RANDOMIZED, OPEN-LABEL NON-INFERIORITY TRIALS EVALUATING DISCONTINUATION VERSUS CONTINUATION OF HYPERTONIC SALINE OR DORNASE ALFA IN MODULATOR TREATED PEOPLE WITH CYSTIC FIBROSIS: RESULTS FROM THE SIMPLIFY STUDY

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SUMMARY

Background: Reducing treatment burden is a priority for people with cystic fibrosis (CF) whose health has benefited from using newer modulators that substantially increase cystic fibrosis transmembrane conductance regulator (CFTR) protein function. The SIMPLIFY study

included two parallel, randomized, open-label controlled trials to independently test the effects of discontinuing nebulized hypertonic saline (HS) or dornase alfa (DA) in individuals treated with the CFTR modulator elexacaftor/tezacaftor/ivacaftor (ETI). This study is registered with www.clinicaltrials.gov (NCT04378153).

Methods: Individuals 12 years old using ETI and either or both nebulized therapies for 90 days were eligible. Participants on both HS and DA were randomized to one of the two trials, and those on a single therapy were assigned to the applicable trial. All were then randomized 1:1 to continue or discontinue therapy for 6 weeks. The primary objective for each trial was to determine whether discontinuing is non-inferior (NI) to continuing, measured by the 6-week change in % predicted forced expiratory volume in one second (ppFEV$_1$).

Findings: A total of 370 and 477 participants with an average ppFEV$_1$ of 96.9% were randomized in the HS and DA trials, respectively. Discontinuing treatment was non-inferior to continuing with respect to the 6-week change in ppFEV$_1$ in both the HS (per protocol [PP] population: n=133 discontinued, n=140 continued, difference=−0.32%, 95% CI:−1.25,0.60) and DA (PP population: n=199 discontinued, n=193 continued, difference = 0.35%, 95% CI: −0.45,1.14) trials according to a pre-specified −3% NI margin, with consistent results in the intent-to-treat populations. Secondary endpoints including lung clearance index and patient-reported symptom scores also demonstrated no meaningful differences, with few experiencing increased respiratory events.

Interpretation: In individuals with CF on ETI with relatively well-preserved pulmonary function, discontinuing as compared to continuing daily HS or DA for six weeks did not result in clinically meaningful differences in pulmonary function or symptoms.

Introduction

Cystic fibrosis (CF) is an autosomal recessive disease caused by mutations in the cystic fibrosis transmembrane conductance regulator gene (*CFTR)*, which encodes an epithelial anion channel responsible for hydrating secretions in multiple organs.[1] Inadequate CFTR function in the lungs perpetuates a destructive cycle of mucociliary dysfunction, infection, and inflammation,[2–4] which accelerates loss of lung function and contributes to substantial morbidity and mortality.[5] Dornase alfa (DA) and hypertonic saline (HS), inhaled mucoactive therapies with unique but complementary mechanisms, facilitate clearance of airway secretions by addressing downstream manifestations of CFTR dysfunction including high amounts of extracellular DNA in mucus and airway surface dehydration, respectively.[6,7] In randomized, placebo-controlled trials, these medications resulted in improvements in lung function, amelioration of respiratory symptoms, and reduced risk of pulmonary exacerbation.[6–8] They are also included in CF clinical practice guidelines.[9,10] However, people with CF (pwCF) dedicate considerable time and effort daily to these inhaled therapies, which contributes to high treatment burden.[11]

Based on the presence of at least one copy of the F508del-CFTR mutation, approximately 90% of pwCF are candidates for orally administered modulators that substantially, though incompletely, restore CFTR function. Clinical trials of the newest modulator combination, elexacaftor/tezacaftor/ivacaftor (ETI), demonstrated unparalleled improvements in lung function and respiratory symptoms and lower risk of pulmonary exacerbations,[12,13] marking a watershed moment in the history of CF care. In post-approval research, ETI reduced objective indicators of airway mucus plugging,[14] identifying overlap and potential redundancy between modulator-induced CFTR restoration and inhaled mucoactive therapies. The ongoing necessity of medications that improve airway mucus clearance downstream of CFTR is now unclear. As simplifying treatment burden remains a top CF community research priority,[15,16] and data suggest that pwCF taking ETI are using other chronic therapies less frequently,[17] it is an opportune time to rigorously evaluate the effects of discontinuing burdensome inhaled therapies such as DA and HS in pwCF on modulator drugs that markedly improve CFTR function.

The SIMPLIFY study was designed with important input from the CF community,[16] and included two parallel, multicenter, open-label randomized, controlled non-inferiority trials to determine the effects of discontinuing DA or HS among pwCF established on ETI.[18] For each trial, we hypothesized that discontinuing as compared to continuing inhaled therapy has no clinically meaningful impact on lung function, thereby providing evidence to support simplifying care regimens in pwCF with preserved lung function who benefit from ETI.

Role of the Funding Source

This study was funded by the CF Foundation and designed by the study PIs in collaboration with the CF Therapeutics Development Network (CF TDN). The funder of the study had no role in study design, data collection, or data analysis. Data were collected by local site investigators and analyzed by the TDN Coordinating Center at Seattle Children's Research Institute. JPC is included as a co-author employed by the sponsor and provided insight into interpretation and writing of the manuscript along with all other co-authors. The corresponding and senior authors had final responsibility for the decision to submit for publication.

METHODS

Study Design and Participants

Details of the study design have been described[18] with additional information provided in the Supplementary Appendix. SIMPLIFY is a master protocol with two concurrent 6-week randomized, open-label, controlled non-inferiority trials, each of which is designed to evaluate the independent effect of discontinuing versus continuing HS (Trial A) or DA (Trial B) (Supplement, Figure S1). The study was conducted in the United States (U.S.) at participating sites in the CF TDN. An independent review board approved the trial protocol and informed consent forms. All enrolled participants, or their legal guardians, provided written informed consent (and assent, when appropriate). Individuals with CF ages 12–17 years with percent-predicted forced expiratory volume in one second (ppFEV$_1$) 70 and those 18 years of age with ppFEV$_1$ 60 were eligible to enroll if they had been on ETI and

either or both mucoactive therapies (3% hypertonic saline and/or dornase alfa) for at least 90 days prior to screening (Week −2). Full eligibility criteria are provided in Table S1.

Randomization and Masking

Enrolled participants were followed during a two-week screening period and were then eligible for randomization into Trial A or B conditional on reported adherence to their inhaled drug therapy (HS and/or DA), >70% compliance with electronic recording of daily medication use, no absolute decrease in ppFEV$_1$ of 10%, clinical stability, and no acute use of antibiotics or corticosteroids for respiratory symptoms (Table S1). At Week 0, participants treated with only HS or DA were enrolled in Trial A or Trial B (as applicable) and randomized 1:1 to either continue or discontinue therapy. Concurrent users of HS and DA remained on both therapies during the screening period and were first randomized to participate in Trial A or Trial B and then randomized to continue vs. discontinue the applicable therapy in their assigned study. Individuals on both HS and DA could participate sequentially in both trials upon reassessment of individual study eligibility. Participants were randomized 1:1 to continue or discontinue therapy in each trial using permuted blocks of varying size, stratified by Week 0 ppFEV$_1$ (90, <90), single or concurrent use of HS and/or DA, prior SIMPLIFY study participation (yes/no), and age (18 vs < 18). Further randomization details provided in the Supplement. Although there was no masking to treatment assignment for individual participants or their clinicians, aggregate study results were blinded and tightly controlled by the TDN Coordinating Center with only the study's Data Monitoring Committee (DMC) and select unblinded study team members with access to interim study data.

Procedures

All randomized participants were followed and assessed over a 6-week period with study visits at Weeks 2 and 6 post-randomization. Sex at birth was recorded by the investigators as documented in the medical record. Protocol adherence to continue or discontinue therapy was measured using daily electronic assessments based on time-triggered ecological momentary assessment (EMA) documenting use or non-use of therapy.[19–22] At the completion of each 6-week trial, participants were asked to complete electronic questionnaires every 28 days for up to 24 weeks to assess medication use patterns and use of additional antibiotics after study completion, and these data will be presented elsewhere.

Objectives and Outcomes

The primary objective of each trial determined whether discontinuing therapy is *non-inferior* to continuing therapy, as measured by the 6-week mean absolute change in ppFEV$_1$.[23] Secondary objectives included evaluating the safety of discontinuing therapy as measured by comparing adverse event rates between arms and proportions of participants that changed their assigned treatment regimen. Secondary outcomes included 6-week changes in the lung clearance index at 2.5% of the starting gas concentration (LCI$_{2.5}$) measured by nitrogen multiple breath washout (MBW) among a sub-cohort enrolled at 27 participating sites trained and certified to perform MBW as described previously,[24] and patient reported outcomes (PROs) including the Chronic Respiratory Infection Symptom Score

(CRISS)[25] and Cystic Fibrosis Questionnaire-Revised Respiratory Domain Score (CFQ-R).[26] Additional secondary outcomes included the proportion of participants who initiated acute antibiotics courses, were hospitalized, or experienced a pulmonary exacerbation defined according to expanded Fuchs criteria.[27]

Statistical Analysis

The primary analysis for each trial was conducted on the per-protocol (PP) population (Supplement). The intent-to-treat (ITT) population was used for safety and sensitivity analyses with and without accounting for missing data (see Supplement for methods). Analysis of Variance (ANOVA) models adjusted for randomization strata were used to estimate the 6-week change within treatment arms and the difference between treatment arms in the 6-week change in $ppFEV_1$ for each trial with corresponding 95% confidence intervals (CIs). Within-arm estimates of change were by least-squares means (LS means). A non-inferiority margin of -3% for the difference between arms in the 6-week change in $ppFEV_1$ was established *a priori* with community input and clinical consensus during scientific review of the protocol.[18] Pre-defined subgroup analyses were conducted. Differences between treatment groups in continuous secondary efficacy outcomes were estimated analogous to the primary outcome. Differences in secondary binary outcomes were estimated using logistic regression adjusting for randomization strata.

The type I error for the primary hypothesis was based on a one-sided 0.025 alpha-level test, reporting a two-sided 95% CI. A sample size of 400 enrolled per trial with assumed attrition and exclusions from the PP population less than 20% would result in at least 308 included in the primary analysis. Assuming a standard deviation for the 6-week change in $ppFEV_1$ equal to 8.4,[12,28] 308 participants provided 88% power to detect non-inferiority with a margin of -3% assuming no effect of discontinuation. Interim safety data were reviewed every 6 months by a Data Monitoring Committee (DMC) from the CFF Data Safety Monitoring Board (DSMB).

RESULTS

The 6-week multi-center randomized trials in the SIMPLIFY study were conducted from September 2020 to July 2022 at 80 sites in the CF TDN in the U.S. The DA trial enrolled faster due to a higher proportion of enrollees using monotherapy with DA rather than HS, consistent with the broader U.S. CF population.[29] The DA trial achieved its enrollment milestone in October 2021 but was provided DMC approval to over-enroll, with both trials completing enrollment in May 2022 just short of the enrollment milestones for the HS trial (see Supplement).

A total of 672 unique participants were assessed for eligibility across 1021 screening visits, resulting in 847 total randomizations across both studies among 594 unique participants (Figure 1). A subset of 253 (43%) of the 594 participants were using both HS and DA and participated in both trials. Upon completion of the screening period, eligible participants were randomly assigned to either discontinue (n=184 in HS trial, n=240 DA trial) or continue (n=186 HS trial, n=237 DA trial) treatment in each trial. Treatment arms within and across studies were well matched (Table 1) with a notably high average $ppFEV_1$ across the

entire study cohort of 97%. The majority (64% of 511) of participants with specific ETI start dates recorded, beyond confirmed recording of 90 days of use necessary for eligibility, were using ETI for 12 months or longer at the time of randomization into their first or only trial.

Randomized participants met eligibility after a two-week screening which required 70% compliance with electronic daily medication use reporting and 70% adherence to applicable therapies. Of the 1021 study screenings, 46 (5%) and 28 (3%) did not result in randomization due to lack of adequate compliance or adherence, respectively (Figure 1). Compliance with electronic daily medication usage reporting during the 6-week trial continued to be high, with 303 (82%) and 422 (89%) of 370 and 477 participants overall in the HS and DA trials, respectively, achieving 70% compliance. The 6-week average reported treatment regimen adherence to either discontinue or continue therapy was also high at 96% and 98% amongst the 184 and 186 participants in the HS trial, respectively, and 97% and 96% amongst the 240 and 237 participants in the DA trial, respectively. The 6-week average reported ETI adherence was even higher across treatment arms in both trials (99%), with consistent reported use of airway clearance therapy (ACT) throughout the study (Table S2).

A total of 273 of 370 (74%) participants in the HS and 392 of 477 (82%) in the DA study comprised the per-protocol population, with reasons for exclusion provided in Figure 1. Participant characteristics were comparable between the ITT and PP study populations for both trials (Tables S3-S4).

The average change in ppFEV$_1$ during the two-week run-in period and prior to randomization was 0.12% in the HS trial (n=370, 95% CI: −0.27,0.50) and 0.11% in the DA trial (n=477, 95% CI: −0.22,0.43). The absolute change in ppFEV$_1$ from baseline (Week 0) to Week 6 in the PP population of the HS trial was −0.19% (n=133, 95% CI: −0.85,0.48) in the discontinuation arm as compared to 0.14% (n=140, 95% CI: −0.51,0.78) in the continuation arm, reflecting a between-group difference (discontinuation minus continuation) of −0.32% (95% CI: −1.25, 0.60) (Figure 2). In the PP population of the DA trial, a mean 6-week change of 0.18% was observed in the discontinuation arm (n=199, 95% CI: −0.38,0.74) as compared to −0.16% in the continuation arm (n=193, 95% CI: −0.73,0.41), with between-group difference 0.35% (95% CI: −0.45,1.14) (Figure 2). In both trials, NI was established with the lower bounds of the 95% CI for the treatment differences exceeding the pre-defined threshold of −3%.[18] Sensitivity analyses using the ITT population produced consistent treatment effect estimates (Figure 2), and estimates were additionally consistent across pre-defined subgroups (Figure 3 and S2) as well as for the change in ppFEV$_1$ from Week 0 to Week 2 and Week −2 to Week 6 (Tables S5-S6). While the study was not powered to detect significant differences between subgroups, the lower bound of the CIs consistently exceeded the NI margin with the exception of the smallest subgroups with the widest CIs in both directions including those not using ACT, non-white study participants, and Hispanic or Latino participants. Notably, consistent results were seen between those participating in one versus both trials; additional analyses of the subgroups participating in both trials will be presented elsewhere. Graphical displays of individual participant 6-week changes in ppFEV$_1$ are provided in Figures S4 and S5.

LCI$_{2.5}$ was obtained among a subset of participants with demonstrated comparability to the main trial cohort (Table S7-S8). Among participants in the PP population in the HS trial, a 6-week mean absolute change in LCI$_{2.5}$ of 0.17 (n=31, 95% CI: −0.09,0.43) was observed in the discontinuation arm as compared to 0.11 in the continuation arm (n=28, 95% CI: −0.16,0.38), with associated treatment difference 0.06 (95% CI: −0.31,0.44). Among participants in the PP population in the DA trial, a 6-week mean change of −0.11 (n=40, 95% CI: −0.29,0.08) was observed in the discontinuation arm as compared to 0.00 in the continuation arm (n=42, 95% CI: −0.18,0.19), with associated treatment difference −0.11 (95% CI: −0.37,0.15). Confidence interval bounds for the treatment differences exclude the smallest published treatment-associated changes in LCI$_{2.5}$ equal to 0.5 (Figure 2).[30] Sensitivity analyses in the ITT population and as a relative change demonstrated consistency (Figure S5).

Baseline respiratory symptom scores measured through the CRISS and CFQ-R (respiratory domain) indicated a low prevalence of symptoms among the participants in each trial, averaging 11.5 (standard deviation [sd] 12.2) and 94.1 (sd=9.9) in the HS trial and 12.0 (sd=11.8) and 95.0 (sd=7.9) in the DA trial, respectively. Larger numbers in CRISS represent more symptoms while larger numbers in CFQ-R represent fewer symptoms. There were no significant differences between treatment arms in 6-week CRISS or CFQ-R symptom score changes in either trial or across analysis populations (Figure S6). In the PP population, the treatment difference (discontinuation minus continuation) in the 6-week change in CRISS score was −1.5 in the HS trial (95% CI: −4.0,0.9) and 1.0 in the DA trial (95% CI: −1.0,3.0). Upper bounds of the 95% CIs exclude a previously suggested minimally important difference of 11.[31] Similarly, the treatment difference in the 6-week change in CFQ-R score was 0.2 in the HS trial (95% CI: −1.7,2.1) and −0.9 in the DA trial (95% CI: −2.4,0.6). The lower CI bounds exclude a previously established minimal clinically important difference of −4.[32] Incidence of protocol defined pulmonary exacerbations and hospitalizations were infrequent and comparable between treatment groups for each trial (Table S9-S10).

There were no treatment-related serious adverse events reported in either trial and the majority of trial participants experienced no adverse events during the 6-week trial (Table 2). Higher relative percentages of participants experienced at least one adverse event in the discontinuation versus continuation arms in the HS trial (35%, 64 of 184 vs. 24%, 44 of 186 participants) and in the DA trial (37%, 89 of 240 vs. 23%, 55 of 237 participants), predominantly driven by respiratory AEs (Table 2). However, no single AE was observed in more than 7% of participants within a given trial arm. Post-hoc analyses demonstrated that differences in respiratory AEs were more prominent among a small subset of participants with ppFEV$_1$ <70% (Table S11), although no systematic associations were identified between baseline ppFEV$_1$ and change in ppFEV$_1$ (Figure S7).

DISCUSSION

SIMPLIFY is the first study to test whether pwCF who are clinically stable on CFTR modulator drug therapy that substantially restores CFTR function, specifically ETI, can discontinue either inhaled DA or HS without experiencing a meaningful decline in lung

function. Through randomized, controlled non-inferiority trials, our study demonstrated that the individual discontinuation of either inhaled therapy was not associated with diminished lung function as measured by the 6-week change in $ppFEV_1$. These results are strengthened by lack of meaningful changes in $LCI_{2.5}$ and patient-reported respiratory outcome scores. There were no significant safety concerns with overall low rates of adverse events across both treatment arms, though slightly higher respiratory adverse event rates were observed in those discontinuing, which were more prominent in the small subgroup representing 7% or less of the total trial populations with lower lung function ($ppFEV_1$ 60 to <70%). Collectively, these data point to an important opportunity to reevaluate daily treatment requirements wherein routine use of certain longstanding inhaled therapies may not be required to maintain pulmonary function in individuals likely experiencing substantial drug-induced restoration of CFTR function and relatively good pulmonary health as a result of ETI.[12,17,28]

SIMPLIFY was designed to test for the non-inferiority of discontinuing versus continuing therapy with respect to the 6-week change in $ppFEV_1$, assessed using a pre-defined non-inferiority margin of −3% derived with community input.[18] Notably, a study summarizing the trade-offs people with CF were willing to make to reduce treatment burden published after the establishment of the NI margin used in SIMPLIFY suggested that people were willing to accept a 4.4% reduction in $ppFEV_1$ (95% CI: 2.6,6.3) or −2.3 years of additional life expectancy (95% CI: 1.3,3.3) to halve the time spent on inhaled medicines.[33] Based on the lower bounds of the CIs for the treatment effects observed in our study, we were able to rule out declines of more than −1.3% $ppFEV_1$ associated with discontinuing HS and −0.6% with discontinuing DA among this study population. While the PP population was the primary analysis population, consistent results were observed in the ITT population and across several relevant subgroups. Confidence in the interpretation of the primary endpoint was increased by results from the $LCI_{2.5}$ endpoint, available among a subset of participants at sites that performed MBW. LCI is a more sensitive measure of change in pulmonary function—particularly in pwCF who have preserved $ppFEV_1$.[34–38] In the youngest and healthiest populations with CF studied, $LCI_{2.5}$ changes as small as 0.9 were observed for a 4-week study period of DA and as small as 0.5 were observed over a 48-week study of HS.[30,35,36,39] Despite a much older study population in SIMPLIFY, the mean differences in $LCI_{2.5}$ change were near zero and the 95% CI bounds excluded an undesirable effect of discontinuation.

The 6-week period to continue or discontinue each inhaled therapy was carefully considered when designing this study.[18] Adherence to the assigned regimen and other prescribed therapies is critically important to confirming or refuting non-inferiority. A relatively short study period undoubtedly improves adherence to enable a more robust examination of the physiological effects of discontinuing therapy. It is equally important to ask whether six weeks was sufficient to capture changes in lung function. Several studies of DA consistently show a maximum impact on $ppFEV_1$ within 7 days of starting therapy and a return to baseline within 2–3 weeks after stopping the medication.[6,40–43] Recent small studies of children in Canada and Denmark reported changes in $LCI_{2.5}$ within one month after starting or stopping DA, respectively.[35,44] Reports of the effects of HS on pulmonary function also find maximum effect and return to baseline for $ppFEV_1$ or LCI within 4 weeks or by the

first study visit.[7,36,39,45] We are not aware of data demonstrating an independent, delayed effect on lung function beyond the first several weeks when starting or stopping either inhaled therapy. Collectively, these studies indicate that the 6-week observational period in SIMPLIFY, which was necessary to maximize adherence to treatment regimen, was suitable to observe changes in ppFEV$_1$ or LCI after discontinuing HS or DA. We recognize that longer-term changes in pulmonary function were not directly tested in this study and therefore could occur despite the lack of evidence indicating latent and/or time-dependent effects on lung function from historical trials.[6,7,41,46]

It is vital to recognize the study population when interpreting these findings. As the first large-scale trial to test withdrawal of pre-existing daily therapy, we intentionally recruited a healthier population based on ppFEV$_1$ criteria of 70% for adolescents (ages 12–17y) and 60% for adults. The mean ppFEV$_1$ in SIMPLIFY was 97% (mean age 22 years). For comparison, an ongoing real-world observational study of ETI use in the U.S., which had no baseline criteria for lung function, recently reported the mean ppFEV$_1$ at 6 months into ETI use was just over 90% with mean age of 25 years.[17] The results of SIMPLIFY may not represent what would occur in pwCF with pulmonary function significantly outside the range observed in our study population. Within this study, a small number of adults with ppFEV$_1$ 60 to <70% were enrolled, and in this group, more respiratory adverse events were reported in those randomized to stop an inhaled medication. Baseline ppFEV$_1$ did not appear systematically associated with change in ppFEV$_1$ and the majority of respiratory adverse events were mild or moderate. Importantly however, this may suggest greater caution when considering changes to daily therapy in individuals with more advanced CF pulmonary disease.

We carefully monitored self-reported adherence to study therapy (DA and/or HS), ETI, and mechanical airway clearance through a daily electronic questionnaire. To be randomized, participants had to complete 70% of daily questionnaires over 2 weeks during screening and report use of their baseline therapies 70% of all days reported. This design element successfully enriched for a study population with high adherence to study assignment, near 100% for ETI and >95% for adherence to their assigned treatment (i.e., discontinue or continue the inhaled medication). Our adherence rates in these 6-week trials are higher than expected in longer term studies and higher than what can be expected in real-world use of medications or other daily therapies in pwCF.[47] When testing for non-inferiority of discontinuing versus continuing therapy, it is desirable to create the most extreme setting to produce the most conservative treatment effect (e.g. in this case allowing for greater declines in lung function to be observed). Lesser adherence to the assigned treatment regimens would be more likely to demonstrate non-inferiority between treatment arms as actual use would overlap more. This is particularly true for studies involving discontinuation of medications or therapies that remain available to study participants. Thus, lesser adherence to HS or DA in clinical use is unlikely to affect the generalizability of our findings under idealized conditions, but it is unknown whether such high adherence to the study protocol extends to other aspects of health maintenance and if that would impact the generalizability of our findings. Adherence to ETI was also high in this study, and it is possible that the effects of discontinuation of therapy would differ among those non-adherent to modulator therapy. Additional research into perspectives on participation in the SIMPLIFY study, including

reporting daily therapy use, was conducted in a complementary qualitative study (QUEST, NCT04320381) and will be reported separately.

Respiratory symptoms were measured using the CFQ-R respiratory domain and CRISS scores, which indicated remarkably low presence of symptoms at baseline across the cohort. The observed differences in scores between those discontinuing vs. continuing inhaled DA or HS were negligible with confidence intervals excluding minimum clinically important differences for these instruments.[31,32] SIMPLIFY was not designed or powered to evaluate risk of acute pulmonary exacerbation, so we cannot assess whether there is greater risk associated with discontinuing therapy independent of unobserved changes in $ppFEV_1$, LCI, or respiratory symptoms. An ongoing pragmatic clinical trial being conducted in the United Kingdom (CF-STORM, EudraCT number 2020–005864-77) and a U.S. registry-based real-world study (HERO-2, NCT04798014) are currently considering the effects of withdrawing inhaled mucoactive therapies on lung function over longer observational periods and may provide additional important data regarding the impact of treatment withdrawal on pulmonary exacerbations.

Hospitalizations, acute antibiotic use, and serious adverse events occurred in only a few participants in each trial and did not differ between treatment arms. Overall absolute adverse event rates were low and no significant safety concerns were identified. A markedly lower proportion of participants experienced an adverse event across all arms of the SIMPLIFY study than was observed in a comparable duration (4-week) trial of ETI versus tezacaftor/ivacaftor, whereby approximately two-thirds experienced at least one adverse event across treatment groups.[28] No single AE in SIMPLIFY was reported in 7% of participants, though a relative increased rate of respiratory related AEs was reported in the discontinuation as compared to continuation arm of both trials amidst overall low absolute rates. These AEs were mostly mild upper and lower respiratory symptoms and were found more often in participants with baseline $ppFEV_1$ <70%. It is possible that discontinuing daily inhaled therapy resulted in increased upper or lower respiratory symptoms for some and must be considered particularly for those with lower lung function. Notably, this study could not adequately blind (i.e., placebo) these familiar inhaled medications for participants and site investigators, and it is unclear whether this fact impacted self-reported symptoms or decisions to restart therapy in a handful of participants. The SIMPLIFY study was conducted during the SARS-CoV-2 pandemic and social distancing measures that may have reduced the overall rates of acute respiratory illness. What impact this may have had on our safety data is unclear, as low rates of acute pulmonary exacerbations were demonstrated in those on ETI even prior to the pandemic reaching the U.S.[12]

This study has certain limitations, including the aforementioned inability to blind participants in the study, particularly for longstanding inhaled therapies with visible characteristics and distinctive taste. Further, home electronic adherence monitoring devices were unfeasible. Thus, daily self-reporting methods were used as supported in other settings and developed in collaboration with the CF Foundation's Success with Therapies Consortium (STRC).[18] Consistent and high reporting throughout the trials, small differences in adherence rates between oral ETI and other inhaled therapies, and minimal $ppFEV_1$ change between screening and randomization visits all strengthen our confidence in the

accuracy of daily reporting in this study. Further limitations include the higher baseline ppFEV$_1$ and much lower rate of acute pulmonary exacerbation in this study population as compared with historical study populations in trials of HS and DA and the intentional 6-week observational period as discussed above. As is inherent to clinical trials, the average treatment responses reported may not predict individual experience if discontinuing either HS or DA. While there was no suggestion of differential findings across subgroups, the study was not adequately powered to test for these differences. Additional studies will also be required to address critical questions surrounding the necessity and timing of initiation of these traditional standard of care therapies, particularly in young pediatric populations with well-preserved lung function in the presence of ETI or similar CFTR restorative drugs. This study also did not examine withdrawal of regular mechanical airway clearance therapy, and additional research would be needed to understand the effects of altering such foundational therapies.

In summary, the results of SIMPLIFY indicate that among a study population of adolescents and adults with CF who have relatively good lung function established on ETI, clinically meaningful declines in pulmonary function did not occur with short-term discontinuation of daily use of inhaled medications that work on downstream manifestations of CFTR dysfunction in the airway, specifically HS and DA. It is recognized that clinicians and pwCF must partner to make individualized decisions with available evidence from SIMPLIFY and forthcoming studies regarding the continuance of chronic HS or DA in the setting of ETI use. It is reasonable to hypothesize that pwCF on potent modulator drug therapy may still benefit from inhaled DA and HS when experiencing increased respiratory symptoms or as part of a regimen to address acute pulmonary exacerbations. A substudy measuring changes in mucociliary clearance through nuclear medicine imaging was conducted in SIMPLIFY and will be published separately. These data may provide additional evidence to show whether discontinuing DA or HS for 6 weeks resulted in physiological changes in the airway. An as-necessary approach to these medications may facilitate knowledge gained from long term studies that consider impact on health stability over time. We are grateful to the CF community and study teams that contributed to SIMPLIFY and hope these results will inform shared decision making for many pwCF benefiting from CFTR restorative therapies now and in the future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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RESEARCH IN CONTEXT

Evidence Before this Study

The highly effective modulator elexacaftor/tezacaftor/ivacaftor (ETI) substantially restores cystic fibrosis transmembrane conductance regulator (CFTR) protein function and improves mucociliary clearance, thereby reducing mucus accumulation and airway obstruction. It is unknown whether additional therapies developed to improve mucus clearance from the lungs of people with CF, specifically hypertonic saline (HS) and dornase alfa (DA), remain clinically necessary in individuals treated with ETI. Studies assessing the impact of discontinuing such therapies will contribute critical evidence towards determining whether standard of care can be modified to reduce treatment burden after establishment of a highly effective modulator. Currently there are no large randomized, controlled trials that have tested the effects of withdrawing a chronic daily therapy after establishment of CFTR modulators.

Added Value of this Study

SIMPLIFY is the first study to assess the impact of discontinuing standard of care therapy after establishment of ETI in adolescents and adults 12 years of age and older. The study was comprised of two parallel randomized, open-label, controlled trials that independently tested whether discontinuation of either HS or DA is non-inferior to continuation of therapy over a 6-week study period as measured by the primary outcome, change in percent predicted forced expiratory volume in one second ($ppFEV_1$). The 6-week observational period is consistent with the time frame for which the effects of DA and HS on lung function have been observed in prior studies. Secondary objectives evaluated whether there were meaningful changes in lung clearance index (LCI), safety, and patient reported outcomes during the 6-week study period.

Implications of All the Available Evidence

Among adolescents and adults with CF established on ETI with relatively good lung function, discontinuation of either HS or DA did not result in clinically meaningful changes in lung function including $ppFEV_1$ and LCI at 2.5 starting concentration ($LCI_{2.5}$). No significant safety concerns were identified with overall low rates of adverse events, although slightly higher rates were observed in those discontinuing inhaled therapies and appeared more likely to occur in those with lower lung function. SIMPLIFY is the first study to provide evidence suggesting discontinuation of burdensome inhaled therapies such as HS or DA is not associated with short-term lung function changes among individuals benefiting from ETI. Collectively, the results provide an opportunity to reevaluate daily treatment requirements, wherein longstanding use of certain inhaled medications may not be required to maintain pulmonary function in individuals receiving drugs known to substantially improve CFTR function and respiratory health.
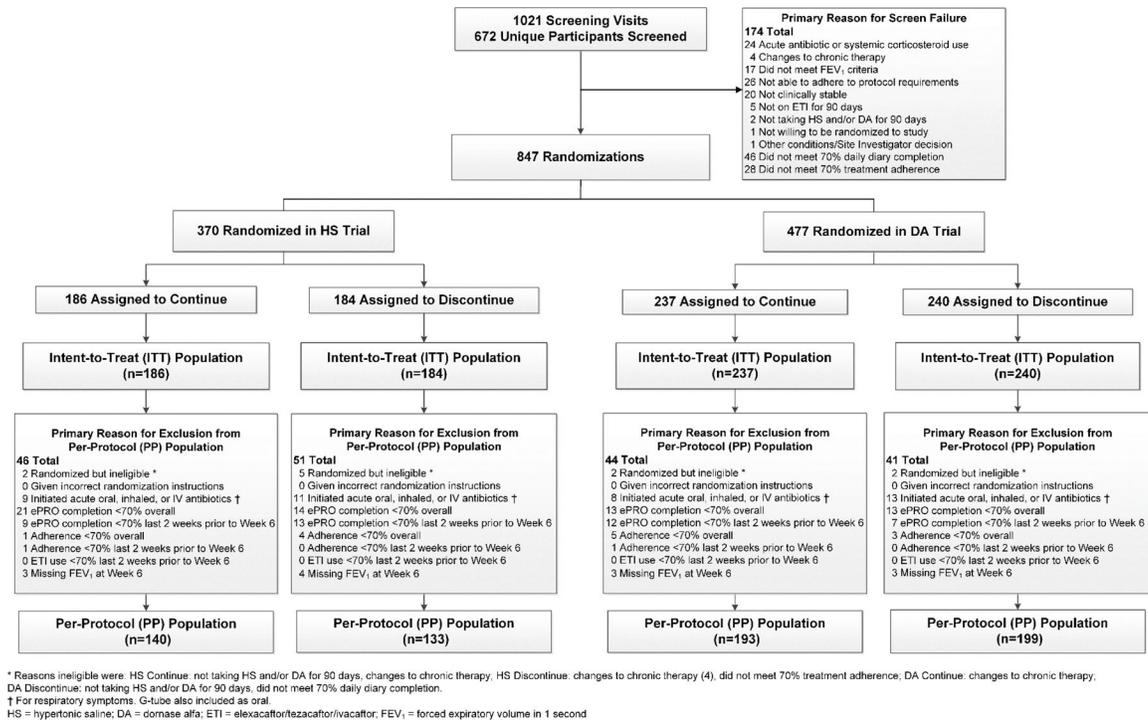
Figure 1.
Flow of Study Participants
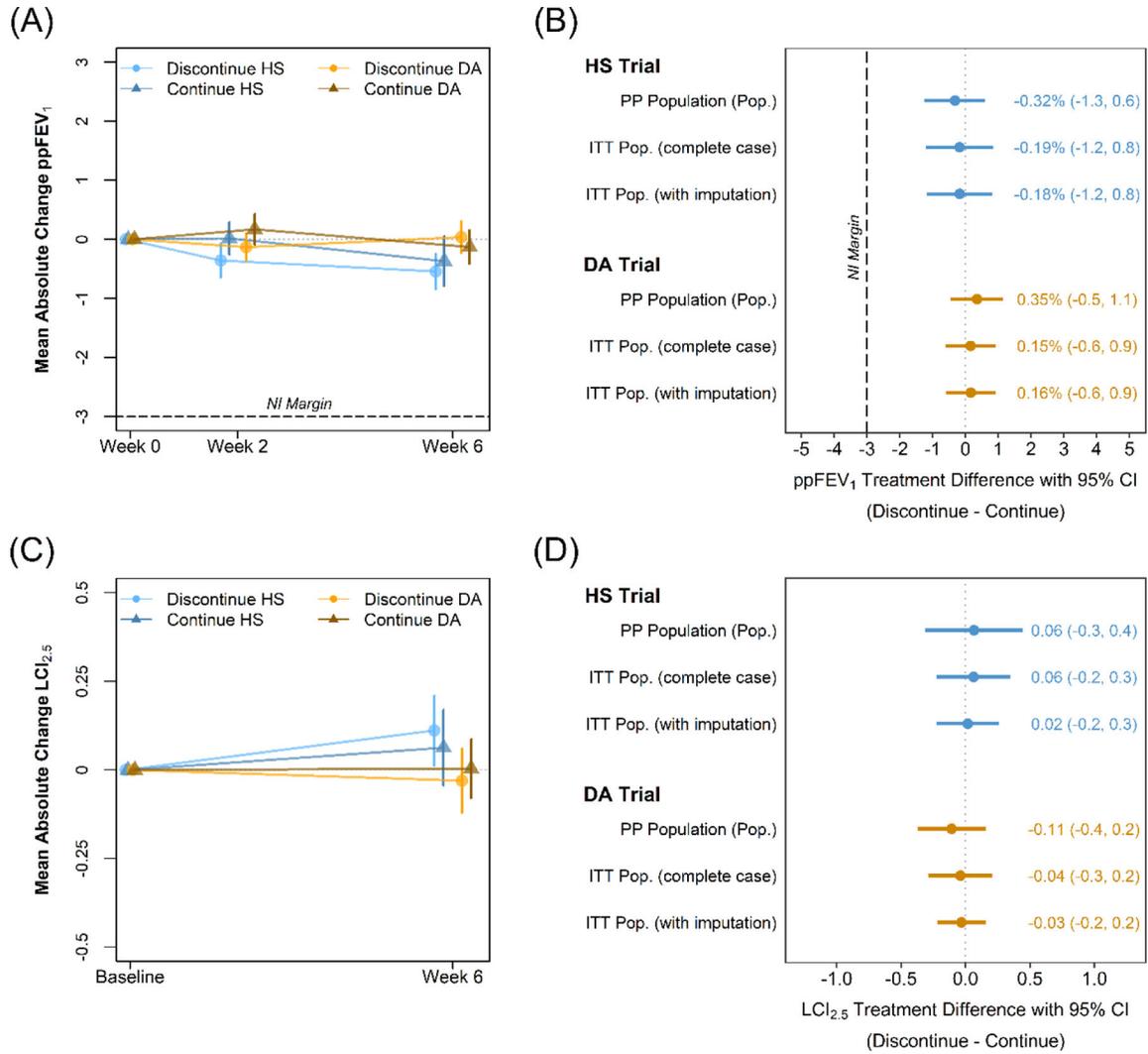
Figure 2.

Unadjusted mean absolute changes from baseline in (A) $ppFEV_1$ and (C) $LCI_{2.5}$ among all randomized participants. Bars indicate standard errors. Estimated differences between the discontinuation and continuation arms in the 6-week change in (B) $ppFEV_1$ and (D) $LCI_{2.5}$ among the primary PP population and ITT population with and without imputation to account for missing data. Treatment differences adjusted for randomization strata.
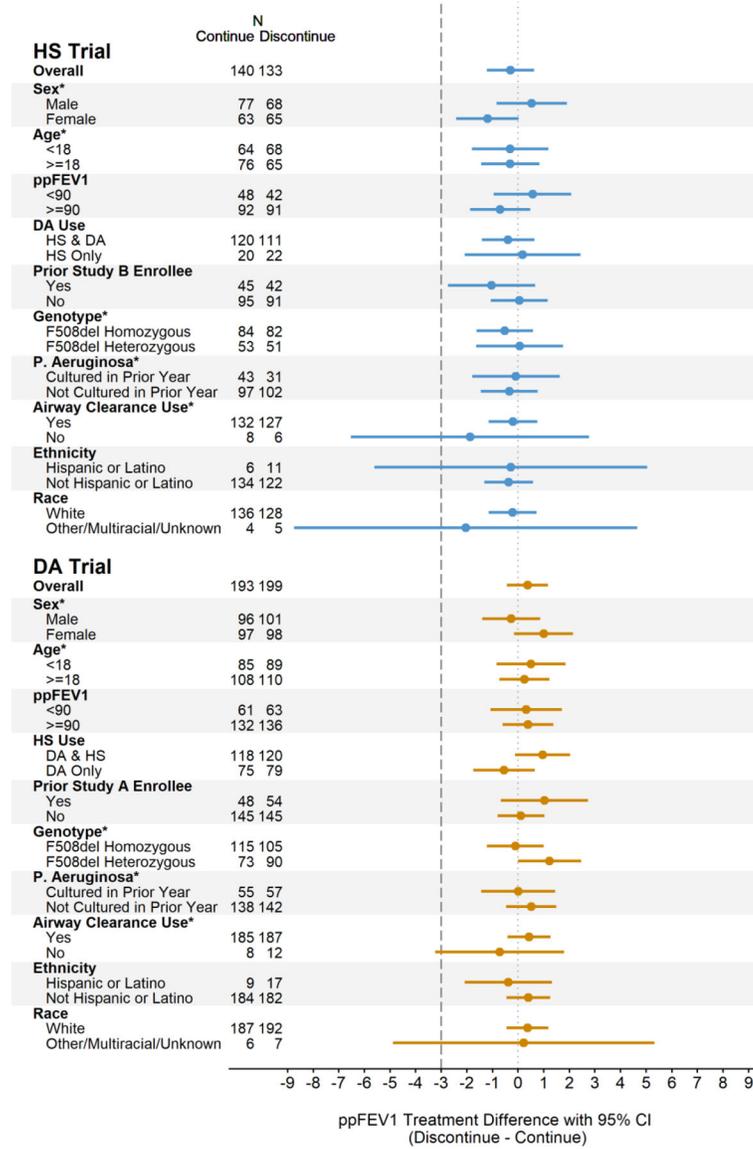
Figure 3.
Difference between the discontinuation and continuation treatment arms in the 6-week change in ppFEV$_1$ among subgroups in the PP population in the HS trial and DA trial. Treatment differences adjusted for randomization strata. Pre-defined subgroups noted with *. Sensitivity analyses in the ITT population provided in Figure S2.

Table 1.

Demographic and Baseline Characteristics of Randomized Participants

	Hypertonic Saline (HS) Trial			Dornase Alfa (DA) Trial		
	Continue N=186	Discontinue N=184	Total N=370	Continue N=237	Discontinue N=240	Total N=477
Sex at Birth						
Male	99 (53.2%)	97 (52.7%)	196 (53.0%)	117 (49.4%)	127 (52.9%)	244 (51.2%)
Female	87 (46.8%)	87 (47.3%)	174 (47.0%)	120 (50.6%)	113 (47.1%)	233 (48.8%)
Age (years)						
N	186	184	370	237	240	477
Mean (SD)	22.4 (10.73)	21.7 (10.28)	22.0 (10.50)	23.2 (11.50)	21.9 (9.19)	22.6 (10.41)
Age Distribution						
12 to <18	92 (49.5%)	90 (48.9%)	182 (49.2%)	108 (45.6%)	110 (45.8%)	218 (45.7%)
18 to <24	39 (21.0%)	37 (20.1%)	76 (20.5%)	48 (20.3%)	51 (21.3%)	99 (20.8%)
24 to <30	18 (9.7%)	32 (17.4%)	50 (13.5%)	31 (13.1%)	32 (13.3%)	63 (13.2%)
30	37 (19.9%)	25 (13.6%)	62 (16.8%)	50 (21.1%)	47 (19.6%)	97 (20.3%)
Race						
White	182 (97.8%)	176 (95.7%)	358 (96.8%)	227 (95.8%)	231 (96.3%)	458 (96.0%)
Black or African American	1 (0.5%)	2 (1.1%)	3 (0.8%)	4 (1.7%)	1 (0.4%)	5 (1.0%)
Asian	0 (0%)	1 (0.5%)	1 (0.3%)	1 (0.4%)	0 (0%)	1 (0.2%)
American Indian or Alaskan Native	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)	1 (0.2%)
Native Hawaiian or Other Pacific Islander	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Other/Unknown [*]	3 (1.6%)	5 (2.7%)	8 (2.2%)	5 (2.1%)	7 (2.9%)	12 (2.5%)
Ethnicity						
Hispanic or Latino	6 (3.2%)	14 (7.6%)	20 (5.4%)	15 (6.3%)	19 (7.9%)	34 (7.1%)
ot Hispanic or Latino	180 (96.8%)	170 (92.4%)	350 (94.6%)	222 (93.7%)	221 (92.1%)	443 (92.9%)
Genotype Group						
F508del Homozygous	111 (59.7%)	111 (60.3%)	222 (60.0%)	140 (59.1%)	129 (53.8%)	269 (56.4%)
F508del Heterozygous	72 (38.7%)	71 (38.6%)	143 (38.6%)	91 (38.4%)	106 (44.2%)	197 (41.3%)
Other/Unknown	3 (1.6%)	2 (1.1%)	5 (1.4%)	6 (2.5%)	5 (2.1%)	11 (2.3%)
FEV_1(% predicted)						
N	186	184	370	237	240	477
Mean (SD)	97.2 (16.50)	96.7 (17.17)	97.0 (16.82)	97.2 (16.32)	96.5 (17.34)	96.8 (16.83)
FEV_1(% predicted) Distribution						
<60	1 (0.5%)	1 (0.5%)	2 (0.5%)	3 (1.3%)	1 (0.4%)	4 (0.8%)
60 to <70	10 (5.4%)	13 (7.1%)	23 (6.2%)	11 (4.6%)	20 (8.3%)	31 (6.5%)
70 to <90	53 (28.5%)	46 (25.0%)	99 (26.8%)	63 (26.6%)	57 (23.8%)	120 (25.2%)
90 to <100	33 (17.7%)	45 (24.5%)	78 (21.1%)	51 (21.5%)	53 (22.1%)	104 (21.8%)
100	89 (47.8%)	79 (42.9%)	168 (45.4%)	109 (46.0%)	109 (45.4%)	218 (45.7%)
$LCI_{2.5}$ [†]						

	Hypertonic Saline (HS) Trial			Dornase Alfa (DA) Trial		
	Continue N=186	Discontinue N=184	Total N=370	Continue N=237	Discontinue N=240	Total N=477
N	47	52	99	61	69	130
Mean (SD)	7.8 (2.15)	8.2 (2.56)	8.0 (2.37)	7.9 (1.77)	8.2 (2.73)	8.1 (2.32)
Prior Study Enrollee	62 (33.3%)	62 (33.7%)	124 (33.5%)	64 (27.0%)	65 (27.1%)	129 (27.0%)
Current Chronic Therapy						
DA	156 (83.9%)	154 (83.7%)	310 (83.8%)	237 (100%)	240 (100%)	477 (100%)
HS	186 (100%)	184 (100%)	370 (100%)	147 (62.0%)	148 (61.7%)	295 (61.8%)
ETI	186 (100%)	184 (100%)	370 (100%)	237 (100%)	240 (100%)	477 (100%)
Airway clearance	178 (95.7%)	174 (94.6%)	352 (95.1%)	228 (96.2%)	226 (94.2%)	454 (95.2%)
Inhaled antibiotic (Continuous)	7 (3.8%)	2 (1.1%)	9 (2.4%)	3 (1.3%)	6 (2.5%)	9 (1.9%)
Inhaled antibiotic (Cycled)	51 (27.4%)	43 (23.4%)	94 (25.4%)	50 (21.1%)	56 (23.3%)	106 (22.2%)
Inhaled antibiotic (Continuous Alternating)	17 (9.1%)	15 (8.2%)	32 (8.6%)	25 (10.5%)	23 (9.6%)	48 (10.1%)
Oral antibiotic	85 (45.7%)	81 (44.0%)	166 (44.9%)	103 (43.5%)	104 (43.3%)	207 (43.4%)
Ibuprofen	8 (4.3%)	15 (8.2%)	23 (6.2%)	20 (8.4%)	21 (8.8%)	41 (8.6%)
Systemic steroids	1 (0.5%)	2 (1.1%)	3 (0.8%)	2 (0.8%)	3 (1.3%)	5 (1.0%)
Previous Modulator Use[‡]						
Ivacaftor	8 (4.3%)	1 (0.5%)	9 (2.4%)	7 (3.0%)	12 (5.0%)	19 (4.0%)
Lumacaftor/Ivacaftor	49 (26.3%)	54 (29.3%)	103 (27.8%)	69 (29.1%)	62 (25.8%)	131 (27.5%)
Tezacaftor/Ivacaftor	45 (24.2%)	43 (23.4%)	88 (23.8%)	53 (22.4%)	55 (22.9%)	108 (22.6%)
Positive Microbiology Culture (past year)[§]						
Pseudomonas aeruginosa	57 (30.6%)	39 (21.2%)	96 (25.9%)	63 (26.6%)	66 (27.5%)	129 (27.0%)
Staphylococcus aureus	118 (63.4%)	137 (74.5%)	255 (68.9%)	163 (68.8%)	158 (65.8%)	321 (67.3%)
Methicillin-resistant staphylococcus aureus	34 (18.3%)	40 (21.7%)	74 (20.0%)	56 (23.6%)	54 (22.5%)	110 (23.1%)
Stenotrophomonas maltophilia	9 (4.8%)	11 (6.0%)	20 (5.4%)	19 (8.0%)	9 (3.8%)	28 (5.9%)
Achromobacter xylosoxidans	1 (0.5%)	2 (1.1%)	3 (0.8%)	4 (1.7%)	4 (1.7%)	8 (1.7%)
Burkholderia cepacia complex	3 (1.6%)	2 (1.1%)	5 (1.4%)	4 (1.7%)	4 (1.7%)	8 (1.7%)
Haemophilus influenzae	9 (4.8%)	5 (2.7%)	14 (3.8%)	12 (5.1%)	8 (3.3%)	20 (4.2%)
Mycobacterium abscessus	2 (1.1%)	1 (0.5%)	3 (0.8%)	1 (0.4%)	2 (0.8%)	3 (0.6%)
Mycobacterium avium complex	1 (0.5%)	3 (1.6%)	4 (1.1%)	4 (1.7%)	3 (1.3%)	7 (1.5%)

Data are mean (SD) or n (%). Percentages may not sum to 100 in each category due to rounding.

[*] Other includes participants of more than one race.

[†] LCI result could be obtained at either the Week −2 or Week 0 Visit.

[‡] Participants may fall into more than one category of prior modulator use.

[§] Culture results obtained clinically within 12 months prior to screening.

Table 2.

Overview of Safety Outcomes

	Hypertonic Saline (HS) Trial		Dornase Alfa (DA) Trial	
	Continue N=186	Discontinue N=184	Continue N=237	Discontinue N=240
Participants with any SAE, n (%)	1 (0.5%)	2 (1.1%)	0 (0.0%)	0 (0.0%)
Abdominal Pain	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)
Infective Pulmonary Exacerbation	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Suicidal ideation	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)
Participants with any AE, n (%)	44 (23.7%)	64 (34.8%)	55 (23.2%)	89 (37.1%)
Maximum AE Severity, n (%) [*]				
Mild	23 (52.3%)	41 (64.1%)	36 (65.5%)	62 (69.7%)
Moderate	20 (45.5%)	18 (28.1%)	15 (27.3%)	24 (27.0%)
Severe [†]	1 (2.3%)	4 (6.3%)	4 (7.3%)	3 (3.4%)
Life Threatening [‡]	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)
Participants with at least one respiratory AE, n (%)	22 (11.8%)	30 (16.3%)	24 (10.1%)	47 (19.6%)
Participants with AE leading to Treatment Regimen Modification, n (%)	1 (0.5%)	5 (2.7%)	2 (0.8%)	7 (2.9%)
Participants with AE leading to Physician Directed Modification, n (%)	1 (0.5%)	0 (0.0%)	1 (0.4%)	4 (1.7%)
Participants with Most Common AEs, n (%) [§]				
Cough	7 (3.8%)	7 (3.8%)	10 (4.2%)	16 (6.7%)
Nasal Congestion	10 (5.4%)	5 (2.7%)	4 (1.7%)	11 (4.6%)
Chest Discomfort	1 (0.5%)	6 (3.3%)	1 (0.4%)	11 (4.6%)
Sputum Increased	3 (1.6%)	3 (1.6%)	2 (0.8%)	9 (3.8%)
COVID-19	2 (1.1%)	6 (3.3%)	1 (0.4%)	6 (2.5%)
Infective Pulmonary Exacerbation	5 (2.7%)	3 (1.6%)	3 (1.3%)	7 (2.9%)
Myalgia	2 (1.1%)	1 (0.5%)	1 (0.4%)	6 (2.5%)
Headache	3 (1.6%)	4 (2.2%)	6 (2.5%)	4 (1.7%)

Data are n (%).

[*] Percentages out of participants with any AE.

[†] The AEs classified as severe were the following, participants could have more than one severe event: Hypertonic Saline Continue: infective pulmonary exacerbation; Hypertonic Saline Discontinue: abdominal pain, chest discomfort, juvenile idiopathic arthritis, nasal congestion, pulmonary congestion; Dornase Alfa Continue: diarrhoea, eye infection bacterial, rib fracture, upper respiratory tract infection, wrist fracture; Dornase Alfa Discontinue: chest pain, immunization reaction, infective pulmonary exacerbation.

[‡] The AE classified as life threatening was suicidal ideation.

[§] Most common AEs defined as those occurring in at least 2.5% of participants in any treatment group across studies.