missing Week 0 LCI measurement will be replaced by Week -2 LCI, if available	Post-hoc missing data method	9/2021
Listing 12.2 Pregnancies	Added a listing of any pregnancies occurring during the trial	Oversight	3/2021
N/A	A sensitivity analysis repeating the primary endpoint using an alternative per protocol population (with 80% adherence rather than 70% adherence) was specified in the SIMPLIFY design paper [1] but is not included here	Sensitivity analysis determined to be unnecessary.	1/2022

[1] Mayer-Hamblett, Nicole et al. “Evaluating the Impact of Stopping Chronic Therapies after Modulator Drug Therapy in Cystic Fibrosis: The SIMPLIFY Clinical Trial Study Design.” *Ann Am Thorac Soc* vol. 18,8 (2021): 1397-1405. doi:10.1513/AnnalsATS.202010-1336SD.
[2] Anagnostopoulou, Pinelopi, et al. "Normative data for multiple breath washout outcomes in school-aged Caucasian children." *European respiratory journal* 55.4 (2020). doi: 10.1183/13993003.01302-2019
[3] Engberink, Esther Oude, et al. "Inter-test reproducibility of the lung clearance index measured by multiple breath washout." *European Respiratory Journal* 50.4 (2017). doi: 10.1183/13993003.00433-2017

Changes from original SAP approved by:

Dave Nichols, MD Principal Investigator University of Washington/Seattle Children's	8/19/2022 Date
Nicole Mayer-Hamblett Principal Investigator University of Washington/Seattle Children's	8/18/2022 Date
Alex Gifford, MD Principal Investigator Dartmouth-Hitchcock Medical Center	8/24/2022 Date
Margaret Kloster Biostatistician Seattle Children's Hospital	8/24/2022 Date

1. Overview

1.1 Study Rationale and Design

As transformative CFTR modulator drug therapies have become increasingly available to the CF population, many in the CF Community (patients, families and caregivers) are asking if any of their pre-existing therapies can be reduced or eliminated. Motivated by survey results from both the CF Community and Clinician-Investigator groups which indicate very high support for a randomized trial testing the withdrawal of chronic therapies after highly effective modulators, the SIMPLIFY master protocol was developed.

SIMPLIFY is a master protocol with two concurrent randomized trials. It is designed to evaluate the independent effects of discontinuing hypertonic saline (Study A) and dornase alfa (Study B) in people with CF age 12 and older taking elexacaftor/tezacaftor/ivacaftor (ETI) for at least 90 days prior to study screening. Individuals with CF ages 12-17 years with FEV_1% predicted 70% or greater and those 18 years and older with FEV_1% predicted 60% or greater may enroll. There is no upper limit for FEV_1% predicted. Study A and Study B are identical randomized, open label two-arm trials consisting of a 2-week screening period, randomization to either continue or discontinue hypertonic saline (Study A) or dornase alfa (Study B), followed by a 6-week study period. Only those that remain clinically stable and maintain adequate reported adherence to inhaled drug therapy between screening and Visit 1 will be eligible for randomization.

At study entry, participants currently being treated with only hypertonic saline or dornase alfa will be enrolled in Study A or Study B (as applicable) and will be randomized 1:1 to either continue or discontinue their current prescribed therapy. At study entry, participants who are currently being treated with both hypertonic saline and dornase alfa will remain on both therapies during the screening period and then be randomized to Study A (hypertonic saline) or Study B (dornase alfa) as well as randomized (1:1) to continue vs. discontinue the applicable therapy. The randomization to Study A or Study B among participants on both therapies is not optional and is essential to reduce indication bias and ensure comparable populations across studies. After completion of the first study, these participants may subsequently enroll in the alternate study if they meet eligibility criteria.

For participants randomly assigned to continue their therapy during a given study, this therapy should be taken at least once daily according to each participant's pre-existing, clinically prescribed regimen (e.g. daily, twice daily). The concentration of hypertonic saline will also be according to clinical prescription (e.g. 7% sodium chloride or 3.5% sodium chloride). Hypertonic saline concentration must be at least 3%.

Clinical outcomes (FEV_1, antibiotic use, pulmonary exacerbations, and patient reported outcomes), safety (adverse events) and participants' perception of how stopping HS or dornase alfa (or both) would impact their daily life will be evaluated at all sites during each study. Additional measurements will be conducted at selected study sites with the capabilities to conduct these procedures:

- Multiple Breath Washout to evaluate changes in lung clearance index (LCI)
- Mucociliary Clearance (MCC) scans using inhaled radio-labeled particles and imaging techniques to evaluate changes in mucociliary clearance

The primary objectives of the protocol are:

- *Study A:* To determine whether discontinuing hypertonic saline is non-inferior to continuing hypertonic saline among participants on chronic ETI, as measured by the 6-week absolute change in FEV_1 % predicted

- *Study B:* To determine whether discontinuing dornase alfa is non-inferior to continuing dornase alfa among participants on chronic ETI, as measured by the 6-week absolute change in FEV_1 % predicted

The secondary objectives of each study are to evaluate:

- The safety of discontinuing vs. continuing hypertonic saline (Study A) or dornase alfa (Study B)

- The effect of discontinuing vs. continuing hypertonic saline (Study A) or dornase alfa (Study B) on lung clearance index (LCI)

- The effect of discontinuing vs. continuing hypertonic saline (Study A) or dornase alfa (Study B) on other clinical outcomes (e.g., antibiotic events, pulmonary exacerbations, and patient reported outcomes)

1.2 Interim Data Monitoring Committee Reviews

Safety oversight for this trial will be conducted by the Cystic Fibrosis Foundation (CFF) Data Safety Monitoring Board (DSMB; Chair, Lynne M. Quittell, MD). A subcommittee, the Data Monitoring Committee (DMC), will serve on the review board for this trial. A DMC will consist of at least 2 physicians experienced in treating CF and a biostatistician experienced in clinical trial monitoring with an option for adding ad-hoc expertise. 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.

Interim safety reports will be provided for each study on a semi-annual basis starting after the first participant is randomized. These reports will include a summary of screening, enrollment metrics, baseline characteristics, participant withdrawals, protocol violations, and AEs and SAEs tabulated by treatment group. The proportion of patients with significant pulmonary function declines will be summarized as well for these reviews. An unblinded, open review with the DMC and the Sponsor-Investigators of the Screening and Enrollment Report will take place. The safety data summarized by intervention arm will be presented in the closed section of the DMC meeting as detailed in an Interim Report SAP.

In addition, for each study, the scheduled interim review following enrollment and Week 6 visit completion of 25% and 50% of planned sample size allowing for 12% loss to follow-up will include a formal evaluation of excess harm of treatment withdrawal. After interim analysis, if DMC approves, a separate cohort (lower lung function cohort) of approximately 120 subjects ≥ 18 years old with FEV_1 40 to < 60 % predicted will be enrolled into Study A.

2. Report Generation

2.1 Data Flow

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 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. TDNCC also utilizes the Medidata Rave eCOA/ePRO system, a regulatory compliant system which allows subjects in a study using Medidata Rave EDC to complete and submit forms and data for patient-reported outcomes electronically on a mobile device to the Medidata Rave EDC System. Study personnel at each site will register subjects using their unique subject identification number which generates an activation code unique to that subject. Study site personnel provide the subjects with their activation code. The subject downloads the Medidata Rave eCOA/ePRO app to their mobile device and uses their unique activation code to create their ePRO login and password.
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.

2.2 Randomization

At the randomization visit (Week 0), those subjects who are eligible and taking only either hypertonic saline or dornase alfa will be enrolled in the appropriate study (A or B). If both studies remain open to enrollment, those taking both and enrolling for the first time will be randomized to study (A or B) via stratified block randomization, with blocks of size 4. If only one study is open for enrollment, eligible subjects taking both therapies may be enrolled into only the open study. Those taking both and who are eligible and enrolling for the second time may enroll in the study that they were not previously in if that study remains open for enrollment. Within each study (A or B), subjects will be assigned 1:1 to continue or discontinue the applicable therapy by stratified randomization in blocks of size 2. Treatment assignment lists for the cohorts specified by stratification groups (each combination of levels across strata) will be created in SAS 9.4 and uploaded to RTSM in Medidata Rave. Stratifying factors include Week 0 FEV_1 % predicted (≥90%, <90%), treatment combination at Week -2 (single or concurrent use of hypertonic saline and/or dornase alfa), prior study participation (yes/no), and age at Week 0 (≥18 vs < 18). Subjects enrolled in the lower lung function cohort will be similarly randomized to continue or discontinue hypertonic saline and stratified by current dornase alfa use.

2.3 Report Generation

The final statistical reports will describe and justify any deviations from the original statistical plan described herein. Analyses will be performed using SAS 9.4 software and most current version of R. No adjustments for multiple comparisons will be made. 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.

2.4 Definition of the Analysis Populations

Enrollment and screening summaries will be generated using all screened participants. All participant disposition, secondary, exploratory, and safety summaries will be performed using an intent to treat (ITT) population, defined as all participants randomized at Visit 1 (Day 0). The primary analyses in both Study A and Study B will be performed using a per-protocol analysis (PPA) population, as defined below. Sensitivity analyses, repeating the primary analyses, will be done on the ITT population. Secondary analyses will likewise be run on the PPA population and repeated on the ITT population.

PPA is defined by the following criteria:
1. Daily diary completion ("Compliance") from Week 0 (Visit 1) to Week 6 (Visit 3)
    a. >=70% non-missing data
    b. >=70% non-missing in last 2 weeks

2. Daily diary responses from Week 0 (Visit 1) to Week 6 (Visit 3) aligned with randomized treatment ("Adherence")
   a. to assigned treatment regimen (HS or Dnase) among non-missing days overall (>=70%)
   b. to assigned treatment regimen (HS or Dnase) among non-missing days in 2 weeks (>=70%)
3. No initiation of new acute oral, inhaled, or IV antibiotics for respiratory symptoms (rate from ETI trial was ~5%) from Week 0 (Visit 1) to Week 6 (Visit 3)
4. Non-missing FEV at Week 6 (Visit 3)
5. Given the correct randomization instructions
6. Minimum 70% use of ETI among non-missing days in last 2 weeks
7. Eligible at Week -2 (Screening Visit) and at Week 0 (Visit 1, Randomization)

Data from subject disposition visits will be allocated to the nearest subsequently scheduled visit. Missing outcome data in the ITT population for the final primary analysis and for key secondary analyses (CRISS, CFQ-R, and LCI) will be imputed using the least favorable treatment mean in arms discontinuing treatment and using the most favorable treatment mean in arms continuing treatment. Complete case results, including participants based on availability of non-missing values, will also be reported.

3. Overview of Planned Analyses

3.1. Screening Report

3.1.1. Outline of Screening and Enrollment

The overall flow from screening to enrollment is illustrated by a CONSORT diagram. The number of participants screened and eligible are summarized by site. The status of second study screening and enrollment among participants initially on both hypertonic saline and dornase alfa that completed their first study is summarized by first study and by intervention arm.

3.1.2. Screen Failures, Run-in Loss to Follow-up, and Reasons Not Randomized

Screen failure reasons are summarized for Week -2, the initial screening visit. Run-in periods initiated are tracked over time among study participants who are eligible at Week -2. Then, follow-up from Week -2 to Week 0 (Visit 1) is tabulated among participants eligible at initial screening. Participants not completing the Week 0 visit within the allowed window (21 days after the Week -2 visit) are categorized as an incomplete run-in. Finally, reasons for ineligibility at randomization or decision to not randomize are given. Ineligibility reasons are summarized for Week 0 (Visit 1) and by current therapy and prior enrollment status.

3.1.3. Enrollment, Demographics, and Follow-up Overview

Total participants randomized in each study and their eligibility before randomization (Study A, Study B, or both) is summarized overall and broken down by therapy regimen/prior enrollment. Demographic and Week 0 characteristics for unique participants enrolled are summarized among all randomized participants by study. All measures were recorded at Visit 1 unless specified otherwise.

3.2. Study Reports

3.2.1. Summary of Randomization and Study Visit Completion

A CONSORT diagram for the corresponding study (A or B) delineates counts of participants from randomization to per-protocol analysis population inclusion. The cumulative monthly enrollment of

participants randomized into the study is graphically summarized. Participants randomized, withdrawn, and completing the study are tabulated by intervention arm and site.

Completion of each study visit and clinic spirometry at each visit are summarized by intervention arm and overall. Participants are considered to have completed the visit if there is a CRF page with a study date corresponding to that visit.

An overview of analysis populations summarizes the number of participants, by intervention arm and in total, excluded from the per-protocol analysis population for one or more reasons. The reasons for exclusion are also summarized.

3.2.2. Demographics and Characteristics at Week 0

Intervention arms are described and compared with respect to Week 0 demographic and clinical characteristics including age, sex, CFTR genotype, race, height, weight, and all randomization strata. For all summarizations, Week 0 clinical characteristics are defined as measurements obtained at Visit 1 unless specified otherwise.

3.2.3. Summary of Withdrawals, Treatment Assignment and Other Therapy Adherence

The number of participants who withdrew early from the study is tabulated by intervention arm. The reasons for withdrawal and time to withdrawal are also summarized.

The daily therapy ePRO questionnaire completeness, intervention assignment and ETI adherence, and dornase alfa (or hypertonic saline, if Study B) and airway clearance use are summarized by intervention arm for participants who have completed study or withdrawn.

The difference between intervention arms in participants meeting adherence criteria is estimated using logistic regression methods and reported with confidence intervals accounting for randomization strata.

3.2.4. Adverse Events

All reported SAEs and AEs are coded using MedDRA and grouped by system organ class (SOC). The number of (S)AEs is summarized by each intervention arm as follows: (i) The proportion of participants with at least one (S)AE, (ii) The average number of (S)AEs per participant, and (iii) The rate of (S)AEs per participant week of follow-up. Histograms showing the frequency of the number of (S)AEs in each intervention arm are included. The incidence and rate of (S)AEs in each intervention arm is summarized by SOC and preferred term, relationship to arm, and severity. Poisson regression modeling is used to derive rate ratios and 95% confidence intervals. Rates by arm are compared using a two-sided 0.05 level test for Poisson count data. Proportions of participants with at least one (S)AE are also compared between arms with estimated differences and corresponding 95% confidence intervals by the Newcombe-Wilson method without continuity correction; p-values are from a two-sided 0.05 level Fisher's Exact test.

The number and percent of participants changing their assigned therapy due to an adverse event is summarized by intervention arm. The number and percent of participants changing their assigned therapy when directed by a physician because of an adverse event is also summarized.

3.2.5. Hospitalizations and Pulmonary Function Decline

The number of hospitalizations is summarized within each intervention arm as follows: (i) The proportion of participants with at least one hospitalization, (ii) The average number of hospitalizations per participant, (iii) The rate of hospitalizations per participant week of follow-up, and (iv) The number of days hospitalized per participant. Poisson regression modeling is used to

derive rate ratios and 95% confidence intervals. Rates by arm are compared using a two-sided 0.05 level test for Poisson count data. Proportions of participants with at least one hospitalization are also compared between arms with estimated differences and corresponding 95% confidence intervals by the Newcombe-Wilson method without continuity correction; p-values are from a two-sided 0.05 level Fisher's Exact test. The difference between intervention arms in participants hospitalized is estimated using logistic regression methods and reported with confidence intervals accounting for randomization strata.

The proportions of participants with a significant decline in FEV_1 % predicted from Week 0 are also summarized by intervention arm.

3.2.6. Analyses of Primary Endpoint

The primary endpoint is the difference between arms in the change in FEV_1 % predicted from Week 0 (Visit 1) to Week 6 (Visit 3). The primary analysis for non-inferiority is conducted on the per-protocol analysis (PPA) population. An ANOVA model is used to adjust for dichotomous randomization strata: Week 0 FEV_1 % predicted, treatment combination at screening, prior study enrollment, and Week 0 age. The estimated effect of discontinuation and corresponding 95% confidence interval are reported, and the p-value is evaluated for a one-sided alpha-level 0.025 test of non-inferiority with a margin of -3% absolute change in FEV_1 % predicted. An unadjusted estimate is also provided.

The primary analysis is repeated in the ITT population. Missing outcome data in the ITT population were imputed using the least favorable treatment mean in arms discontinuing treatment and the most favorable treatment mean in arms continuing treatment. In this case, the least (most) favorable treatment mean is defined as the mean of the arm with the greater negative (positive) change from Week 0 to Week 6. Complete case results, including participants based on availability of non-missing values, are also reported.

3.2.7. Spirometry Results

Absolute and relative changes in spirometry measures from Week -2 (screening) to Week 0 (Visit 1) and from Week 0 (Visit 1) to each post-randomization visit are summarized. Mean differences between intervention arms at each visit and corresponding 95% confidence intervals are presented. Changes from Week 0 (Visit 1) to Week 6 (Visit 3) are assessed using a two-sample, two-sided t-test. Additionally, the absolute change in FEV_1 % predicted from Screening to Week 0 (Visit 1) is compared between intervention arms using an ANOVA model adjusting for randomization strata. A forest plot qualitatively comparing treatment effects by subgroup will be shown for the following characteristics: Week 0 FEV_1 % predicted, treatment combination at screening, prior study enrollment, Week 0 age, sex at birth, pseudomonas aeruginosa positive culture in past year, genotype, concurrent chronic airway clearance therapy and randomization strata.

3.2.8. Exacerbation and Concomitant Medication Parameters

The number of protocol-defined and physician identified pulmonary exacerbations (PEx) experienced by participants from Week 0 (Visit 1) to Week 6 (Visit 3) are summarized by intervention arm as follows: (i) The total number of PEx, (ii) The rate of PEx per participant week of follow-up, (iii) The average number of PEx per participant, (iv) The proportion of participants with at least one PEx, and (v) the total requiring antibiotics (acute IV, oral, or inhaled) or hospitalization. Poisson regression modeling is used to derive rate ratios and 95% confidence intervals. Rates by arm are compared using a two-sided 0.05 level test for Poisson count data. Proportions of participants with at least pulmonary exacerbation are also compared between arms with estimated differences and corresponding 95% confidence intervals by the Newcombe-

Wilson method without continuity correction; p-values are from a two-sided 0.05 level Fisher's Exact test.

Also summarized is the frequency of signs and symptoms for protocol-defined PEx for each intervention arm and overall. The difference between intervention arms in participants experiencing a protocol-defined PEx is estimated using logistic regression methods and reported with confidence intervals accounting for randomization strata.

The difference between intervention arms in participants initiating acute antibiotics is estimated using logistic regression methods and reported with confidence intervals accounting for randomization strata.

3.2.9. Summary of CRISS and CFQ-R scores

Absolute changes in CRISS and CFQ-R, respiratory domain, from screening to Week 0 (Visit 1) and from Week 0 (Visit 1) to each post-randomization visit are summarized. Mean differences between intervention arms at each visit and corresponding 95% confidence intervals are presented. Changes from Week 0 (Visit 1) to Week 6 (Visit 3) are assessed using a two-sample, two-sided t-test. Additionally, the changes in CRISS and CFQ-R, respiratory domain, between intervention arms are compared between intervention arms using an ANOVA model adjusting for randomization strata.

3.2.10. Summary of Anthropometric Measures

Absolute changes in weight (kg), weight percentile, BMI (kg/m^2), and BMI percentile from screening to Week 0 (Visit 1) and from Week 0 (Visit 1) to each post-randomization visit are summarized. Mean differences between intervention arms at each visit and corresponding 95% confidence intervals are presented. Changes from Week 0 (Visit 1) to Week 6 (Visit 3) are assessed using a two-sample, two-sided t-test.

3.2.11. Summary of Lung Clearance Index (LCI)

Demographics and baseline characteristics of the subset participants with multiple breath washout procedure completed are summarized as described in Section 3.1.3. Absolute and relative change in Lung Clearance Index (LCI) from screening to Week 0 (Visit 1) and from Week 0 (Visit 1) to each post-randomization visit are summarized. Mean differences between intervention arms at each visit and corresponding 95% confidence intervals are presented. Changes from Week 0 (Visit 1) to Week 6 (Visit 3) are assessed using a two-sample, two-sided t-test. Additionally, the changes in LCI between intervention arms are compared between intervention arms using an ANOVA model adjusting for randomization strata.

3.2.12. Listings

Listings will include protocol violations and deviations. A listing of pregnancies will also be included if any are reported during follow-up.

3.2.13. Lower Lung Function (LLF) Cohort

The lower lung function cohort monitoring and outcomes will be summarized in a separate report from Study A. Among those enrolled in the lower lung function cohort, descriptive safety summaries will be provided for the differences between treatment arms in the change in FEV1 % predicted, adverse event rates, and proportion of participants non-adherent to assigned therapy after randomization. Non-adherence will include definitions based on three distinct outcomes: a change action relative to assigned treatment following an adverse event, <70% adherence overall post-randomization, and <70% adherence in the last 2 weeks prior to Week 6. Treatment arms will be formally compared within this cohort to determine if assignment to STOP Taking

hypertonic saline results in clinically meaningfully inferior outcomes as compared to the KEEP Taking hypertonic saline. The primary analysis population will be ITT, with PP analyses reported if indicated for sensitivity. For all analyses with a model adjusted for randomization strata, the only stratification variable included is treatment combination at screening.

The following exhibits will be excluded from the LLF reports:
Screening Tables 1.2 and 3.1. Screening Figure 2.1. Study Figure 3.1. Also, Study Table 6.1 and Figure 6.1 will be excluded from interim reports.

The following are other modifications to the LLF report exhibits:

Screening exhibits remove components referencing Study B or use of dornase alfa only, which are not applicable to the LLF cohort. Screening tables present overall summaries only (i.e., do not include columns further broken down by treatment regimen and prior enrollment).

Demographic summaries remove the age category of >=12 to <18 years and modify the FEV_1 % predicted categories (<40, >=40 to <50, >=50 to <60, >60). Study Table 4.11 also uses modified FEV_1 % predicted categories (<50, >=50).

SIMPLIFY
Overview of SIMPLIFY Enrollment Across Studies
Final Report

PROTOCOL NUMBER: SIMPLIFY-IP-19

PROTOCOL TITLE: A Master Protocol to Test the Impact of Discontinuing Chronic Therapies in People with Cystic Fibrosis on Highly Effective CFTR Modulator Therapy (SIMPLIFY)

PRINCIPAL INVESTIGATORs:

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FUNDING AGENCIES: Cystic Fibrosis Foundation, Inc. (CFF)

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1 Outline of Screening and Enrollment

Figure 1.1. CONSORT Diagram

This figure illustrates participant exclusions and withdrawals from screening to randomization.

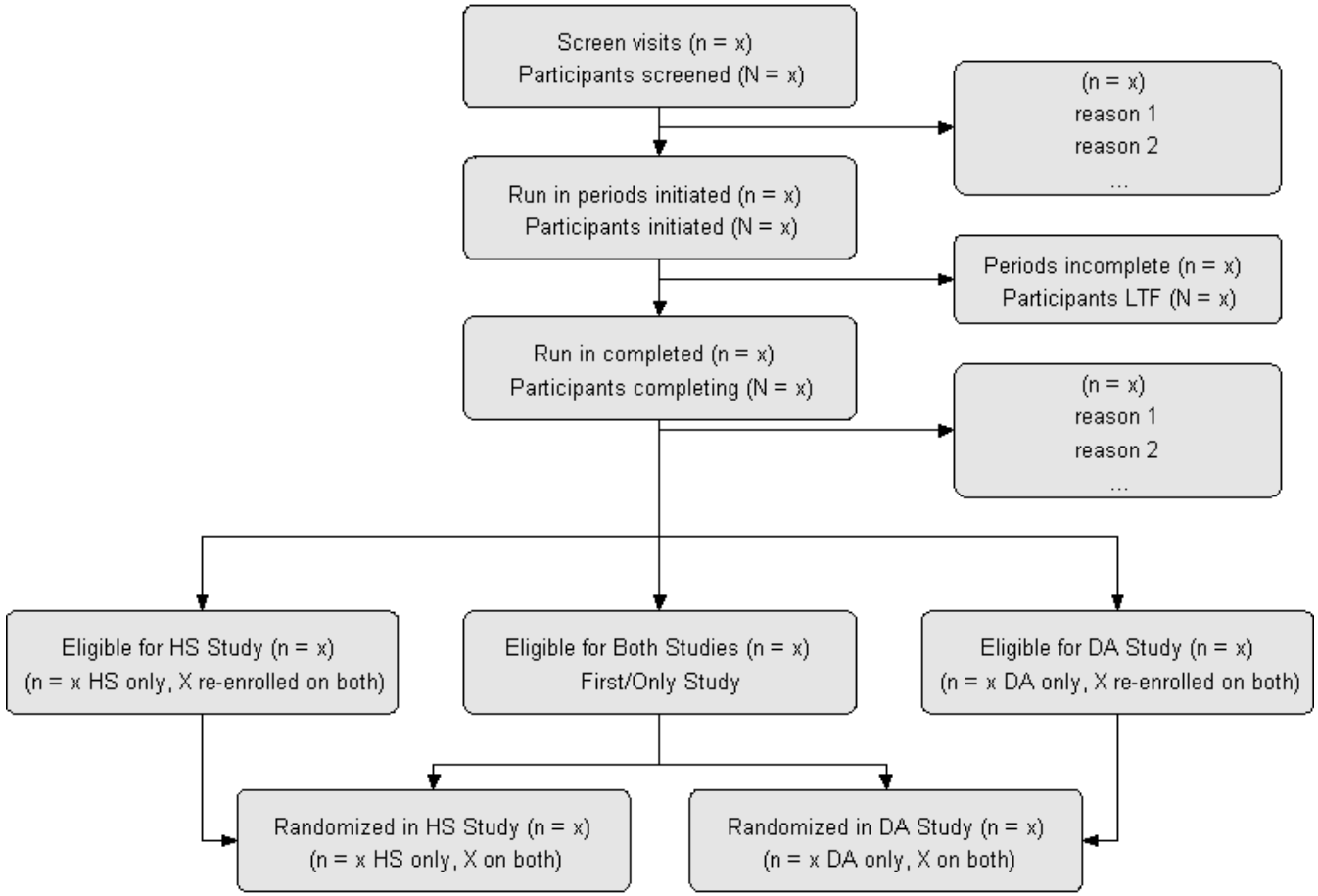

Table 1.1. Overview of Screening and Eligibility by Site

This table summarizes all study participants screened and eligible to be randomized to a study arm.

Site	All Screening Visits[1] Screening Visit No. Visits	All Screening Visits[1] Week 0 No. Visits	All Participants Screened Screening Visit N	All Participants Screened Week 0 N	Eligible [2] HS Only [3] N	Eligible [2] DA Only [3] N	Eligible [2] Both [3] N	Eligible [2] Prior Enrollee N	Eligible [2] Unknown [4] N
Site 1 Site 2 Site 3 Site N									
Total									

[1] Participants could be screened multiple times. The total number of screening visits is provided followed by the number of unique participants screened.
[2] Eligible is defined as all participants who passed eligibility criteria at screening visit and Week 0 (Visit 1). Cohort is determined by the 'Prior Study Enrollment and Current Therapy' eCRF.
[3] Participants who have not been previously enrolled are summarized in HS Only, DA Only, and Both columns.
[4] If form is incomplete, participant is allocated to unknown column.

Table 1.2. Summarization of Re-screening and Re-Enrollment (ITT population; CLOSED Report Only)

This table summarizes the status of second study screening and enrollment among participants on both hypertonic saline and dornase alfa that completed their first study. Participants may be eligible to enroll into Study B after completing Study A or vice versa.

	Prior Enrollment of Participants on both HS and DA that Completed First Study [1] (N=x)					
	Study A (Hypertonic Saline)			Study B (Dornase alfa)		
Status of Second Study Enrollment	STOP Taking (N=x)	KEEP Taking (N=x)	Total (N=x)	STOP Taking (N=x)	KEEP Taking (N=x)	Total (N=x)
Not Screened, n(%)						
Screened, n(%) [2]						
Randomized, n(%)						

[1] A participant is considered to have completed participation in the first study if their Week 6 (Visit 3) date is available.
[2] Screened includes everyone evaluated at initial screening visit but not (or not yet) randomized.

2 Screen Failures, Run-in Loss to Follow-up, and Reasons Not Randomized

Table 2.1. Summary of Screen Failures at Initial Screen

This table summarizes screen failures at screening visit by current therapy regimen and/or participation in prior study.

	HS Only [1]	DA Only [1]	Both [1]	Previously Enrolled (Prior Study A)	Previously Enrolled (Prior Study B)	Unknown [2]	Overall
Screening Visit							
Number of unique participants assessed for eligibility, N							
Number of unique participants with any screen failure, N							
Number of screenings, N [3]							
Number of screen fail visits, N [4]							
Reasons for screen fail, n(%) [5]							
Consent reasons							
Demographics reasons							
Disease History reasons							
Concomitant Medication and Treatment reasons							
Participants consented but not yet screened, N							

[1] Participants who have not been previously enrolled are summarized in HS Only, DA Only, and Both columns.
[2] Unable to determine current therapy regimen and/or prior study enrollment due to incomplete forms.
[3] Participants could screen more than once. X participants were screened more than once, of whom X were randomized.
[4] Participants could fail screening more than once.
[5] Percentages are based on the number of screen fail visits.
Ineligible reasons are due to failure to meet the corresponding inclusion criteria in the protocol:

Consent

A. Written informed consent (and assent when applicable) obtained from subject or subject's legal guardian.
B. Enrolled in the CFF Patient Registry.
C. For the 6-week study duration, willingness to either continue or discontinue daily use of hypertonic saline or dornase alfa (as applicable to Study A or Study B) based on randomization and according to the clinically prescribed routine (i.e., at least once daily).
D. Is willing and able to adhere to the study visit schedule and other protocol requirements including willingness and ability to provide information using electronic questionnaires loaded onto a personal device (e.g., smartphone or tablet).
E. For subjects who enter the SIMPLIFY Master Protocol taking both hypertonic saline and dornase alfa at the time of entry into their first study: Willingness to be randomized to either Study A or Study B.

Demographics

A. Age >= 12 years at the Screening Visit.

Disease History

A. Diagnosis of CF.
B. Forced expiratory volume in 1 second (FEV_1) >= 70 % predicted at the Screening Visit if < 18 years old,

and >= 60 % predicted at Screening Visit if >= 18 years old.

C. Clinically stable with no significant changes in health status within the 7 days prior to and including the Screening Visit.
D. No active smoking or vaping.
E. Has no other conditions that, in the opinion of the Site Investigator/designee, would preclude informed consent or assent, make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.

Concomitant Medications and Treatments

A. Current treatment with elexacaftor/tezacaftor/ivacaftor (ETI) for at least the 90 days prior to and including the Screening Visit and willing to continue daily use for the duration of the study.
B. Currently taking hypertonic saline (at least 3%) and/or dornase alfa for at least the 90 days prior to and including the Screening Visit and willing to continue daily use for the 2-week screening period.
C. Ability to tolerate albuterol or levalbuterol (Xopenex).
D. No use of an investigational drug within 28 days prior to and including the Screening Visit.
E. No changes to chronic therapy (e.g., ibuprofen, azithromycin, inhaled tobramycin, aztreonam lysine) within 28 days prior to and including the Screening Visit. This includes new airway clearance routines.
F. No acute use of antibiotics (oral, inhaled or IV) or acute use of systemic corticosteroids for respiratory tract symptoms within 7 days prior to and including the Screening Visit.
G. No chronic use of systemic corticosteroids at a dose equivalent to = 10mg per day of prednisone within 28 days prior to and including the Screening Visit.
H. No antibiotic treatment for nontuberculous mycobacteria (NTM) within 28 days prior to and including the Screening Visit.

Figure 2.1. Run-in Periods Initiated by Month

This figure summarizes cumulative run-in periods initiated among eligible patients at screening (Week -2) over time in calendar months as of Month XX, YYYY.

Table 2.2. Summary of Follow-up from Week -2 (Initial Screening) to Week 0 (Visit 1)

This table summarizes follow-up from Week -2 (initial screening) to Week 0 (Visit 1) by current therapy regimen and/or participation in prior study.

	HS Only [1]	DA Only [1]	Both [1]	Previously Enrolled (Prior Study A)	Previously Enrolled (Prior Study B)	Unknown [2]	Overall
Number of unique participants initiating a run-in period, N [3]							
Number of unique participants with any incomplete run-in period out of window, N							
Number of unique participants currently in run-in, N [4]							
Number of run-in periods, N [5]							
Number of incomplete run-in periods out of window, N [6]							
Reasons for incomplete run-in periods out of window, n (%) [7]							
Ineligible at Week 0 (Visit 1) due to withdrawn consent/LTF							
Ineligible at Week 0 (Visit 1) for other reasons							

[1] Participants who have not been previously enrolled are summarized in HS Only, DA Only, and Both columns.
[2] Unable to determine current therapy regimen and/or prior study enrollment due to incomplete forms.
[3] Equal to the number of participants eligible at one or more screening visits
[4] Eligible at screening visit but not yet out of window for Week 0 (Visit 1).
[5] Participants could have more than one run-in period. X participants had multiple run-in periods, of whom X were randomized in a study.
[6] Incomplete run-in period is defined by Visit 1 not done. Participants may have incomplete run-in periods more than once.
[7] Percentages are based on the number of run-in periods initiated.

Table 2.3. Summary of Ineligible for Randomization or Not Randomized for Other Reasons at Week 0 (Visit 1)

This table summarizes study participants who were ineligible at Week 0 (Visit 1). Any consented participant who is excluded from the study before randomization is considered ineligible. Also summarized are participants who were eligible but not randomized at Week 0 (Visit 1).

	HS Only [1]	DA Only [1]	Both [1]	Previously Enrolled (Prior Prior Study A)	Previously Enrolled (Prior Prior Study B)	Unknown [2]	Overall
Week 0 Visit							
Number of unique participants assessed for eligibility at Week 0, N							
Number of unique participants ineligible at Week 0, N							
Number of assessments for eligibility at Week 0, N [3]							
Number of visits with ineligible assessments, N [4]							
Reasons ineligible, n (%) [5]							
Consent reasons							
Disease History reasons							
Concomitant Medication reasons							
Number of participants eligible but not randomized, N							
Reasons not randomized, n (%) [6]							
Reason 1							
Reason N							

[1] Participants who have not been previously enrolled are summarized in HS Only, DA Only, and Both columns.
[2] Unable to determine current therapy regimen and/or prior study enrollment due to incomplete forms.
[3] Participants could screen more than once. X participants were screened more than once, of whom X were randomized.
[4] Participants could fail screening more than once.
[5] Percentages are based on the number of screen fail visits.
Ineligible reasons are due to failure to meet the corresponding inclusion criteria in the protocol:

Consent
A. Is willing and able to adhere to the study visit schedule and other protocol requirements.

Disease History
A. No absolute decrease in FEV_1 % predicted of >= 10% between the Screening Visit and Visit 1.
B. Clinically stable with no significant changes in health status between the Screening Visit and Visit 1.

Concomitant Medications
A. No acute use of antibiotics (oral, inhaled or IV) or acute use of systemic corticosteroids for respiratory tract symptoms from the Screening Visit to Visit 1.
B. More than 70% compliance with submission of daily ePRO questionnaires in the up to 13 days prior to Visit 1.
C. Among the daily ePRO questionnaires submitted in the up to 13 days prior to Visit 1, at least 70% adherence with taking ETI and as applicable, hypertonic saline and/or dornase alfa, as reported from Screening to Visit 1.

[6] Percentages are based on the number of not randomized participants with a completed Enrollment Status Form.

3 Enrollment, Demographics, and Follow-up Overview

Table 3.1. Summary of Randomization in Each Study

This table shows the total participants randomized in each study and their eligibility before randomization (Study A, Study B, or both). Eligibility is summarized overall and broken down by therapy regimen/prior enrollment.

	Randomized in Study A (HS) (N =)	Randomized in Study B (DA) (N =)
Eligible for only Study A (HS)	N=x (%)	
On HS Only[1]	n (%)	
Previously Enrolled in Study B[1]	n (%)	
Eligible for Both Studies [2]	N=x(%)	
Eligible for only Study B (DA)	N=0 (0%)	
On DA Only[1]	0 (0%)	
Previously Enrolled in Study A[1]	0 (0%)	

[1] Denominator for percentage is based on study eligibility.
[2] Includes subjects on both HS and DA at first or only study.

Table 3.2. Summary of Demographics and Week 0 Characteristics

This table summarizes demographic and Week 0 characteristics among all randomized participants by study and for unique participants. All measures were recorded at Visit 1 unless specified otherwise.

	Study A (HS) (N =)	Study B (DA) (N =)	First/Only Study (N =)
Sex at birth			
Male			
Female			
Age (years)			
N			
Mean (SD)			
Median			
Min, Max			
Age Distribution (years)			
≥12 to <18			
≥18 to <24			
≥24 to <30			
≥ 30			
Race [1]			
White			
Black or African American			
Asian			
American Indian or Alaska Native			
Native Hawaiian or Other Pacific Islander			
Unknown/Other			
Ethnicity			
Hispanic or Latino			
Not Hispanic or Latino			
Genotype Group [2]			
F508del Homozygous			
F508del Heterozygous			
Other/Unknown			
Height (cm) at Screening Visit			
N			
Mean (SD)			
Median			
Min, Max			
Height Percentile (%) at Screening Visit [3]			
N			
Mean (SD)			
Median			
Min, Max			
Weight (kg)			
N			

	Mean (SD)			
	Median			
	Min, Max			
Weight Percentile (%) [3]				
	N			
	Mean (SD)			
	Median			
	Min, Max			
Body Mass Index (kg/m^2)				
	N			
	Mean (SD)			
	Median			
	Min, Max			
BMI Percentile (%) [3]				
	N			
	Mean (SD)			
	Median			
	Min, Max			
FEV_1 (liters)				
	N			
	Mean (SD)			
	Median			
	Min, Max			
FEV_1 (% predicted) [4]				
	N			
	Mean (SD)			
	Median			
	Min, Max			
FEV_1 (% predicted) Distribution [4]				
	<60			
	≥60 to <70			
	≥70 to <90			
	≥90 to <100			
	≥100			
Sweat Chloride (mEq/L) [5]				
Pre-ETI Result				
	N			
	Mean (SD)			
	Median			
	Min, Max			
Post-ETI Result				
	N			
	Mean (SD)			
	Median			
	Min, Max			
Current Hypertonic Saline Use [6]				

Yes			
No			
Current Dornase Alfa Use [6]			
Yes			
No			
Current Chronic Therapy [7]			
ETI [8]			
Airway clearance [9]			
Inhaled antibiotic (Continuous)			
Inhaled antibiotic (Cycled)			
Inhaled antibiotic (Continuous Alternating)			
Oral antibiotic			
Ibuprofen			
Systemic steroids			
Previous Modulator Use [10]			
Ivacaftor			
Lumacaftor/Ivacaftor			
Tezacaftor/Ivacaftor			
Positive Microbiology Culture (past year) [11]			
Pseudomonas aeruginosa			
Staphylococcus aureus			
Methicillin-resistant Staphylococcus aureus			
Stenotrophomonas maltophilia			
Achromobacter xylosoxidan			
Burkholderia cepacia complex			
Haemophilus influenzae			
Mycobacterium abscessus			
Mycobacterium avium complex			

[1] Other includes participants of more than one race.
[2] Other refers to participants with two known non-F508del CFTR mutations. Genotype is unknown if one or both alleles are unknown.
[3] Percentiles are derived using CDC/WHO standards for participants up to 20 years old.
[4] FEV_1 % predicted is calculated using the Global Lung Initiative multi-ethnic reference equations for ages 3-95.
[5] Sweat Chloride may not be available.
[6] As determined by the 'Prior Study Enrollment and Current Therapy' eCRF.
[7] Indicated as '28 days prior to Screening Visit ' on the Concomitant Medications and Therapies eCRF.
[8] May not be 100% due to incomplete data entry or unresolved queries.
[9] Includes airway clearance by route chest PT/vest.
[10] Participants may fall into more than one category of prior modulator use.
[11] Summarized are culture results obtained clinically anytime within 12 months prior to Screening Visit from OP swab, expectorated sputum, induced sputum, or BAL.

Table 3.3. Number of Study Visits and Spirometry Completed and Follow-Up Time by Study (ITT population)

This table summarizes the number of participants completing each scheduled study visit and call among all randomized subjects. Also summarized is median follow-up time.

	Study A (HS) (N=)	Study B (DA) (N=)	First/Only Study (N=)
Study Visit [1]			
Week 0 (Visit 1) Completed, n(%)[2]			
Spirometry Completed, n(%)[3]			
Week 2 (Visit 2) Expected, n(%)[2,4]			
Week 2 (Visit 2) Completed, n(%)[3]			
Spirometry Completed, n(%)[3]			
Week 4 (Call) Expected, n(%) [2,4]			
Week 4 (Call) Completed, n(%)[3]			
Week 6 (Visit 3) Expected, n(%)[2,4]			
Week 6 (Visit 3) Completed, n(%)[3]			
Spirometry Completed, n(%)[3]			
Median follow up time (days) [5]			

[1] A study visit is considered 'completed' if there exists a completed CRF page with a study date corresponding to that visit number.
[2] Percent out of column total.
[3] Percent out of immediately prior row total.
[4] A study visit is “expected” if the visit is completed or should have occurred per the protocol schedule allowing for a visit window. End of window plus 7 days for data entry is 24 days since randomization for Week 2 (Visit 2), 38 days since randomization for Week 4 (Call), and 56 days since randomization for Week 6 (Visit 3).
[5] Follow-up time is calculated as days from randomization (Week 0).

SIMPLIFY
Final Report on Study A (Hypertonic Saline)

PROTOCOL NUMBER:	SIMPLIFY-IP-19
PROTOCOL TITLE:	A Master Protocol to Test the Impact of Discontinuing Chronic Therapies in People with Cystic Fibrosis on Highly Effective CFTR Modulator Therapy (SIMPLIFY)
PRINCIPAL INVESTIGATORs:	Dave Nichols, MD University of Washington/Seattle Children's Nicole Mayer-Hamblett, PhD University of Washington/Seattle Children's Alex Gifford, MD Dartmouth-Hitchcock Medical Center
FUNDING AGENCIES:	Cystic Fibrosis Foundation, Inc. (CFF)
PREPARED BY:	CF Therapeutics Development Network Coordinating Center: Nicole Mayer-Hamblett, PhD Katherine Odem-Davis, PhD Michelle Skalland, MS
RELEASE DATE:	Month XX, 2020

1 Summary of Randomization and Study Visit Completion

Figure 1.1. CONSORT

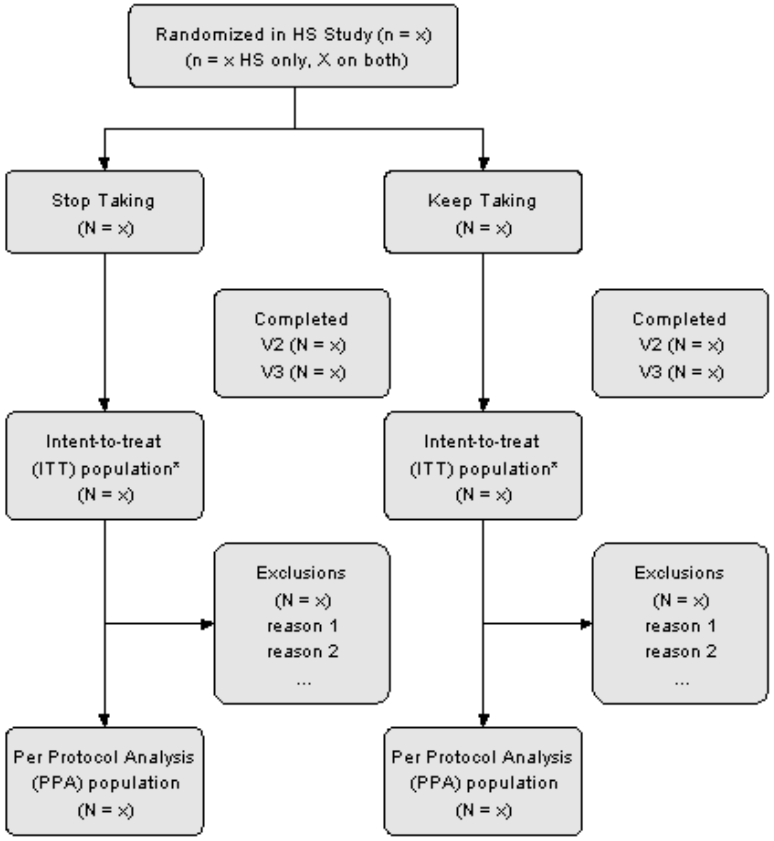

Figure 1.2. Enrollment by Month

The figure below displays cumulative enrollment of participants overall and stratified by cohort (i.e., HS only, HS both (first study), re-enrollee (prior enrollment in DA study)) randomized in Study A (hypertonic saline) over time in calendar months as of Month MM, YYYY. The figure also includes the overall projected enrollment and totals.

Table 1.1. Overview of Enrollment by Site

This table summarizes all study participants randomized to a study arm. Further, participants randomized in Study A (hypertonic saline) are summarized for each site, along with withdrawals, study completions, and number of participants ongoing on study.

Site	Randomized [1] within Study X Hypertonic Saline Only [2] STOP Taking N	Randomized [1] within Study X Hypertonic Saline Only [2] KEEP Taking N	Randomized [1] within Study X Hypertonic Saline Only [2] Total N	Randomized [1] within Study X Both [2] STOP Taking N	Randomized [1] within Study X Both [2] KEEP Taking N	Randomized [1] within Study X Both [2] Total N	Randomized [1] within Study X Prior Enrollee [2] STOP Taking N	Randomized [1] within Study X Prior Enrollee [2] KEEP Taking N	Randomized [1] within Study X Prior Enrollee [2] Total N	All Randomized [1] within Study X STOP Taking N	All Randomized [1] within Study X KEEP Taking N	All Randomized [1] within Study X Total N	Withdrawn [3] from Study X STOP Taking N	Withdrawn [3] from Study X KEEP Taking N	Withdrawn [3] from Study X Total N	Completed Study [4] in Study X STOP Taking N	Completed Study [4] in Study X KEEP Taking N	Completed Study [4] in Study X Total N	Ongoing on Study [5] in Study X STOP Taking N	Ongoing on Study [5] in Study X KEEP Taking N	Ongoing on Study [5] in Study X Total N
Site 1																						
Site 2																						
Site 3																						
Site N																						
Total																						

[1] Randomized is defined as all participants who were allocated to a study arm in the Study A (hypertonic saline) at Week 0 (Visit 1). Remaining participants that are taking both hypertonic saline and dornase alfa at the time of screening were randomized within the other study (dornase alfa).
[2] As determined by the 'Prior Study Enrollment and Current Therapy' eCRF.
[3] Withdrawn is defined as those randomized participants who withdrew from the study early and did not complete the study. Reasons for withdrawal are listed in Table 3.1..
[4] Completed study is defined as having a visit date at the last study visit at Week 6 (Visit 3).
[5] Number of ongoing study participants is based on a data cut-off of DDMMMYYYY. [Column and footnote excluded from Final Report]

Table 1.2. Number of Study Visits and Spirometry Completed and Follow-Up Time by Study Arm (ITT population)

This table summarizes the number of participants completing each scheduled study visit and call among all randomized subjects. Also summarized is median follow-up time.

	STOP Taking (N=)	KEEP Taking (N=)	Total (N=)
Study Visit [1]			
Week 0 (Visit 1) Completed, n(%)[2]			
Spirometry Completed, n(%)[3]			
Week 2 (Visit 2) Expected, n(%)[2,4]			
Week 2 (Visit 2) Completed, n(%)[3]			
Spirometry Completed, n(%)[3]			
Week 4 (Call) Expected, n(%) [2,4]			
Week 4 (Call) Completed, n(%)[3]			
Week 6 (Visit 3) Expected, n(%)[2,4]			
Week 6 (Visit 3) Completed, n(%)[3]			
Spirometry Completed, n(%)[3]			
Median follow up time (days) [5]			

[1] A study visit is considered 'completed' if there exists a completed CRF page with a study date corresponding to that visit number.
[2] Percent out of column total.
[3] Percent out of immediately prior row total.
[4] A study visit is “expected” if the visit is completed or should have occurred per the protocol schedule allowing for a visit window. End of window plus 7 days for data entry is 24 days since randomization for Week 2 (Visit 2), 38 days since randomization for Week 4 (Call), and 56 days since randomization for Week 6 (Visit 3).
[5] Follow-up time is calculated as days from randomization (Week 0).

Table 1.3. Overview of Analysis Populations

This table summarizes the number of participants excluded from the per-protocol analysis (PPA) population for one or more reasons.

	STOP Taking (N=)	KEEP Taking (N=)	Total (N=)
Number of participants randomized in study (ITT population) who have completed or withdrawn, N			
Number of participants included in PPA population, n(%) [1]			
Number of participants excluded from PPA population, n(%) [1]			
Number of reasons for exclusion from PPA population, N [1, 2]			
Reasons for exclusion from PPA population, n (%) [1, 2]:			
Daily diary completion (Compliance): <70% non-missing data			
Daily diary completion (Compliance): <70% non-missing in last 2 weeks [3]			
Daily diary adherence to assigned treatment regimen among non-missing days overall <70%			
Daily diary adherence to assigned treatment regimen among non-missing days in last 2 weeks<70% [3]			
Initiation of new acute oral, inhaled, or IV antibiotics for respiratory symptoms [4]			
Missing FEV_1 at Week 6 (Visit 3)			
Randomized but not Eligible at either Week -2 (Screening) or Week 0 (Visit 1) [5]			
Given the incorrect randomization instructions			
<70% use of ETI among non-missing days in last 2 weeks [3]			

[1] Among participants randomized in study who have completed or withdrawn.
[2] Participants can be excluded from the PPA population for more than one reason.
[3] Last 2 weeks is from day of Week 6 study visit (Visit 3).
[4] G-tube also included as oral.
[5] Determined to not be eligible at Week -2 (Screening) or at Week 0 (Visit 1) after randomization.

2 Demographics and Characteristics at Week 0

Table 2.1. Summary of Demographics and Characteristics at Week 0

This table summarizes demographic and Week 0 characteristics among all randomized participants by intervention arm and by population. All measures were recorded at Visit 1 unless specified otherwise.

	ITT Population		PPA Population	
	STOP Taking (N=)	**KEEP Taking (N=)**	**STOP Taking (N=)**	**KEEP Taking (N=)**
Sex at birth				
Male				
Female				
Age (years)				
N				
Mean (SD)				
Median				
Min, Max				
Age Distribution (years)				
≥12 to <18				
≥18 to <24				
≥24 to <30				
≥ 30				
Race[1]				
White				
Black or African American				
Asian				
American Indian or Alaska Native				
Native Hawaiian or Other Pacific Islander				
Unknown/Other				
Ethnicity				
Hispanic or Latino				
Not Hispanic or Latino				
Genotype Group [2]				
F508del Homozygous				
F508del Heterozygous				
Other/Unknown				
Height (cm) at Screening Visit				
N				
Mean (SD)				
Median				
Min, Max				

Height Percentile (%)at Screening Visit [3]					
	N				
	Mean (SD)				
	Median				
	Min, Max				
Weight (kg)					
	N				
	Mean (SD)				
	Median				
	Min, Max				
Weight Percentile (%) [3]					
	N				
	Mean (SD)				
	Median				
	Min, Max				
Body Mass Index (kg/m^2)					
	N				
	Mean (SD)				
	Median				
	Min, Max				
BMI Percentile (%) [3]					
	N				
	Mean (SD)				
	Median				
	Min, Max				
FEV_1 (liters)					
	N				
	Mean (SD)				
	Median				
	Min, Max				
FEV_1 (% predicted) [4]					
	N				
	Mean (SD)				
	Median				
	Min, Max				
FEV_1 (% predicted) Distribution [4]					
	<60				
	≥60 to <70				
	≥70 to <90				
	≥90 to <100				
	≥100				
Sweat Chloride (mEq/L) [5]					
Pre-ETI Result					
	N				
	Mean (SD)				
	Median				

Min, Max				
Post-ETI Result				
N				
Mean (SD)				
Median				
Min, Max				
Previous Enrollment in Study B [6]				
Yes				
No				
Previous Treatment Assignment in Study B [6]				
STOP Taking				
KEEP Taking				
Current Hypertonic Saline Use [6]				
Yes				
No				
Current Dornase Alfa Use [6]				
Yes				
No				
Current Chronic Therapy [7]				
ETI [8]				
Airway clearance [9]				
Inhaled antibiotic (Continuous)				
Inhaled antibiotic (Cycled)				
Inhaled antibiotic (Continuous Alternating)				
Oral antibiotic				
Ibuprofen				
Systemic steroids				
Previous Modulator Use [10]				
Ivacaftor				
Lumacaftor/Ivacaftor				
Tezacaftor/Ivacaftor				
Positive Microbiology Culture (past year) [11]				
Pseudomonas aeruginosa				
Staphylococcus aureus				
Methicillin-resistant Staphylococcus aureus				
Stenotrophomonas maltophilia				
Achromobacter xylosoxidan				
Burkholderia cepacia complex				
Haemophilus influenzae				
Mycobacterium abscessus				
Mycobacterium avium complex				

[1] Other includes participants of more than one race.
[2] Other refers to participants with two known non-F508del CFTR mutations. Genotype is unknown if one or both alleles are unknown.
[3] Percentiles are derived using CDC/WHO standards for participants up to 20 years old.

[4] FEV_1 % predicted is calculated using the Global Lung Initiative multi-ethnic reference equations for ages 3-95.
[5] Sweat Chloride may not be available.
[6] As determined by the 'Prior Study Enrollment and Current Therapy' eCRF. [Exclude hypertonic row from Study A (HS) and exclude dornase alfa row from Study B (DA).]
[7] Indicated as '28 days prior to Screening Visit ' on the Concomitant Medications and Therapies eCRF.8] Summarized are culture results obtained clinically anytime within 12 months prior to Screening Visit from OP swab, expectorated sputum, induced sputum, or BAL.
[8] May not be 100% due to incomplete data entry or unresolved queries.
[9] Includes airway clearance by route chest PT/vest.
[10] Participants may fall into more than one category of prior modulator use.
[11] Summarized are culture results obtained clinically anytime within 12 months prior to Screening Visit from OP swab, expectorated sputum, induced sputum, or BAL.

3 Summary of Withdrawals, Intervention Assignment, and Therapy Adherence

Table 3.1. Summary of Withdrawals (ITT population)

This table summarizes withdrawals between Week 0 (Visit 1) and Week 6 (Visit 3) among all randomized participants by intervention arm.

	STOP Taking (N=)	KEEP Taking (N=)	Total (N=)
Withdrew from Study, n (%)			
Reason for Withdrawal, n (%) [1]			
Protocol Violation			
Adverse Event [2]			
Participant Decision			
Lost to Follow-Up (LTF)			
Death			
Other			
Time to Withdrawal (days) [3]			
Mean (SD)			
Median			
Min, Max			

[1] Percentages are based on number of withdrawals.
[2] Participant x withdrew from study due to adverse event y.
[3] Time to withdrawal is from randomization (Week 0). The maximum withdrawal is 60 days following randomization at the Week 0 visit, which is the time of loss to follow-up (LTF).

Table 3.2. Submission Completeness of ePRO Daily Study Adherence Questionnaire

This table summarizes the completeness of submissions (compliance) for the daily study adherence questionnaire from Week 0 (Visit 1/randomization) to Week 6 (Visit 3) by intervention arm among subjects who have completed study or withdrawn. Also summarized is completeness of submissions for the two weeks prior to Week 0.

		STOP Taking (N=)	KEEP Taking (N=)	Total (N=)
Intent to Treat Population				
Number of Expected Daily Submissions from Week 0 to Week 6				
	N			
	Mean (SD)			
	Median			
	Min, Max			
Submission Completeness from Week 0 to Week 6 [1], %				
	N			
	Mean (SD)			
	Median			
	Min, Max			
Submission Completeness in Last 2 Weeks Prior to Week 0 [1,2], %				
	N			
	Mean (SD)			
	Median			
	Min, Max			
Submission Completeness in Last 2 Weeks Prior to Week 6 [1,3], %				
	N			
	Mean (SD)			
	Median			
	Min, Max			
Difference in Submission Completeness in Last 2 Weeks (Prior to Week 6 – Prior to Week 0) [1,2,3], %				
	N			
	Mean (SD)			
	Median			
	Min, Max			
≥70% Compliance Overall from Week 0 to Week 6				
	n (%)			
≥70% Compliance in Last 2 Weeks Prior to Week 6 [3]				
	n (%)			
≥70% Compliance Overall and in Last 2 Weeks Prior to Week 6 [3]				
	n (%)			

Per Protocol Analysis Population				
Number of Expected Daily Submissions from Week 0 to Week 6				
	N			
	Mean (SD)			
	Median			
	Min, Max			
Submission Completeness from Week 0 to Week 6 [1], %				
	N			
	Mean (SD)			
	Median			
	Min, Max			
Submission Completeness in Last 2 Weeks Prior to Week 0 [1,2], %				
	N			
	Mean (SD)			
	Median			
	Min, Max			
Submission Completeness in Last 2 Weeks Prior to Week 6 [1], %				
	N			
	Mean (SD)			
	Median			
	Min, Max			
Difference in Submission Completeness in Last 2 Weeks (Prior to Week 6 – Prior to Week 0) [1,2], %				
	N			
	Mean (SD)			
	Median			
	Min, Max			
≥70% Compliance Overall from Week 0 to Week 6				
	n (%)			
≥70% Compliance in Last 2 Weeks Prior to Week 6				
	n (%)			
≥70% Compliance Overall and in Last 2 Weeks Prior to Week 6				
	n (%)			

[1] Compliance for each participant is defined as Y/X, multiplied by 100, where X is the number of expected submissions and Y is the number of actual submissions.
[2] Two weeks prior to Week 0 includes questionnaires from the 13 days prior to Week 0 (Visit 1) as well as a 14th questionnaire if and only if completed on day of visit.
[3] Excludes participants who withdrew prior to the end of the window for Week 6.

Table 3.3. Intervention Assignment Adherence

This table summarizes intervention assignment adherence in terms of the protocol defined therapy regimen (i.e., continue taking hypertonic saline or discontinue taking hypertonic saline) from Week 0 (Visit 1) to Week 6 (Visit 3) among subjects who have completed study or withdrawn. Adherence in this table is based on the ePRO daily study adherence questionnaire. Only randomized participants for whom we have questionnaire submissions for will be considered evaluable for this table.

		STOP Taking (N=)	KEEP Taking (N=)	Total (N=)
Intent to Treat Population				
Number of Daily Submissions from Week 0 to Week 6				
	N			
	Mean (SD)			
	Median			
	Min, Max			
Percent Treatment Assignment Adherence from Week 0 to Week 6 [1], %				
	N			
	Mean (SD)			
	Median			
	Min, Max			
Number of Daily Submissions in Last 2 Weeks Prior to Week 0 [2]				
	N			
	Mean (SD)			
	Median			
	Min, Max			
Percent of Submissions Hypertonic Saline Consistent with Use at Screening in Last 2 Weeks Prior to Week 0 [1,2], %				
	N			
	Mean (SD)			
	Median			
	Min, Max			
Number of Daily Submissions in Last 2 Weeks Prior to Week 6 [3]				
	N			
	Mean (SD)			
	Median			
	Min, Max			
Percent Treatment Assignment Adherence in Last 2 Weeks Prior to Week 6 [1,4], %				
	N			
	Mean (SD)			
	Median			
	Min, Max			
Difference in Treatment Assignment Adherence or Consistent Use of Hypertonic Saline in Last 2 Weeks				

(Prior to Week 6 – Prior to Week 0) [1,2,4], %				
	N			
	Mean (SD)			
	Median			
	Min, Max			
≥70% Adherence Overall from Week 0 to Week 6				
	n (%)			
≥70% Adherence in Last 2 Weeks Prior to Week 6 [4]				
	n (%)			
≥70% Adherence Overall and in Last 2 Weeks Prior to Week 6 [4]				
	n (%)			
Per Protocol Analysis Population				
Number of Daily Submissions from Week 0 to Week 6				
	N			
	Mean (SD)			
	Median			
	Min, Max			
Percent Treatment Assignment Adherence from Week 0 to Week 6 [1], %				
	N			
	Mean (SD)			
	Median			
	Min, Max			
Number of Daily Submissions in Last 2 Weeks Prior to Week 0 [2]				
	N			
	Mean (SD)			
	Median			
	Min, Max			
Percent of Submissions Hypertonic Saline Consistent with Use at Screening in Last 2 Weeks Prior to Week 0 [1,2], %				
	N			
	Mean (SD)			
	Median			
	Min, Max			
Number of Daily Submissions in Last 2 Weeks Prior to Week 6				
	N			
	Mean (SD)			
	Median			
	Min, Max			
Percent Treatment Assignment Adherence in Last 2 Weeks Prior to Week 6 [1], %				
	N			
	Mean (SD)			
	Median			
	Min, Max			
Difference in Treatment Assignment Adherence in Last 2 Weeks (Prior to Week 6 – Prior to Week 0) [1,2], %				

	N Mean (SD) Median Min, Max			
≥70% Adherence Overall from Week 0 to Week 6	n (%)			
≥70% Adherence in Last 2 Weeks Prior to Week 6	n (%)			
≥70% Adherence Overall and in Last 2 Weeks Prior to Week 6	n (%)			

[1] Adherence for each participant is defined as Y/X, multiplied by 100, where X is the number of days participant submitted the questionnaire and Y is the number of days participant followed treatment assignment.
[2] Two weeks prior to Week 0 includes questionnaires from the 13 days prior to Week 0 (Visit 1) as well as a 14th questionnaire if and only if completed on day of visit.
[3] Excludes participants who withdrew prior to the end of the window for Week 6.
[4] Excludes participants who withdrew prior to the end of the window for Week 6 or had no submissions in the last 2 weeks period (i.e., adherence not calculable).

Table 3.4. ETI Adherence

This table summarizes therapy adherence for elexacaftor/tezacaftor/ivacaftor (ETI) from Week 0 (Visit 1) to Week 6 (Visit 3) among subjects who have completed study or withdrawn. Adherence in this table is based on the ePRO daily study adherence questionnaire. Only randomized participants for whom we have questionnaire submissions for will be considered evaluable for this table.

		STOP Taking (N=)	KEEP Taking (N=)	Total (N=)
Intent to Treat Population				
Number of Daily Submissions from Week 0 to Week 6				
	N			
	Mean (SD)			
	Median			
	Min, Max			
ETI Adherence from Week 0 to Week 6 [1], %				
	N			
	Mean (SD)			
	Median			
	Min, Max			
Number of Daily Submissions in Last 2 Weeks Prior to Week 0 [2]				
	N			
	Mean (SD)			
	Median			
	Min, Max			
ETI Adherence in Last 2 Weeks Prior to Week 0 [1,2], %				
	N			
	Mean (SD)			
	Median			
	Min, Max			
Number of Daily Submissions in Last 2 Weeks Prior to Week 6 [3]				
	N			
	Mean (SD)			
	Median			
	Min, Max			
ETI Adherence in Last 2 Weeks Prior to Week 6 [1,4], %				
	N			
	Mean (SD)			
	Median			
	Min, Max			
Difference in ETI Adherence in Last 2 Weeks (Prior to Week 6 – Prior to Week 0) [1,2,4], %				
	N			
	Mean (SD)			

	Median Min, Max			
≥70% Adherence Overall from Week 0 to Week 6	n (%)			
≥70% Adherence in Last 13 Days Prior to Week 6 [4]	n (%)			
≥70% Adherence Overall and in Last 13 Days Prior to Week 6 [4]	n (%)			
Per Protocol Analysis Population				
Number of Daily Submissions from Week 0 to Week 6				
	N Mean (SD) Median Min, Max			
ETI Adherence from Week 0 to Week 6 [1], %				
	N Mean (SD) Median Min, Max			
Number of Daily Submissions in Last 2 Weeks Prior to Week 0 [2]				
	N Mean (SD) Median Min, Max			
ETI Adherence in Last 2 Weeks Prior to Week 0 [1, 2], %				
	N Mean (SD) Median Min, Max			
Number of Daily Submissions in Last 2 Weeks Prior to Week 6				
	N Mean (SD) Median Min, Max			
ETI Adherence in Last 2 Weeks Prior to Week 6 [1], %				
	N Mean (SD) Median Min, Max			
Difference in ETI Adherence in Last 2 Weeks (Prior to Week 6 – Prior to Week 0) [1,2], %				
	N Mean (SD) Median Min, Max			
≥70% Adherence Overall from Week 0 to Week 6				

≥70% Adherence in last 13 Days Prior to Week 6	n (%)			
≥70% Adherence Overall and in last 13 Days Prior to Week 6	n (%)			

[1] Adherence for each participant is defined as Y/X, multiplied by 100, where X is the number of days participant submitted the questionnaire and Y is the number of days participant took ETI.
[2] Two weeks prior to Week 0 includes questionnaires from the 13 days prior to Week 0 (Visit 1) as well as a 14th questionnaire if and only if completed on day of visit.
[3] Excludes participants who withdrew prior to the end of the window for Week 6.
[4] Excludes participants who withdrew prior to the end of the window for Week 6 or had no submissions in the last 2 weeks period (i.e., adherence not calculable).

Table 3.5. Dornase Alfa and Airway Clearance Therapy Use

This table summarizes daily use of dornase alfa and airway clearance as reported in the ePRO daily study adherence questionnaire from Week 0 (Visit 1) to Week 6 (Visit 3) among subjects who have completed study or withdrawn. Only randomized participants for whom we have questionnaire submissions for will be considered evaluable for this table.

		STOP Taking (N=)	KEEP Taking (N=)	Total (N=)
Intent to Treat Population				
Number of Daily Submissions from Week 0 to Week 6				
	N			
	Mean (SD)			
	Median			
	Min, Max			
Percent of Submissions with Dornase Alfa Use Reported [1], %				
	N			
	Mean (SD)			
	Median			
	Min, Max			
Percent of Submissions Dornase Alfa Consistent with Use at Screening [2], %				
	N			
	Mean (SD)			
	Median			
	Min, Max			
Percent of Submissions with Airway Clearance Use Reported [1], %				
	N			
	Mean (SD)			
	Median			
	Min, Max			
Per Protocol Analysis Population				
Number of Daily Submissions from Week 0 to Week 6				
	N			
	Mean (SD)			
	Median			
	Min, Max			
Percent of Submissions with Dornase Alfa Use Reported [1], %				
	N			
	Mean (SD)			
	Median			
	Min, Max			
Percent of Submissions Dornase Alfa Consistent with Use at Screening [2], %				
	N			
	Mean (SD)			
	Median			

Percent of Submissions with Airway Clearance Use Reported [1], %	Min, Max N Mean (SD) Median Min, Max			

[1] Percent for each participant is defined as Y/X, multiplied by 100, where X is the number of days participant submitted the questionnaire and Y is the number of days participant reported doing therapy.
[2] Percent for each participant is defined as Y/X, multiplied by 100, where X is the number of days participant submitted the questionnaire and Y is the number of days participant followed same therapy regimen as compared to screening, as determined by 'Current Medication and Prior SIMPLIFY Enrollment' eCRF (e.g., therapy use during study if reported as having used therapy at screening).

Table 3.6. Logistic Regression Model Results for Odds of Meeting Adherence Criteria (ITT population Final Report Only)

This table summarizes the estimate (as odds ratio) comparing the proportion of participants meeting the adherence criteria (i.e., intervention arm adherence ≥70% overall and ≥70% last two weeks prior to week 6. For further details, refer to Table 3.3) between intervention arms from Week 0 (Visit 1) to Week 6 (Visit 3) using a logistic regression model. Each participant is only counted once in the model (i.e., outcome is 1 if participant met adherence criteria. Otherwise, outcome is 0). The models summarized are for an unadjusted model and one that adjusts for the randomization strata: (Week 0 FEV_1 % Predicted (≥90% or <90%), therapy combination at screening (single or concurrent use of hypertonic saline and/or dornase alfa), prior study participation (yes or no), and age (≥18 years or < 18 years)).

Model Covariates		STOP Taking Proportion Estimate (N =)	KEEP Taking Proportion Estimate (N =)	Odds Ratio (95% CI)	P-value
Model Unadjusted					
Intervention Arm:	STOP Taking hypertonic saline [1]				
Model Adjusted for Randomization Strata					
Intervention Arm:	STOP Taking hypertonic saline [1]				
Randomization Strata:	FEV_1 % Predicted ≥90% [2]				
	On both HS and Dnase [3]				
	Prior study enrollment [4]				
	Age ≥18 years [5]				

[1] Compared to reference level, KEEP taking hypertonic saline.
[2] Compared to reference level,FEV_1 % Predicted < 90% at Week 0.
[3] Compared to reference level,one therapy at Screening.
[4] Compared to reference level,no prior study enrollment.
[5] Compared to reference level,age <18 years at Week 0.

Figure 3.1. Forest Plot Comparing of Odds of Meeting Adherence Criteria Across Baseline Factors (ITT population Optional for Final Report Only)

This figure summarizes the estimate (as odds ratio) comparing the proportion of participants meeting the adherence criteria between intervention arms from Week 0 (Visit 1) to Week 6 (Visit 3) using univariate logistic regression models for each randomization strata (Week 0 FEV_1 % Predicted (≥90% or <90%), treatment combination at screening (single or concurrent use of hypertonic saline and/or dornase alfa), prior study participation (yes or no), and age (≥18 years or < 18 years)) and other baseline factors. A point estimate and 95% confidence interval is presented for each baseline factor compared.

4 Summary of Adverse Events

Table 4.1. Serious Adverse Event Overview (ITT population)

The total number of serious adverse events (SAEs) is presented in this table. All events occurring from Week 0 (Visit 1) through the end of follow-up are included. The rate of occurrence is equal to the number of events divided by the total number of follow-up weeks in each intervention arm.

	STOP Taking (N=x)	KEEP Taking (N=x)		P-value [Final Report Only]
Total number of SAEs				
SAE rate [1]			Rate Ratio (95% CI)[2]	P-value[2]
Avg. Number of SAEs per person				
Number (%) of Participants with at least one SAE			Difference (95% CI)[3]	P-value[4]

[1] The total number of follow-up weeks in STOP taking intervention arm is X and in KEEP taking intervention arm is X.
[2] Poisson regression is used to calculate the rate ratio, corresponding 95% CI and p-value. The ratio is STOP Taking / KEEP Taking.
[3] 95% confidence interval calculated using the Newcombe-Wilson method without continuity correction. The difference is STOP Taking – KEEP Taking.
[4] The p-value is obtained from the Fisher's exact test. Included in Final Report only.

Figure 4.1. Number of Serious Adverse Events per Participant by Intervention Arm (ITT population)

The number of serious adverse events per participant is displayed in the histogram below for each intervention arm. The numbers at the top of the bars indicate the number of participants that experienced the given number of serious adverse events.

Figure 4.2. Incidence of Serious Adverse Events by System Organ Class (ITT population)

The left panel shows the proportion of participants experiencing at least one SAE for each System Organ Class (SOC) by intervention arm. The right panel shows the difference in proportions including the 95% Newcombe-Wilson confidence interval (CI). The panels are sorted by the difference in proportions between intervention arms such that SOCs with SAEs occurring more frequently in the stop taking arm as compared to the keep taking arm are listed higher.

Table 4.2. Incidence of Serious Adverse Events (ITT population)

This table summarizes the incidence of all adverse events denoted as serious by the investigator. The rate of occurrence is equal to the number of events divided by the total number of follow-up weeks in each intervention arm. A more detailed description of each serious adverse event can be found in Listing 4.1.

	STOP Taking (N=x)				KEEP Taking (N=x)				
SYSTEM ORGAN CLASS	**Participants**		**Events**		**Participants**		**Events**		**Rate Ratio (95% CI)[2]**
Preferred Term	**n**	**%**	**n**	**Rate[1]**	**n**	**%**	**n**	**Rate[1]**	
SOC 1									Rate Ratio (95% CI)
Pref. Term 1									
Pref. Term 2									
...Pref. Term X									
SOC X									Rate Ratio (95% CI)
Pref. Term 1									
Pref. Term 2									
...Pref. Term X									

[1] The total number of follow-up weeks in STOP taking intervention arm is X and in KEEP taking intervention arm is X.
[2] 95% CI is calculated using Poisson regression. The ratio is STOP Taking / KEEP Taking.

Table 4.3. Serious Adverse Events by Relation to Intervention Arm (ITT population)

This table displays the incidence of all serious adverse events by relatedness to intervention arm. The rate of occurrence is equal to the number of events divided by the total number of follow-up weeks in each intervention arm.

	STOP Taking (N=x)				KEEP Taking (N=x)				Rate Ratio (95% CI)[2]
	Participants		Events		Participants		Events		
	n	%	n	Rate [1]	n	%	n	Rate [1]	
Unrelated									
Possibly									
Probably									
Definitely									

[1] The total number of follow-up weeks in STOP taking intervention arm is X and in KEEP taking intervention arm is X.
[2] 95% CI is calculated using Poisson regression. The ratio is STOP Taking / KEEP Taking.

Table 4.4. Serious Adverse Events by Severity Summary (ITT population)

This table displays the incidence of all serious adverse events by severity. The rate of occurrence is equal to the number of events divided by the total number of follow-up weeks in each intervention arm.

	STOP Taking (N=x)				STOP Taking (N=x)					
	Participants		Events		Participants		Events		Difference in proportions (95% CI)[2]	P-value[3] [Final Report Only]
	n	%	n	Rate [1]	n	%	n	Rate [1]		
Mild (Grade 1)										
Moderate (Grade 2)										
Severe (Grade 3)										
Life-Threatening (Grade 4)										
Death (Grade 5)										
≥ Severe (Grade 3)									Difference (95% CI)	P-value

[1] The total number of follow-up weeks in STOP taking intervention arm is X and in KEEP taking intervention arm is X.
[2] 95% CI calculated using the Newcombe-Wilson method without continuity correction. The difference is STOP Taking – KEEP Taking.
[3] The p-value is obtained from the Fisher's exact test. Included in Final Report only.

Table 4.5. Serious Adverse Events by Assigned Therapy Regimen Modification Summary (ITT population)

This table summarizes the proportion of participants changing their assigned therapy regimen (i.e., participants restarting hypertonic saline therapy in 'stop taking' arm and participants stopping hypertonic saline therapy in 'keep taking' arm) due to a serious adverse event (SAE). Also summarized are those that were physician directed to change their assigned therapy regimen.

	STOP Taking (N=x)	KEEP Taking (N=x)		P-value [Final Report Only]
Total number of SAEs				
Total number (%) of SAEs requiring modification				
Number (%) of Participants changing therapy regimen due to SAE			Difference (95% CI)[1]	P-value[2]
Total number (%) of SAEs requiring modification as directed by physician				
Number (%) of Participants changing therapy regimen as directed by physician due to SAE			Difference (95% CI)[1]	P-value[2]

[1] 95% confidence interval calculated using the Newcombe-Wilson method without continuity correction. The difference is STOP Taking – KEEP Taking.
[2] The p-value is obtained from the Fisher's exact test. Included in Final Report only.

Listing 4.1. SAE Narratives: Clinical Tracking Spreadsheet

Participant ID	Intervention Arm	Date of Randomization	Date of SAE	Date Site Learned of SAE	Date SAE Report Rec'd	Relationship to Intervention Arm	Expectedness	Narrative

Table 4.6. Adverse Event Overview (ITT population)

The total number of adverse events (AEs) is presented in this table. All events occurring from randomization (Visit 1) through the end of follow-up are included. The rate of occurrence is equal to the number of events divided by the total number of follow-up weeks in each intervention arm. This table includes both serious and non-serious adverse events.

	STOP Taking (N=x)	KEEP Taking (N=x)		P-value [Final Report Only]
Total number of AEs				
AE rate [1]			Rate Ratio (95% CI)[2]	P-value[2]
Avg. Number of AEs per person				
Number (%) of Participants with at least one AE			Difference (95% CI)[3]	P-value[4]

[1] The total number of follow-up weeks in STOP taking intervention arm is X and in KEEP taking intervention arm is X.
[2] Poisson regression is used to calculate the rate ratio, corresponding 95% CI and p-value. The ratio is STOP Taking / KEEP Taking.
[3] 95% confidence interval calculated using the Newcombe-Wilson method without continuity correction. The difference is STOP Taking – KEEP Taking.
[4] The p-value is obtained from the Fisher's exact test. Included in Final Report only.

Figure 4.3. Number of Adverse Events per Participant by Intervention Arm (ITT population)

The number of adverse events per participant is displayed in the histogram below for each intervention arm. The numbers at the top of the bars indicate the number of participants that experienced the given number of adverse events.

Figure 4.4. Incidence of Adverse Events by System Organ Class (ITT population)

The left panel shows the proportion of participants experiencing at least one AE for each System Organ Class (SOC) by intervention arm. The right panel shows the difference in proportions including the 95% Newcombe-Wilson confidence interval (CI). The panels are sorted by the difference in proportions between intervention arms such that SOCs with AEs occurring more frequently in the stop taking arm as compared to the keep taking arm are listed higher.

Table 4.7. Incidence of Adverse Events (ITT population)

This table summarizes the incidence of all adverse events by the investigator. The rate of occurrence is equal to the number of events divided by the total number of follow-up weeks in each intervention arm. This table includes both serious and non-serious adverse events.

	STOP Taking (N=x)				KEEP Taking (N=x)				
SYSTEM ORGAN CLASS	**Participants**		**Events**		**Participants**		**Events**		**Rate Ratio (95% CI)[2]**
Preferred Term	**n**	**%**	**n**	**Rate[1]**	**n**	**%**	**n**	**Rate[1]**	
SOC 1									Rate Ratio (95% CI)
Pref. Term 1									
Pref. Term 2									
...Pref. Term X									
SOC X									Rate Ratio (95% CI)
Pref. Term 1									
Pref. Term 2									
...Pref. Term X									

[1] The total number of follow-up weeks in STOP taking intervention arm is X and in KEEP taking intervention arm is X.
[2] 95% CI is calculated using Poisson regression. The ratio is STOP Taking / KEEP Taking.

Table 4.8. Adverse Events by Relation to Intervention Arm (ITT population)

This table displays the incidence of all adverse events by relatedness to intervention arm. The rate of occurrence is equal to the number of events divided by the total number of follow-up weeks in each intervention arm. This table includes both serious and non-serious adverse events.

	STOP Taking (N=x)				KEEP Taking (N=x)				Rate Ratio (95% CI)[2]
	Participants		Events		Participants		Events		
	N	%	n	Rate [1]	n	%	n	Rate [1]	
Unrelated									
Possibly									
Probably									
Definitely									

[1] The total number of follow-up weeks in STOP taking intervention arm is X and in KEEP taking intervention arm is X.
[2] 95% CI is calculated using Poisson regression. The ratio is STOP Taking / KEEP Taking.

Table 4.9. Adverse Events by Severity Summary (ITT population)

This table displays the incidence of all adverse events by severity. The rate of occurrence is equal to the number of events divided by the total number of follow-up weeks in each intervention arm. This table includes both serious and non-serious adverse events.

	STOP Taking (N=x)				KEEP Taking (N=x)				Difference in proportions (95% CI)[2]	P-value[3] [Final Report Only]
	Participants		Events		Participants		Events			
	n	%	n	Rate [1]	n	%	n	Rate [1]		
Mild (Grade 1)										
Moderate (Grade 2)										
Severe (Grade 3)										
Life-Threatening (Grade 4)										
Death (Grade 5)										
≥ Severe (Grade 3)									Difference (95% CI)	P-value

[1] The total number of follow-up weeks in STOP taking intervention arm is X and in KEEP taking intervention arm is X.
[2] 95% CI calculated using the Newcombe-Wilson method without continuity correction. The difference is STOP Taking – KEEP Taking.
[3] The p-value is obtained from the Fisher's exact test. Included in Final Report only.

Table 4.10. Adverse Events by Assigned Therapy Regimen Modification Summary (ITT population)

This table summarizes the proportion of participants changing their assigned therapy regimen (i.e., participants restarting hypertonic saline therapy in 'stop taking' arm and participants stopping hypertonic saline therapy in 'keep taking' arm) due to an adverse event (AE). Also summarized are those that that were physician directed to change their assigned therapy regimen.

	STOP Taking (N=x)	KEEP Taking (N=x)	Difference in proportions (95% CI)[1]	P-value [2][Final Report Only]
Total number of AEs				
Total number (%) of AEs requiring modification				
Number (%) of Participants changing therapy regimen due to AE			Difference (95% CI)	P-value
Total number (%) of AEs requiring modification as directed by physician				
Number (%) of Participants changing therapy regimen as directed by physician due to AE			Difference (95% CI)	P-value

[1] 95% confidence interval calculated using the Newcombe-Wilson method without continuity correction. The difference is STOP Taking – KEEP Taking.
[2] The p-value is obtained from the Fisher's exact test. Included in Final Report only.

Table 4.11. Respiratory Adverse Event Overview (ITT population)

The total number of adverse events within the respiratory, thoracic and mediastinal disorders system organ class (Respiratory AEs) is presented in this table overall and by FEV1 (% predicted) category at Week 0 (Visit 1). All events occurring from randomization (Visit 1) through the end of follow-up are included. This table includes both serious and non-serious adverse events within the respiratory, thoracic and mediastinal disorders system organ class.

	STOP Taking (N=x)	KEEP Taking (N=x)	
All Participants, n (%)			
Total follow-up (weeks)			
Total number of Respiratory AEs			
Respiratory AE rate [1]			Rate Ratio (95% CI) [2]
Avg. number of Respiratory AEs per person			
Number (%) of participants with at least one Respiratory AE			Prop. Diff (95% CI) [3]
FEV_1 (% predicted) <70%, n (%)			
Total follow-up (weeks)			

	STOP Taking (N=x)	KEEP Taking (N=x)	
Total number of Respiratory AEs			
Respiratory AE rate [1]			Rate Ratio (95% CI) [2]
Avg. number of Respiratory AEs per person			
Number (%) of participants with at least one Respiratory AE			Prop. Diff (95% CI) [3]
FEV_1 (% predicted) >=70 to <90%, n (%)			
Total follow-up (weeks)			
Total number of Respiratory AEs			
Respiratory AE rate [1]			Rate Ratio (95% CI) [2]
Avg. number of Respiratory AEs per person			
Number (%) of participants with at least one Respiratory AE			Prop. Diff (95% CI) [3]
FEV_1 (% predicted) >=90 to <100%, n (%)			
Total follow-up (weeks)			
Total number of Respiratory AEs			
Respiratory AE rate [1]			Rate Ratio (95% CI) [2]
Avg. number of Respiratory AEs per person			
Number (%) of participants with at least one Respiratory AE			Prop. Diff (95% CI) [3]
FEV_1 (% predicted) >=100%, n (%)			
Total follow-up (weeks)			
Total number of Respiratory AEs			
Respiratory AE rate [1]			Rate Ratio (95% CI) [2]
Avg. number of Respiratory AEs per person			
Number (%) of participants with at least one Respiratory AE			Prop. Diff (95% CI) [3]

[1] The rate of occurrence is equal to the number of events divided by the total number of follow-up weeks in each intervention arm for the corresponding FEV_1 (% predicted) subgroup.
[2] Poisson regression is used to calculate the rate ratio and corresponding 95% CI. The ratio is STOP Taking / KEEP Taking.
[3] 95% confidence interval calculated using the Newcombe-Wilson method without continuity correction. The difference is STOP Taking - KEEP Taking.

5 *Hospitalizations and Pulmonary Function Decline*

Table 5.1. Overview of Hospitalizations (ITT population)

This table presents the number of participants hospitalized, number of hospitalization events, and the number of days hospitalized between Week 0 (Visit 1) and the end of follow-up.

	STOP Taking (N=)	KEEP Taking (N=)	Total (N=)		P-value [Final Report only]
Hospitalizations Events					
Number of Hospitalization Events per Patient: N (%)					
At least one				Difference (95% CI) [2]	p-value [2]
0					
1					
2					
3					
Total Number of Hospital Events					
Mean number of Events/Participant Rate per Week [1]				Rate Ratio (95% CI) [3]	p-value [3]
Hospitalization Days					
Mean Number of Days Hospitalized per Patient (SD)				Rate Ratio (95% CI) [3]	p-value [3]
Median					
Min, Max					

[1] The rate per week is calculated as the total number of hospitalization events divided by the total weeks of follow up for each intervention arm. The total number of follow-up weeks in STOP taking intervention arm is X and in KEEP taking intervention arm is X.
[2] 95% confidence interval for the difference in proportions is calculated using the Newcombe-Wilson method without continuity correction. The p-value is obtained from the Fisher's exact test. The difference is STOP Taking – KEEP Taking.
[3] Poisson regression is used to calculate the rate ratio, corresponding 95% CI and p-value. The ratio is STOP Taking / KEEP Taking.

Table 5.2. Logistic Regression Model Results for Odds of Participant Hospitalization (ITT population)

This table summarizes the estimate (as odds ratio) comparing the proportion of participants hospitalized between intervention arms from Week 0 (Visit 1) to Week 6 (Visit 3) using a logistic regression model. Each participant is only counted once in the model (i.e., outcome is 1 if participant was hospitalized at least once between Week 0 and Week 6. Otherwise, outcome is 0). The models summarized are for an unadjusted model and one that adjusts for the randomization strata: (Week 0 FEV_1 % Predicted (≥90% or <90%), therapy combination at screening (single or concurrent use of hypertonic saline and/or dornase alfa), prior study enrollment (yes or no), and Week 0 age (≥18 years or < 18 years)).

Model Covariates	STOP Taking Proportion Estimate (N =)	KEEP Taking Proportion Estimate (N =)	Odds Ratio (95% CI)	P-value
Model Unadjusted				
Intervention Arm: STOP Taking hypertonic saline [1]				
Model Adjusted for Randomization Strata				
Intervention Arm: STOP Taking hypertonic saline [1]				
Randomization Strata:				
FEV_1 % Predicted ≥90% [2]				
On both HS and Dnase [3]				
Prior study enrollment [4]				
Age ≥18 years [5]				

[1] Compared to reference level, KEEP taking hypertonic saline.
[2] Compared to reference level,FEV_1 % Predicted < 90% at Week 0 (Visit 1).
[3] Compared to reference level,one therapy at Week -2 (Screening).
[4] Compared to reference level,no prior study enrollment.
[5] Compared to reference level,age <18 years at Week 0 (Visit 1).

Table 5.3. Summary of Pulmonary Function Decline (ITT population)

This table summarizes the proportion of randomized participants with a significant decline in FEV_1 % Predicted from Week 0 (Visit 1).

	STOP Taking (N=x)	KEEP Taking (N=x)	Difference (95% CI) [2]
Number of Participants With FEV_1 Measure Completed			
At Either Week 2 or Week 6, N			
At Week 2, N			
At Week 6, N			
≥ 5% Decline in FEV_1 % Predicted from Week 0 [1]			
Number of Participants at Week 2 or Week 6, n (%)			Difference (95% CI)
Number of Participants at Week 2, n (%)			Difference (95% CI)
Number of Participants at Week 6, n (%)			Difference (95% CI)
≥ 10% Decline in FEV_1 % Predicted from Week 0 [1]			
Number of Participants at Week 2 or Week 6, n (%)			Difference (95% CI)
Number of Participants at Week 2, n (%)			Difference (95% CI)
Number of Participants at Week 6, n (%)			Difference (95% CI)

[1] Percentages are based on number of participants with FEV_1 measure completed at the corresponding visit or visits.
Declines are absolute changes in FEV_1% predicted.
[2] 95% confidence interval for difference in proportions is calculated using the Newcombe-Wilson method without continuity correction. The difference is STOP Taking – KEEP Taking.

6 *Summary of Primary Endpoint – 6-week Change in FEV_1 % Predicted*

Table 6.1.a. Results from ANOVA Model for Change in FEV_1 (% Predicted) (PPA population; Final Report)

The primary endpoint, absolute change in FEV_1 (% predicted) from Week 0 (Visit 1) to Week 6 (Visit 3), is compared between intervention arms using Analysis of Variance adjusted for dichotomous randomization strata: Week 0 FEV_1, treatment combination at screening, prior study enrollment, and Week 0 age. An unadjusted estimate is also provided.

Model Covariates	STOP Taking Mean Estimate (N=)	KEEP Taking Mean Estimate (N=)	Δ FEV1 (% Predicted) Estimate (95% CI)	P-value [8]
Model Unadjusted				
Intervention Arm: STOP Taking hypertonic saline [1,2]				
Model Adjusted for Randomization Strata				
Intervention Arm: STOP Taking hypertonic saline [2,3]				
Randomization Strata:				
FEV_1 % Predicted ≥90% [4]				
On both HS and Dnase [5]				
Prior study enrollment [6]				
Age ≥18 years [7]				

[1] The overall unadjusted intervention arm difference (STOP Taking - KEEP Taking) is estimated using a two sample t-test.
[2] Compared to reference level, KEEP taking hypertonic saline.
[3] Least Squares Mean Estimates from model with weighting proportional to observed frequencies of randomization factor combinations in the data.
[4] Compared to reference level,FEV_1 % Predicted < 90% at Week 0 (Visit 1).
[5] Compared to reference level,one therapy at Week -2 (Screening).
[6] Compared to reference level,no prior study enrollment.
[7] Compared to reference level,age <18 years at Week 0 (Visit 1).
[8] One-sided test for non-inferiority

Table 6.1.b Interim Results for Change in FEV_1 (% Predicted) (ITT population Interim Report)

The primary endpoint, absolute change in FEV_1 (% predicted) from Visit 1 (Randomization) to Week 6 (Visit 3), is compared between treatment arms using Analysis of Variance adjusted for randomization strata. An unadjusted estimate is also provided.

		STOP Taking Mean Estimate (N=)	KEEP Taking Mean Estimate (N=)	Difference Unadjusted (95% CI) [1]	Difference Adjusted for Randomization Strata (95% CI) [2]	Excess Harm Boundary [3]	Alpha Spending (proportion)
Planned Analyses							
	Interim 1 (n =)						
	Interim 2 (n =)						
Conducted Interims							
	Interim 1 (n =)						
	Interim 2 (n =)						

[1] 95% confidence interval calculated using two-sample t-test. The difference is STOP Taking – KEEP Taking.
[2] Adjusted for randomization strata: On both HS and DA (vs. only DA) at screening, Age (≥18 vs. <18 years), Week 0 (Visit 1) FEV_1 % Predicted (≥90% vs. <90%), and prior study enrollment (yes vs. no).
[3] The boundary for harm is based on hypothesis tests evaluating whether the estimated difference between arms (STOP Taking – KEEP Taking) for the absolute change in FEV_1 (% predicted) is less than the pre-specified margin for harm (-1.5), assuming a common standard deviation of 8.4, a one-sided 0.025 alpha level, and a Pocock adjustment for group sequential monitoring at two planned analyses. Harm is detected if the point estimate for the adjusted difference is less than the corresponding Excess Harm Boundary.

Table 6.2. Sensitivity Analysis: Results from ANOVA Model for Change in FEV_1 (% Predicted) (ITT population; Final Report)

The primary endpoint, absolute change in FEV_1 (% predicted) from Week 0 (Visit 1) to Week 6 (Visit 3), is compared between intervention arms using Analysis of Variance adjusted for dichotomous randomization strata: Week 0 FEV_1% predicted, treatment combination at screening, prior study enrollment, and Week 0 age. An unadjusted estimate is also provided.

Model Covariates	STOP Taking Mean Estimate (N=)	KEEP Taking Mean Estimate (N=)	Δ FEV_1 (% Predicted) Estimate (95% CI)	P-value [9]
Complete Case	**(N=)**	**(N=)**		
Model Unadjusted				
Intervention Arm: STOP Taking hypertonic saline [1,2]				
Model Adjusted for Randomization Strata				
Intervention Arm: STOP Taking hypertonic saline [2,3]				
Randomization Strata:				
FEV_1 % Predicted ≥90% [4]				
On both HS and Dnase [5]				
Prior study enrollment [6]				
Age ≥18 years [7]				
Imputed Week 6 FEV_1 (% predicted) [8]	**(N=)**	**(N=)**		
Model Unadjusted				
Intervention Arm: STOP Taking hypertonic saline [1,2]				
Model Adjusted for Randomization Strata				
Intervention Arm: STOP Taking hypertonic saline [2,3]				
Randomization Strata:				
FEV_1 % Predicted ≥90% [4]				
On both HS and Dnase [5]				
Prior study enrollment [6]				
Age ≥18 years [7]				

[1] The overall unadjusted intervention arm difference (STOP Taking - KEEP Taking) is estimated using a two sample t-test.
[2] Compared to reference level, KEEP taking hypertonic saline.
[3] Least Squares Mean Estimates from regression model with weighting proportional to observed frequencies of randomization factor combinations in the data.
[4] Compared to reference level,FEV_1 % Predicted < 90% at Week 0 (Visit 1).
[5] Compared to reference level,one therapy at Week -2 (Screening).
[6] Compared to reference level,no prior study enrollment.
[7] Compared to reference level,age <18 years at Week 0 (Visit 1).
[8] Missing values are imputed using the least favorable treatment mean in arms discontinuing treatment and using most favorable treatment mean in arms continuing treatment.

[9] One-sided test for non-inferiority

Figure 6.1.a. Observed Treatment Effect Confidence Intervals in Relation to Non-inferiority Margin (Primary Analysis: PPA population; Sensitivity Analysis: ITT population; Final Report)

This figure displays the observed treatment effect along with corresponding 2-sided 95% confidence intervals. The dashed line at x=Δ indicates the non-inferiority margin; the tinted region indicates the zone of inferiority. Panel (a) shows results for PP population (unadjusted and adjusted for covariates) and panel (b) show results for ITT population (unadjusted and adjusted for covariates).

[1] Missing values are imputed using the least favorable treatment mean in arms discontinuing treatment and using most favorable treatment mean in arms continuing treatment. (Final report ITT)

Figure 6.1.b. Interim Analysis Boundary for Excess Harm (Interim Report)

This figure displays the observed treatment effect adjusted for randomization strata and corresponding 2-sided 95% confidence interval. The gray region indicates the zone of Excess Harm with interim boundaries. The boundaries for harm are based on hypothesis tests evaluating whether the estimated difference between arms (STOP Taking – KEEP Taking) for the absolute change in FEV_1 (% predicted) is significantly less than the Excess Harm Margin of -1.5 (dashed line), assuming a common standard deviation of 8.4, a one-sided 0.025 alpha level, and a Pocock adjustment for group sequential monitoring at two planned analyses. The statistical criteria for detecting Excess Harm is met if the observed treatment effect estimate falls within the gray region.

7 Summary of Spirometry Results

Figure 7.1. Mean FEV_1 (% Predicted) and Mean Absolute Change in FEV_1 (% Predicted) over Time (PPA and ITT population for Final Report, ITT for Interim Report)

The left column of figures display the mean FEV_1 (% Predicted) and the right column of figures display mean absolute change in FEV_1 (% Predicted) from Week 0 (Randomization) to each post-randomization visit for both intervention arms. 95% pointwise confidence intervals (using t-distribution approximation) are included at each time point. The number of participants at each time point is included in a legend below each figure. The top row corresponds to PPA population and the bottom row corresponds to ITT population.

Figure 7.2. Waterfall Plot of Absolute Changes in FEV_1 (% Predicted) (PPA population for Final Report, ITT for comprehensive Interim Report)
This figure displays absolute changes in FEV_1 (% Predicted) for subjects from Week 0 (Randomization) to Week 6 (Visit 3). Each bar represents one subject, colored by intervention arm and ordered by increasing absolute change.

Table 7.1. Summary of FEV_1 (% Predicted) Results (PPA and ITT population for Final Report, ITT for Interim Report)

This table summarizes the FEV_1 (% Predicted) results at Week -2 (Screening), Week 0 (Randomization), Week 2 (Visit 2), and Week 6 (Visit 3). Changes from are also given with reference visit as indicated (either Week -2 or Week 0). Relative change is calculated as 100 * (post visit value – reference value) / (reference value).

Visit	Statistic	STOP Taking (N=)	KEEP Taking (N=)	Difference (95% CI)[1]	P-value[1] [Final Report Only]
Week -2 (Screening)	N(%) Mean (SD) Median Min, Max				
Week 0 (Randomization)	N(%) Mean (SD) Median Min, Max				
Absolute Change (Week -2 to Week 0)	N(%) Mean (SD) Median Min, Max				
Relative Change (Week -2 to Week 0)	N(%) Mean (SD) Median Min, Max				
Week 2 (Visit 2)	N(%) Mean (SD) Median Min, Max				
Absolute Change (Week 0 to Week 2)	N(%) Mean (SD) Median Min, Max				
Relative Change (Week 0 to Week 2)	N(%) Mean (SD) Median Min, Max				
Difference in Absolute Changes (Week 0 to Week 2 minus Week -2 to Week 0)	N(%) Mean (SD) Median Min, Max				
Week 6 (Visit 3)	N(%) Mean (SD) Median Min, Max				

Absolute Change (Week 0 to Week 6) Relative Change (Week 0 to Week 6)	N(%) Mean (SD) Median Min, Max N(%) Mean (SD) Median Min, Max				

[1] 95% confidence interval and p-value are calculated using a two-sample t-test. The difference is STOP Taking – KEEP Taking.

Table 7.2. Summary of FEV_1 (% Predicted) Results by Subgroup (PPA and ITT populations for Final Report)

This table shows the observed treatment effect along with corresponding 2-sided 95% confidence intervals among various subgroups. The included subgroups are based on sex at birth, age at Week 0, FEV1 (% predicted) at Week 0, treatment combination at screening, prior study enrollment, genotype, Pa positive in prior year and concurrent use of airway clearance therapies.

		ITT		PPA	
Subgroup		N	**Δ FEV_1 (% Predicted) Estimate (95% CI) [1]**	N	**Δ FEV_1 (% Predicted) Estimate (95% CI) [1]**
Overall					
Sex					
	Female				
	Male				
Age					
	<18				
	>=18				
FEV_1 percent predicted					
	<90				
	>=90				
DA or HS use					
	HS and DA				
	HS or DA				
Prior Study Enrollee					
	Yes				
	No				
Genotype					
	F508del Homozygous				
	F508del Heterozygous				
PA in prior year					
	Yes				
	No				
Airway Clearance Therapy Use					
	Yes				
	No				

[1] The unadjusted intervention arm difference (STOP Taking - KEEP Taking) is estimated using a two sample t-test.

Figure 7.3. Summary of FEV_1 (% Predicted) Results by Subgroup (PPA and ITT populations for Final Report)

This figure displays the observed treatment effect along with corresponding 2-sided 95% confidence intervals among various subgroups. The included subgroups are based on sex at birth, age at Week 0, FEV1 (% predicted) at Week 0, treatment combination at screening, prior study enrollment, genotype, Pa positive in prior year and concurrent use of airway clearance therapies The line at x=-3 indicates the non-inferiority margin. Results are displayed for both the PPA population and ITT population.

Figure 7.4. Mean Relative Change in FEV_1 (Liters) over Time (PPA and ITT population for Final Report, ITT for Interim Report)

This figure displays the mean relative change in FEV_1 (Liters) from Visit 1 (Randomization) to each post-randomization visit for both intervention arms. 95% pointwise confidence intervals (using t-distribution approximation) are included at each time point. The number of participants at each time point is included in a legend below the figure.

Figure 7.5. Waterfall Plot of Relative Changes in FEV_1 (Liters) (PPA population for Final Report, ITT for comprehensive Interim Report)
This figure displays relative changes in FEV_1 (Liters) for subjects from Week 0 (Randomization) to Week 6 (Visit 3). Each bar represents one subject, colored by intervention arm and ordered by increasing relative change.

Table 7.3. Summary of FEV_1 (Liters) Results (PPA and ITT population for Final Report, ITT for Interim Report)

This table summarizes the FEV_1 (L) results at Week -2 (Screening), Week 0 (Randomization), Week 2 (Visit 2), and Week 6 (Visit 3). Changes from are also given with reference visit as indicated (either Week -2 or Week 0). Relative change is calculated as 100 * (post visit value – reference value) / (reference value)

Visit	Statistic	STOP Taking (N=)	KEEP Taking (N=)	Difference (95% CI)[1]	P-value[1] [Final Report only]
Week -2 (Screening)	N(%) Mean (SD) Median Min, Max				
Week 0 (Randomization)	N(%) Mean (SD) Median Min, Max				
Absolute Change (Week -2 to Week 0)	N(%) Mean (SD) Median Min, Max				
Relative Change (Week -2 to Week 0)	N(%) Mean (SD) Median Min, Max				
Week 2 (Visit 2)	N(%) Mean (SD) Median Min, Max				
Absolute Change (Week 0 to Week 2)	N(%) Mean (SD) Median Min, Max				
Relative Change (Week 0 to Week 2)	N(%) Mean (SD) Median Min, Max				
Difference in Absolute Changes (Week 0 to Week 2 minus Week -2 to Week 0)	N(%) Mean (SD) Median Min, Max				
Week 6 (Visit 3)	N(%) Mean (SD) Median Min, Max				

Absolute Change (Week 0 to Week 6)	N(%) Mean (SD) Median Min, Max				
Relative Change (Week 0 to Week 6)	N(%) Mean (SD) Median Min, Max				

[1] 95% confidence interval and p-value are calculated using a two-sample t-test. The difference is STOP Taking – KEEP Taking.

Table 7.4. Results from ANOVA Model for Change in FEV_1 (% Predicted) During the Run-In Period (PPA population Final Report Only)

Absolute change in FEV_1 (% Predicted) from Week -2 to Week 0, is compared between intervention arms using Analysis of Variance adjusted for dichotomous randomization strata: Week 0 FEV_1, treatment combination at screening, prior study enrollment, and Week 0 age. An unadjusted estimate is also provided.

Model Covariates	STOP Taking Mean Estimate (N=)	KEEP Taking Mean Estimate (N=)	Δ FEV_1 (% Predicted) Estimate (95% CI)	P-value [8]
Model Unadjusted				
Intervention Arm: STOP Taking hypertonic saline [1,2]				
Model Adjusted for Randomization Strata				
Intervention Arm: STOP Taking hypertonic saline [2,3]				
Randomization Strata:				
FEV_1 % Predicted ≥90% [4]				
On both HS and Dnase [5]				
Prior study enrollment [6]				
Age ≥18 years [7]				

[1] The overall unadjusted intervention arm difference (STOP Taking - Keep Taking) is estimated using a two sample t-test.
[2] Compared to reference level, KEEP taking hypertonic saline.
[3] Least Square Means Estimates from model.
[4] Compared to reference level,FEV_1 % Predicted < 90% at Week 0 (Visit 1).
[5] Compared to reference level,one therapy at Week -2 (Screening).
[6] Compared to reference level,no prior study enrollment.
[7] Compared to reference level,age <18 years at Week 0 (Visit 1).
[8] Two-sided test of null hypothesis of no difference

8 Exacerbation and Concomitant Medication Parameters

Table 8.1. Distribution of Antibiotic Use and Protocol-Defined Pulmonary Exacerbations (ITT population)

This table displays the distribution of protocol-defined pulmonary exacerbations (PEx) experienced by the participants from Week 0 (Visit 1) to Week 6 (Visit 3).

	STOP Taking (N=)	KEEP Taking (N=)	Difference (95% CI)	p-value [Final Report Only[
Total Number of Pulmonary Exacerbations [1] Rate of PEx per week of follow-up [2] Average number of PEx per participant			Rate Ratio (95% CI) [5]	p-value[5]
Distribution of Exacerbations, n (%) [1] 0 1 2				
Total no. patients with at least one Pulmonary Exacerbation, n (%)			Difference (95% CI) [6]	p-value[7]
Requiring IV Abx, n (%) [3]				
Requiring Oral Abx, n (%) [3, 4]				
Requiring Inhaled Abx, n (%) [3]				
Requiring Hospitalization, n (%) [3]				

[1] Protocol-Defined PEx. Exacerbations are counted as unique if their first prescription dates occur greater than 20 days apart. Protocol-defined PEx is determined by using Fuchs criteria]: clinical need for antibiotics as indicated by presence of at least 4 of 12 possible signs or symptoms listed below:
- Change in sputum volume or color
- New or increased hemoptysis
- Increased cough
- Increased dyspnea
- Increased malaise, fatigue or lethargy
- Temperature over 38°C
- Anorexia or weight loss
- Sinus pain or tenderness
- Change in sinus discharge
- Change in physical findings on examination of the chest
- Decrease in pulmonary function by 10% or more
- Radiographic changes.

[2] The total number of follow-up weeks in the STOP Taking group is X and in the KEEP Taking group is X.
[3] Percentages are based on total number of patients with at least one pulmonary exacerbation.
[4] Includes g-tube.

[5] Quasi-Poisson regression is used to calculate the rate ratio, 95% CI and corresponding p-values. The ratio is STOP Taking / KEEP Taking.
[6] The 95% confidence interval for difference in proportions is calculated using the Newcombe-Wilson method without continuity correction. The difference is STOP Taking – KEEP Taking.
[7] The p-value is based on the Fisher Exact test. Included in Final Report only.

Table 8.2. Distribution of Physician Identified Pulmonary Exacerbations (ITT population)

This table displays the distribution of physician identified pulmonary exacerbations (PEx) experienced by the participants from Week 0 (Visit 1) to Week 6 (visit 3).

	STOP Taking (N=)	KEEP Taking (N=)	Difference (95% CI)	p-value
Total Number of Pulmonary Exacerbations [1] Rate of PEx per week of follow-up [2] Average number of PEx per participant			Rate Ratio (95% CI) [5]	p-value[5]
Distribution of Exacerbations, n (%) [1] 0 1 2				
Total no. patients with at least one Pulmonary Exacerbation, n (%)			Difference (95% CI) [6]	p-value[7]
Requiring IV Abx, n (%) [3]				
Requiring Oral Abx, n (%) [3, 4]				
Requiring Inhaled Abx, n (%) [3]				
Requiring Hospitalization, n (%) [3]				

[1] Physician identified. Exacerbations are counted as unique if their first prescription dates occur greater than 20 days apart.
[2] The total number of follow-up weeks in the STOP Taking group is X and in the KEEP Taking group is X.
[3] Percentages are based on total number of patients with at least one pulmonary exacerbation.
[4] Includes g-tube.
[5] Quasi-Poisson regression is used to calculate the rate ratio, 95% CI and corresponding p-values. The ratio is STOP Taking / KEEP Taking.
[6] The 95% confidence interval for difference in proportions is calculated using the Newcombe-Wilson method without continuity correction. The difference is STOP Taking – KEEP Taking.
[7] The p-value is based on the Fisher Exact test. Included in Final Report only.

Table 8.3. Frequency of Signs and Symptoms for a Protocol-Defined Pulmonary Exacerbation (ITT population)

This table summarizes the frequency of signs and symptoms for protocol-defined pulmonary exacerbations (PEx) for each treatment group and overall.

	STOP Taking (N=)	KEEP Taking (N=)	Total (N=)
Total Number of PEx, N			
Signs and Symptoms, n (%) [1]			
Change in sputum volume or color			
New or increased hemoptysis			
Increased cough			
Increased dyspnea			
Increased malaise, fatigue or lethargy			
Temperature over 38°C (equivalent to approximately 100.4°F)			
Anorexia or weight loss			
Sinus pain or tenderness			
Change in sinus discharge			
Change in physical findings on examination of the chest			
Decrease in pulmonary function by 10% or more			
Radiographic changes			

[1] The n's correspond to the number of protocol-defined PEx checked 'yes' to having the specified sign and symptom. The denominator for the percentages is based on the total number of protocol-defined PEx for each treatment group.

Table 8.4. Logistic Regression Model Results for Odds of Participants Initiating Acute Antibiotics (ITT population)

This table summarizes the estimate (as odds ratio) comparing the proportion of participants initiating acute antibiotics (routes oral/GI-tube, inhaled, or IV) for respiratory indications between intervention arms from Week 0 (Visit 1) to Week 6 (Visit 3) using a logistic regression model. Each participant is only counted once in the model (i.e., outcome is 1 if participant initiated acute antibiotics between Week 0 and Week 6. Otherwise, outcome is 0). The models summarized are for an unadjusted model and one that adjusts for the randomization strata: Week 0 FEV_1 % Predicted (≥90% or <90%), therapy combination at screening (single or concurrent use of hypertonic saline and/or dornase alfa), prior study enrollment (yes or no), and Week 0 age (≥18 years or < 18 years).

Coefficients		STOP Taking Proportion Estimate (N =)	KEEP Taking Proportion Estimate (N =)	Odds Ratio (95% CI)	P-value
Model Unadjusted					
Intervention Arm:	STOP Taking hypertonic saline [1]				
Model Adjusted for Randomization Strata					
Intervention Arm:					
	STOP Taking hypertonic saline [1]				
Randomization Strata:					
	FEV_1 % Predicted ≥90% [2]				
	On both HS and Dnase [3]				
	Prior study enrollment [4]				
	Age ≥18 years [5]				

[1] Compared to reference level, KEEP taking hypertonic saline.
[2] Compared to reference level,FEV_1 % Predicted < 90% at Week 0 (Visit 1).
[3] Compared to reference level,one therapy at Week -2 (Screening).
[4] Compared to reference level,no prior study enrollment.
[5] Compared to reference level,age <18 years at Week 0 (Visit 1).

Table 8.5. Logistic Regression Model Results for Odds of Participant Experiencing Pulmonary Exacerbations (ITT population; Final Report)

This table summarizes the estimate (as odds ratio) comparing the proportion of participants experiencing at least one protocol-defined pulmonary exacerbation (PEx) between intervention arms from Week 0 (Visit 1) to Week 6 (Visit 3) using a logistic regression model. Each participant is only counted once in the model (i.e., outcome is 1 if participant experienced at least one protocol-defined PEx between Week 0 and Week 6. Otherwise, outcome is 0). The models summarized are for an unadjusted model and one that adjusts for the randomization strata: (Week 0 FEV_1 % Predicted (≥90% or <90%), therapy combination at screening (single or concurrent use of hypertonic saline and/or dornase alfa), prior study participation (yes or no), and age (≥18 years or < 18 years)).

Coefficients	STOP Taking Proportion Estimate (N =)	KEEP Taking Proportion Estimate (N =)	Odds Ratio (95% CI)	P-value
Model Unadjusted				
Intervention Arm: STOP Taking hypertonic saline [1]				
Model Adjusted for Randomization Strata				
Intervention Arm: STOP Taking hypertonic saline [1]				
Randomization Strata:				
FEV_1 % Predicted ≥90% [2]				
On both HS and Dnase [3]				
Prior study enrollment [4]				
Age ≥18 years [5]				

[1] Compared to reference level, KEEP taking hypertonic saline.
[2] Compared to reference level,FEV_1 % Predicted < 90% at Week 0.
[3] Compared to reference level,one therapy at Screening.
[4] Compared to reference level,no prior study enrollment.
[5] Compared to reference level,age <18 years at Week 0.

9 Summary of CRISS and CFQ-R Scores

Figure 9.1. Change in CRISS Score over Time (PPA and ITT population for Final Report; ITT for Interim)

This figure displays the mean absolute change in CRISS score from Week 0 (Visit 1) to each post-randomization visit for both intervention arms. 95% pointwise confidence intervals (using t-distribution approximation) are included at each time point. The number of participants at each time point is included in a legend below the figure. The Chronic Respiratory Infection Symptom Score (CRISS) is derived from a set of questions asking a participant to state the extent of their 8 respiratory symptoms: difficulty breathing, feverishness, tiredness, chills or sweats, cough, coughing up mucus, tightness in the chest, and wheezing. If a symptom is present, the possible answers include “a little”, “somewhat”, “a good deal”, “a great deal”, or “slightly”, “moderately”, “very”, “extremely”. Each respiratory symptom is assigned a score from 0-4 based on the response (0 in the absence of symptom). For each participant, a summed score is then calculated, ranging from 0 to 24. In turn, this score is converted to a 0 to 100 scale. The figure only includes participants who responded to at least 7 questions. A dashed line is also shown to indicate the minimal clinically important difference (MCID) of 11[1].

[1] Goss CH, Caldwell E, Gries KS, Leidy NK, Edwards T, Flume PA, et al. Validation of a novel patient-reported respiratory symptoms instrument in cystic fibrosis CFRSD-CRISS. [abstract]. Pediatr Pulmonol 2013;48(A251):295–296

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Table 9.1. Summary of CRISS Score (PPA and ITT population for Final Report; ITT for Comprehensive Interim)

The following table summarizes, by intervention arm, respiratory symptom severity score at Screening, Week 0 (Visit 1), Week 2 (Visit 2), and Week 6 (Visit 3). Absolute change from Screening to Week 0 and absolute changes from Week 0 for both post-randomization visits are also given. The Chronic Respiratory Infection Symptom Score (CRISS) is derived from a set of questions asking a participant to state the extent of their 8 respiratory symptoms: difficulty breathing, feverishness, tiredness, chills or sweats, cough, coughing up mucus, tightness in the chest, and wheezing. If a symptom is present, the possible answers include “a little”, “somewhat”, “a good deal”, “a great deal”, or “slightly”, “moderately”, “very”, “extremely”. Each respiratory symptom is assigned a score from 0-4 based on the response (0 in the absence of symptom). For each participant, a summed score is then calculated, ranging from 0 to 24. In turn, this score is converted to a 0 to 100 scale. The table only includes participants who responded to at least 7 questions.

Visit		STOP Taking (N=)	KEEP Taking (N=)	Difference (95% CI); P-value [1]
Week -2 (Screening)				
	N (%)			
	Mean (SD)			
	Median			
	Min, Max			
Week 0 (Visit 1/Randomization)				
	N (%)			
	Mean (SD)			
	Median			
	Min, Max			
Absolute Change (Week -2 to Week 0)				
	N (%)			
	Mean (SD)			
	Median			
	Min, Max			
Week 2 (Visit 2)				

Visit		STOP Taking (N=)	KEEP Taking (N=)	Difference (95% CI); P-value [1]
	N (%)			
	Mean (SD)			
	Median			
	Min, Max			
Absolute Change (Week 0 to Week 2)				
	N (%)			
	Mean (SD)			
	Median			
	Min, Max			
Difference in Absolute Changes (Week 0 to Week 2 minus Week -2 to Week 0)				
	N (%)			
	Mean (SD)			
	Median			
	Min, Max			
Week 6 (Visit 3)				
	N (%)			
	Mean (SD)			
	Median			
	Min, Max			
Absolute Change (Week 0 to Week 6)				
	N			
	Mean (SD)			
	Median			
	Min, Max			

[1] 95% confidence interval and p-value are calculated using a two-sample t-test. The difference is STOP Taking – KEEP Taking.

Table 9.2. Results from ANOVA Model for Change in CRISS Score (PPA and ITT population for Final Report)

The following table summarizes the estimate for the difference in the change in CRISS score between intervention arms from Week 0 (Visit 1) to Week 6 (Visit 3) using an Analysis of Variance model. The models summarized are for an unadjusted model and one that adjusts for the randomization strata: Week 0 FEV_1 % Predicted (≥90% or <90%), therapy combination at screening (single or concurrent use of hypertonic saline and/or dornase alfa), prior study enrollment (yes or no), and Week 0age (≥18 years or < 18 years).

Model Covariates	STOP Taking Mean Estimate	KEEP Taking Mean Estimate	Difference (95% CI)	P-value [9]
Per Protocol Analysis Population	**(N=)**	**(N=)**		
Model Unadjusted				
Intervention Arm: STOP Taking hypertonic saline [1, 2]				
Model Adjusted for Randomization Strata				
Intervention Arm: STOP Taking hypertonic saline [2, 3]				
Randomization Strata:				
FEV_1 % Predicted ≥90% [4]				
On both HS and Dnase [5]				
Prior study enrollment [6]				
Age ≥18 years [7]				
Intent to Treat Population [8]	**(N=)**	**(N=)**		
Model Unadjusted				
Intervention Arm: STOP Taking hypertonic saline [1, 2]				
Model Adjusted for Randomization Strata				
Intervention Arm: STOP Taking hypertonic saline [2, 3]				
Randomization Strata:				
FEV_1 % Predicted ≥90% [4]				
On both HS and Dnase [5]				
Prior study enrollment [6]				
Age ≥18 years [7]				

[1] The overall unadjusted intervention arm difference (STOP Taking - KEEP Taking) is estimated using a twosample t-test.
[2]Compared to reference level, KEEP taking hypertonic saline.
[3] Least Squares Mean Estimates from model with weighting proportional to observed frequencies of randomization factor combinations in the data.
[4] Compared to reference level, FEV_1 % Predicted < 90% at Week 0 (Visit 1).
[5] Compared to reference level, one therapy at Week -2 (Screening).
[6] Compared to reference level, no prior study enrollment.
[7] Compared to reference level, age <18 years at Week 0 (Visit 1).

[8] Missing values are imputed using the least favorable treatment mean in arms discontinuing treatment and using most favorable treatment mean in arms continuing treatment.
[9] Two-sided p-value.

Figure 9.2. Change in CFQ-R Respiratory Domain Scaled Score over Time (PPA and ITT population for Final Report)

This figure displays the mean absolute change in CFQ-R respiratory domain scaled score (%) from Week 0 (Visit 1) to each post-randomization visit for both intervention arms. 95% pointwise confidence intervals (using t-distribution approximation) are included at each time point. The number of participants at each time point is included in a legend below the figure. The Cystic Fibrosis Questionnaire-REVISED (adolescents and adults' version) asks a participant six questions related to respiratory symptoms. The respiratory domain scaled score is calculated as follows: 100*([{sum of responses}/{number of responses}]-1)*3 only if {number of responses} ≥ 3; otherwise the score is set to missing. A dashed line indicates the minimal clinically important difference (MCID) of 4[1].

[1] Note that the MCID was determined based on a clinically stable cystic fibrosis population positive for Pseudomonas aeruginosa airway infection. Reference: Quittner, Alexandra L et al. "Determination of the minimal clinically important difference scores for the Cystic Fibrosis Questionnaire-Revised respiratory symptom scale in two populations of patients with cystic fibrosis and chronic Pseudomonas aeruginosa airway infection." Chest vol. 135,6 (2009): 1610-1618. doi:10.1378/chest.08-1190.

Table 9.3. Summary of CFQ-R Respiratory Domain Scaled Score (PPA and ITT population for Final Report)

The following table summarizes, by intervention arm, CFQ-R respiratory domain scaled score (%) at Screening, Week 0 (Visit 1), Week 2(Visit 2), and Week 6 (Visit 3). Absolute change from Screening to Week 0 and absolute changes from Week 0 for both post-randomization visits are also given. The Cystic Fibrosis Questionnaire-REVISED (adolescents and adults' version) asks a participant six questions related to respiratory symptoms. The respiratory domain scaled score is calculated as follows: 100*([{sum of responses}/{number of responses}]-1)*3 only if {number of responses} ≥ 3; otherwise the score is set to missing.

Visit		STOP Taking (N=)	KEEP Taking (N=)	Difference (95% CI); P-value [1]
Week -2 (Screening)				
	N (%)			
	Mean (SD)			
	Median			
	Min, Max			
Week 0 (Visit 1/Randomization)				
	N (%)			
	Mean (SD)			
	Median			
	Min, Max			
Absolute Change (Week -2 to Week 0)				
	N (%)			
	Mean (SD)			
	Median			
	Min, Max			
Week 2 (Visit 2)				
	N (%)			
	Mean (SD)			
	Median			
	Min, Max			
Absolute Change (Week 0 to Week 2)				
	N (%)			
	Mean (SD)			
	Median			
	Min, Max			
Difference in Absolute Changes (Week 0 to Week 2 minus Week -2 to Week 0)				
	N (%)			
	Mean (SD)			
	Median			
	Min, Max			
Week 6 (Visit 3)				
	N (%)			
	Mean (SD)			
	Median			
	Min, Max			
Absolute Change (Week 0 to Week 6)				

Visit		STOP Taking (N=)	KEEP Taking (N=)	Difference (95% CI); P-value [1]
	N			
	Mean (SD)			
	Median			
	Min, Max			

[1] 95% confidence interval and p-value are calculated using a two-sample t-test. The difference is STOP Taking – KEEP Taking.

Table 9.4. Results from ANOVA Model for Change in CFQ-R Respiratory Domain Scaled Score (PPA and ITT population for Final Report)

The following table summarizes the estimate for the difference in the change in CFQ-R respiratory domain scaled score (%) between intervention arms from Week 0 (Visit 1) to Week 6 (Visit 3) using an Analysis of Variance model. The models summarized are for an unadjusted model and one that adjusts for the randomization strata: Week 0 FEV_1 % Predicted (≥90% or <90%), therapy combination at screening (single or concurrent use of hypertonic saline and/or dornase alfa), prior study enrollment (yes or no), and Week 0 age (≥18 years or < 18 years).

Model Covariates	STOP Taking Mean Estimate	KEEP Taking Mean Estimate	Difference (95% CI)	P-value [9]
Per Protocol Analysis Population	**(N=)**	**(N=)**		
Model Unadjusted				
Intervention Arm: STOP Taking hypertonic saline [1, 2]				
Model Adjusted for Randomization Strata				
Intervention Arm: STOP Taking hypertonic saline [2, 3]				
Randomization Strata:				
FEV_1 % Predicted ≥90% [4]				
On both HS and Dnase [5]				
Prior study enrollment [6]				
Age ≥18 years [7]				
Intent to Treat Population [8]	**(N=)**	**(N=)**		
Model Unadjusted				
Intervention Arm: STOP Taking hypertonic saline [1, 2]				
Model Adjusted for Randomization Strata				
Intervention Arm: STOP Taking hypertonic saline [2, 3]				
Randomization Strata:				
FEV_1 % Predicted ≥90% [4]				
On both HS and Dnase [5]				
Prior study enrollment [6]				
Age ≥18 years [7]				

[1] The overall unadjusted intervention arm difference (STOP Taking - KEEP Taking) is estimated using a twosample t-test.
[2] Compared to reference level, KEEP taking hypertonic saline.
[3] Least Squares Mean Estimates from model with weighting proportional to observed frequencies of randomization factor combinations in the data.
[4] Compared to reference level, FEV_1 % Predicted < 90% at Week 0 (Visit 1).
[5] Compared to reference level, one therapy at Week -2 (Screening).
[6] Compared to reference level, no prior study enrollment.

[7] Compared to reference level, age <18 years at Week 0 (Visit 1).
[8] Missing values are imputed using the least favorable treatment mean in arms discontinuing treatment and using most favorable treatment mean in arms continuing treatment.
[9] Two-sided p-value.

Figure 9.3. Change in CFQ-R Treatment Burden Domain Scaled Score over Time (PPA and ITT population for Final Report)

This figure displays the mean absolute change in CFQ-R treatment burden domain scaled score (%) from Week 0 (Visit 1) to each post-randomization visit for both intervention arms. 95% pointwise confidence intervals (using t-distribution approximation) are included at each time point. The number of participants at each time point is included in a legend below the figure. The Cystic Fibrosis Questionnaire-REVISED (adolescents and adults' version) asks a participant three questions related to treatment burden. The treatment burden domain scaled score is calculated as follows: 100*([{sum of responses}/{number of responses}]-1)*3 only if {number of responses} ≥ 2; otherwise the score is set to missing.

Table 9.5. Summary of CFQ-R Treatment Burden Domain Scaled Score (PPA and ITT population for Final Report)

The following table summarizes, by intervention arm, CFQ-R treatment burden domain scaled score (%) at Screening, Week 0 (Visit 1), Week 2 (Visit 2), and Week 6 (Visit 3). Absolute change from Screening to Week 0 and absolute changes from Week 0 for both post-randomization visits are also given. The Cystic Fibrosis Questionnaire-REVISED (adolescents and adults' version) asks a participant three questions related to treatment burden. The treatment burden domain scaled score is calculated as follows: 100*([{sum of responses}/{number of responses}]-1)*3 only if {number of responses} ≥ 2; otherwise the score is set to missing.

Visit		STOP Taking (N=)	KEEP Taking (N=)	Difference (95% CI); P-value [1]
Week -2 (Screening)				
	N (%)			
	Mean (SD)			
	Median			
	Min, Max			
Week 0 (Visit 1/Randomization)				
	N (%)			
	Mean (SD)			
	Median			
	Min, Max			
Absolute Change (Week -2 to Week 0)				
	N (%)			
	Mean (SD)			
	Median			
	Min, Max			
Week 2 (Visit 2)				
	N (%)			
	Mean (SD)			
	Median			
	Min, Max			
Absolute Change (Week 0 to Week 2)				
	N (%)			
	Mean (SD)			
	Median			
	Min, Max			
Difference in Absolute Changes (Week 0 to Week 2 minus Week -2 to Week 0)				
	N (%)			
	Mean (SD)			
	Median			
	Min, Max			
Week 6 (Visit 3)				
	N (%)			
	Mean (SD)			
	Median			
	Min, Max			
Absolute Change (Week 0 to Week 6)				

Visit		STOP Taking (N=)	KEEP Taking (N=)	Difference (95% CI); P-value [1]
	N			
	Mean (SD)			
	Median			
	Min, Max			

[1] 95% confidence interval and p-value are calculated using a two-sample t-test. The difference is STOP Taking – KEEP Taking.

Table 9.6. Results from ANOVA Model for Change in Treatment Burden Scaled Score (PPA and ITT population for Final Report)

The following table summarizes the estimate for the difference in the change in CFQ-R treatment burden domain scaled score (%) between intervention arms from Week 0 (Visit 1) to Week 6 (Visit 3) using an Analysis of Variance model. The models summarized are for an unadjusted model and one that adjusts for the randomization strata: Week 0 FEV_1 % Predicted (≥90% or <90%), therapy combination at screening (single or concurrent use of hypertonic saline and/or dornase alfa), prior study enrollment (yes or no), and Week 0 age (≥18 years or < 18 years). Only participants with a Week 0 CFQ-R treatment burden domain scaled score are included in this model.

Model Covariates	STOP Taking Mean Estimate	KEEP Taking Mean Estimate	Difference (95% CI)	P-value [9]
Per Protocol Analysis Population	**(N=)**	**(N=)**		
Model Unadjusted				
Intervention Arm: STOP Taking hypertonic saline [1, 2]				
Model Adjusted for Randomization Strata				
Intervention Arm: STOP Taking hypertonic saline [2, 3]				
Randomization Strata:				
FEV_1 % Predicted ≥90% [4]				
On both HS and Dnase [5]				
Prior study enrollment [6]				
Age ≥18 years [7]				
Intent to Treat Population [8]	**(N=)**	**(N=)**		
Model Unadjusted				
Intervention Arm: STOP Taking hypertonic saline [1, 2]				
Model Adjusted for Randomization Strata				
Intervention Arm: STOP Taking hypertonic saline [2, 3]				
Randomization Strata:				
FEV_1 % Predicted ≥90% [4]				
On both HS and Dnase [5]				
Prior study enrollment [6]				
Age ≥18 years [7]				

[1] The overall unadjusted intervention arm difference (STOP Taking - KEEP Taking) is estimated using a twosample t-test.
[2] Compared to reference level, KEEP taking hypertonic saline.
[3] Least Squares Mean Estimates from model with weighting proportional to observed frequencies of randomization factor combinations in the data.
[4] Compared to reference level, FEV_1 % Predicted < 90% at Week 0 (Visit 1).
[5] Compared to reference level, one therapy at Week -2 (Screening).
[6] Compared to reference level, no prior study enrollment.

[7] Compared to reference level, age <18 years at Week 0 (Visit 1).
[8] Missing values are imputed using the least favorable treatment mean in arms discontinuing treatment and using most favorable treatment mean in arms continuing treatment.
[9] Two-sided p-value.

Figure 9.4. Distribution of Impact of Changing Daily Therapies Scores (PPA and ITT population for Final Report)

This figure displays the distribution of participant responses to the Impact of Changing Daily Therapies questionnaire at Week 6 (Visit 3) for both intervention arms. The Impact of Changing Daily Therapies questionnaire asks a single question: "If you and your doctor agree in the future it is ok to stop one of these medications (hypertonic saline or dornase alfa), how would this impact your daily life?" The numbers at the top of the bars indicate the number of participants with the given response.

Table 9.7. Summary of Impact of Changing Daily Therapies Scores (PPA and ITT population for Final Report)

The following table summarizes, by intervention arm, Impact of Changing Daily Therapies score at Week 6 (Visit 3). The Impact of Changing Daily Therapies questionnaire asks a single question: "If you and your doctor agree in the future it is ok to stop one of these medications (hypertonic saline or dornase alfa), how would this impact your daily life?" Responses are mapped to numeric scores as follows: "Significantly positive impact" = 3, "Moderately positive impact" = 2, "Minimally positive impact" = 1, "No impact" = 0, "Minimally negative impact" = -1, "Moderately negative impact" = -2, "Significantly negative impact" = -3.

Visit		STOP Taking (N=)	KEEP Taking (N=)	Difference (95% CI); P-value [1]
Week 6 (Visit 3)				
	N (%)			
	Mean (SD)			
	Median			
	Min, Max			

[1] 95% confidence interval and p-value are calculated using a two-sample t-test. The difference is STOP Taking – KEEP Taking.

10 Summary of Anthropometric Measures

Figure 10.1. Change in Weight Percentile over Time for Participants Age < 18 years (PPA and ITT population for Final Report)

This figure displays the mean absolute change in weight percentile from Week 0 (Visit 1) to each post-randomization visit for both intervention arms. 95% pointwise confidence intervals (using t-distribution approximation) are included at each time point. The number of participants at each time point is included in a legend below the figure.

Table 10.1. Summary of Weight Percentile for Participants Age < 18 years (PPA and ITT population for Final Report)

The following table summarizes, by intervention arm, weight percentile at Screening, Week 0 (Visit 1), Week 2 (Visit 2), and Week 6 (Visit 3). Absolute change from Screening to Week 0 and absolute changes from Week 0 for both post-randomization visits are also given.
[see Table 10.2 shell below]

Figure 10.2. Change in Weight (kg) over Time for Participants Age ≥ 18 years (PPA and ITT population for Final Report)

This figure displays the mean absolute change in weight (kg) from Week 0 (Visit 1) to each post-randomization visit for both intervention arms. 95% pointwise confidence intervals (using t-distribution approximation) are included at each time point. The number of participants at each time point is included in a legend below the figure.

Table 10.2. Summary of Weight (kg) for Participants Age ≥ 18 years (PPA and ITT population for Final Report)

The following table summarizes, by intervention arm, weight (kg) at Screening, Week 0 (Visit 1), Week 2 (Visit 2), and Week 6 (Visit 3). Absolute change from Screening to Week 0 and absolute changes from Week 0 for both post-randomization visits are also given.

Visit		STOP Taking (N=)	KEEP Taking (N=)	Difference (95% CI); P-value [1]
Week -2 (Screening)				
	N (%)			
	Mean (SD)			
	Median			
	Min, Max			
Week 0 (Visit 1/Randomization)				
	N (%)			
	Mean (SD)			
	Median			
	Min, Max			
Absolute Change (Week -2 to Week 0)				
	N (%)			
	Mean (SD)			
	Median			
	Min, Max			
Week 2 (Visit 2)				
	N (%)			
	Mean (SD)			
	Median			
	Min, Max			
Absolute Change (Week 0 to Week 2)				
	N (%)			
	Mean (SD)			
	Median			
	Min, Max			
Difference in Absolute Changes (Week 0 to Week 2 minus Week -2 to Week 0)				
	N (%)			
	Mean (SD)			
	Median			
	Min, Max			
Week 6 (Visit 3)				
	N (%)			
	Mean (SD)			
	Median			
	Min, Max			
Absolute Change (Week 0 to Week 6)				
	N			
	Mean (SD)			

Visit		STOP Taking (N=)	KEEP Taking (N=)	Difference (95% CI); P-value [1]
	Median Min, Max			

[1] 95% confidence interval and p-value are calculated using a two-sample t-test. The difference is STOP Taking – KEEP Taking.

Figure 10.3 Change in BMI Percentile over Time for Participants < 18 years (PPA and ITT population for Final Report)

This figure displays the mean absolute change in BMI percentile from Week 0 (Visit 1) to each post-randomization visit for both intervention arms. 95% pointwise confidence intervals (using t-distribution approximation) are included at each time point. The number of participants at each time point is included in a legend below the figure.

Table 10.3 Summary of BMI Percentile for Participants Age < 18 years (PPA and ITT population for Final Report)

The following table summarizes, by intervention arm, BMI percentile at Screening, Week 0 (Visit 1), Week 2 (Visit 2), and Week 6 (Visit 3). Absolute change from Screening to Week 0 and absolute changes from Week 0 for both post-randomization visits are also given.
[see Table 10.4 shell below]

Figure 10.4. Change in BMI (kg/m^2) over Time for Participants Age ≥ 18 years (PPA and ITT population for Final Report)

This figure displays the mean absolute change in BMI (kg/m^2) from Week 0 (Visit 1) to each post-randomization visit for both intervention arms. 95% pointwise confidence intervals (using t-distribution approximation) are included at each time point. The number of participants at each time point is included in a legend below the figure.

Table 10.4. Summary of BMI (kg/m^2) for Participants Age ≥ 18 years (PPA and ITT population for Final Report)

The following table summarizes, by intervention arm, BMI (kg/m^2) at Screening, Week 0 (Visit 1), Week 2 (Visit 2), and Week 6 (Visit 3). Absolute change from Screening to Week 0 and absolute changes from Week 0 for both post-randomization visits are also given.

Visit		STOP Taking (N=)	KEEP Taking (N=)	Difference (95% CI); P-value [1]
Week -2 (Screening)				
	N (%)			
	Mean (SD)			
	Median			
	Min, Max			
Week 0 (Visit 1/Randomization)				
	N (%)			
	Mean (SD)			
	Median			
	Min, Max			
Absolute Change (Week -2 to Week 0)				
	N (%)			
	Mean (SD)			
	Median			
	Min, Max			
Week 2 (Visit 2)				
	N (%)			
	Mean (SD)			
	Median			
	Min, Max			
Absolute Change (Week 0 to Week 2)				
	N (%)			
	Mean (SD)			
	Median			
	Min, Max			
Difference in Absolute Changes (Week 0 to Week 2 minus Week -2 to Week 0)				
	N (%)			
	Mean (SD)			
	Median			
	Min, Max			
Week 6 (Visit 3)				
	N (%)			
	Mean (SD)			
	Median			
	Min, Max			
Absolute Change (Week 0 to Week 6)				
	N			
	Mean (SD)			

Visit		STOP Taking (N=)	KEEP Taking (N=)	Difference (95% CI); P-value [1]
	Median Min, Max			

[1] 95% confidence interval and p-value are calculated using a two-sample t-test. The difference is STOP Taking – KEEP Taking.

11 Summary of Lung Clearance Index (LCI) Results

Table 11.1. Characteristics of Participants with Multiple Breath Wash-out (MBW) procedures completed at Baseline (Week -2 or Week 0 Visit) (PPA and ITT population for Final Report)

This table summarizes demographic and Week 0 characteristics among randomized participants with an acceptable LCI (2.5) measurement at baseline (Week 0 or Week -2) by intervention arm and by population. All measures were recorded at Visit 1 unless specified otherwise.

	LCI Subset (ITT)			LCI Subset (PPA)		
	STOP Taking (N=)	**KEEP Taking (N=)**	**Total (N=)**	**STOP Taking (N=)**	**KEEP Taking (N=)**	**Total (N=)**
Sex at birth						
Male						
Female						
Age (years)						
N						
Mean (SD)						
Median						
Min, Max						
Age Distribution (years)						
≥12 to <18						
≥18 to <24						
≥24 to <30						
≥ 30						
Race[1]						
White						
Black or African American						
Asian						
American Indian or Alaska Native						
Native Hawaiian or Other Pacific Islander						
Unknown/Other						
Ethnicity						
Hispanic or Latino						
Not Hispanic or Latino						
Genotype Group [2]						
F508del Homozygous						
F508del Heterozygous						
Other/Unknown						
Height (cm) at Screening Visit						

N						
Mean (SD)						
Median						
Min, Max						
Height Percentile (%)at Screening Visit [3]						
N						
Mean (SD)						
Median						
Min, Max						
Weight (kg)						
N						
Mean (SD)						
Median						
Min, Max						
Weight Percentile (%) [3]						
N						
Mean (SD)						
Median						
Min, Max						
Body Mass Index (kg/m^2)						
N						
Mean (SD)						
Median						
Min, Max						
BMI Percentile (%) [3]						
N						
Mean (SD)						
Median						
Min, Max						
FEV_1 (liters)						
N						
Mean (SD)						
Median						
Min, Max						
FEV_1 (% predicted) [4]						
N						
Mean (SD)						
Median						
Min, Max						
FEV_1 (% predicted) Distribution [4]						
<60						
≥60 to <70						
≥70 to <90						
≥90 to <100						
≥100						
Sweat Chloride (mEq/L) [5]						

Pre-ETI Result						
N						
Mean (SD)						
Median						
Min, Max						
Post-ETI Result						
N						
Mean (SD)						
Median						
Min, Max						
Previous Enrollment in Study B [6]						
Yes						
No						
Previous Treatment Assignment in Study B [6]						
STOP Taking						
KEEP Taking						
Current Hypertonic Saline Use [6]						
Yes						
No						
Current Dornase Alfa Use [6]						
Yes						
No						
Current Chronic Therapy [7]						
ETI [8]						
Airway clearance [9]						
Inhaled antibiotic (Continuous)						
Inhaled antibiotic (Cycled)						
Inhaled antibiotic (Continuous Alternating)						
Oral antibiotic						
Ibuprofen						
Systemic steroids						
Previous Modulator Use [10]						
Ivacaftor						
Lumacaftor/Ivacaftor						
Tezacaftor/Ivacaftor						
Positive Microbiology Culture (past year) [11]						
Pseudomonas aeruginosa						
Staphylococcus aureus						
Methicillin-resistant Staphylococcus aureus						
Stenotrophomonas maltophilia						
Achromobacter xylosoxidan						
Burkholderia cepacia complex						
Haemophilus influenzae						
Mycobacterium abscessus						
Mycobacterium avium complex						

Table 11.2. Summary of LCI (2.5) Results (PPA and ITT population for Final Report)

This table summarizes the LCI (2.5) results at baseline (Week 0 (Visit 1), if available, or else Week -2 (Screening)) and Week 6 (Visit 3). Changes from baseline to Week 6 are also given. Relative change is calculated as 100 * (post visit value –reference value) / (reference value). Participants without an acceptable LCI (2.5) measurement at baseline (Week 0 or Week -2) are not included.

Visit	Statistic	STOP Taking (N=)	KEEP Taking (N=)	Difference (95% CI)[1]	P-value[1]
Intent to Treat Population					
Baseline (Week 0 or Week -2)	N(%) Mean (SD) Median Min, Max				
Week 6 (Visit 3)	N(%) Mean (SD) Median Min, Max				
Absolute Change (Baseline to Week 6)	N(%) Mean (SD) Median Min, Max				
Relative Change (Baseline to Week 6)	N(%) Mean (SD) Median Min, Max				
Per Protocol Analysis Population					
Baseline (Week 0 or Week -2)	N(%) Mean (SD) Median Min, Max				
Week 6 (Visit 3)	N(%) Mean (SD) Median Min, Max				
Absolute Change (Baseline to Week 6)	N(%) Mean (SD) Median				

	Min, Max				
Relative Change (Baseline to Week 6)	N(%) Mean (SD) Median Min, Max				

[1] 95% confidence interval and p-value are calculated using a two-sample t-test. The difference is STOP Taking – KEEP Taking.

Table 11.3. Results from ANOVA Model for Change in LCI (2.5) (PPA and ITT population for Final Report)

Absolute change in LCI (2.5) from baseline (Week 0 (Visit 1), if available, or else Week -2 (Screening))to Week 6 (Visit 3), is compared between intervention arms using Analysis of Variance adjusted for dichotomous randomization strata: Week 0 FEV_1, treatment combination at screening, prior study enrollment, and Week 0 age. An unadjusted estimate is also provided. Participants without an acceptable LCI (2.5) measurement at baseline (Week 0 or Week -2) are not included.

Model Covariates	STOP Taking Mean Estimate	KEEP Taking Mean Estimate	Difference (95% CI)	P-value [9]
Per Protocol Analysis Population	**(N=)**	**(N=)**		
Model Unadjusted				
Intervention Arm: STOP Taking hypertonic saline [1, 2]				
Model Adjusted for Randomization Strata				
Intervention Arm: STOP Taking hypertonic saline [2, 3]				
Randomization Strata:				
FEV_1 % Predicted ≥90% [4]				
On both HS and Dnase [5]				
Prior study enrollment [6]				
Age ≥18 years [7]				
Intent to Treat Population [8]	**(N=)**	**(N=)**		
Model Unadjusted				
Intervention Arm: STOP Taking hypertonic saline [1, 2]				
Model Adjusted for Randomization Strata				
Intervention Arm: STOP Taking hypertonic saline [2, 3]				
Randomization Strata:				
FEV_1 % Predicted ≥90% [4]				
On both HS and Dnase [5]				
Prior study enrollment [6]				
Age ≥18 years [7]				

[1] The overall unadjusted intervention arm difference (STOP Taking - KEEP Taking) is estimated using a twosample t-test.
[2] Compared to reference level, KEEP taking hypertonic saline.
[3] Least Squares Mean Estimates from model with weighting proportional to observed frequencies of randomization factor combinations in the data.
[4] Compared to reference level, FEV_1 % Predicted < 90% at Week 0 (Visit 1).
[5] Compared to reference level, one therapy at Week -2 (Screening).
[6] Compared to reference level, no prior study enrollment.
[7] Compared to reference level, age <18 years at Week 0 (Visit 1).
[8] Missing values are imputed using the least favorable treatment mean in arms discontinuing treatment and using most favorable treatment mean in arms continuing treatment.

[9] Two-sided p-value.

12 Listings

Listing 12.1. Protocol Violations and Deviations

Participant ID	Intervention Arm	Description	Protocol Reference	Category	Violation Issued?	Corrective Action Required?	Corrective Action Specify	Date of Action	IRB Notification Required?	Date of Notification

Listing 12.2. Pregnancies

Participant ID	Intervention Arm	Description	Start Date	End Date	Outcome