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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Mayer-Hamblett N, Ratjen F, Russell R, et al. Discontinuation versus continuation of hypertonic saline or dornase alfa in modulator treated people with cystic fibrosis (SIMPLIFY): results from two parallel, multicentre, open-label, randomised, controlled, non-inferiority trials. *Lancet Respir Med* 2022; published online Nov 4. https://doi.org/10.1016/S2213-2600(22)00434-9.

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplementary Methods

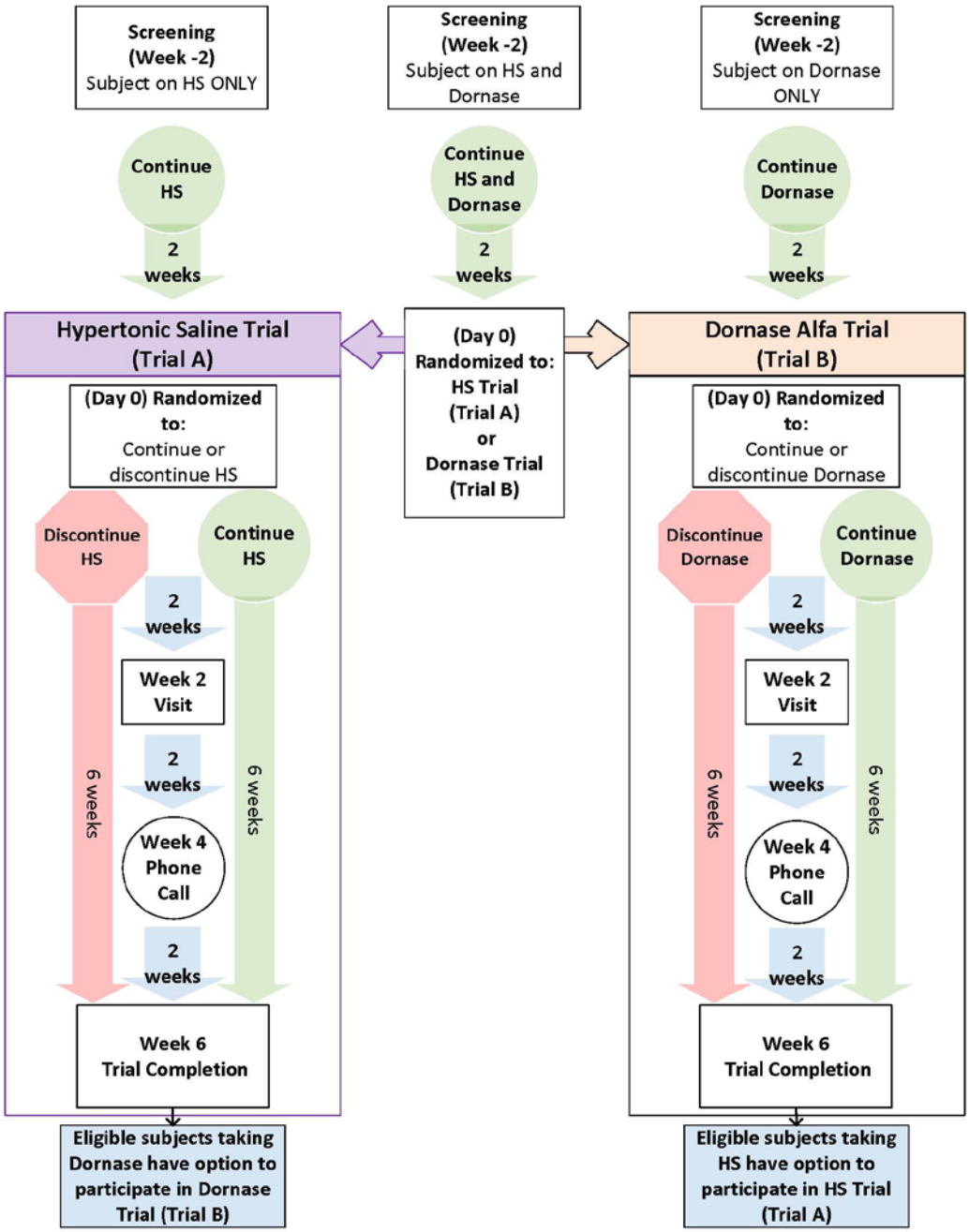
Study Design

Additional study design details have been previously published[1] and are also available in the accompanying protocol.

The SIMPLIFY Study comprises two identical randomized, controlled open label two-arm trials consisting of a two-week screening period, randomization to either continue or discontinue hypertonic saline (HS, Trial A) or dornase alfa (DA, Trial B), followed by a 6-week study period (Figure S1).Visits occurred at weeks -2 (Screening), 0, 2, and 6. Only those that maintained adequate reported adherence to inhaled drug therapy between Screening (Week -2) and Week 0 were eligible for randomization (Table S1). At Week 0, participants currently being 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 their current prescribed therapy. At trial entry, participants currently being treated with both HS and DA remained on both therapies during the screening period and were first randomized to Trial A (HS) or Trial B (DA) as well as randomized (1:1) to continue vs. discontinue the applicable therapy. After completion of the first trial, these participants subsequently could enroll in the alternative trial if they met eligibility criteria, with no time limitation between trials. Re-enrolling participants did not need to remain on the treatment regimen assigned in the first trial but had to meet all eligibility criteria regarding treatment stability prior to entry (Table S1).

Within each trial, randomization was stratified by Week 0 ppFEV$_1$ ($\geq$90, <90), treatment combination at screening (single or concurrent use of HS and/or DA), prior trial participation (yes/no), and age ($\geq$18 vs < 18). For participants randomly assigned to continue their therapy during a given trial, this therapy was expected to be taken at least once daily according to each participant's pre-existing, clinically prescribed regimen (e.g.,daily, twice daily). The concentration of HS was according to clinical prescription with minimum required concentration 3%. All participants were maintained on the same medications (and airway clearance routines) throughout the entire study period (i.e., Screening Visit through Week 6), as medically feasible, with no introduction of new chronic therapies or discontinuation of current chronic therapies except those outlined in the protocol (HS or DA).

Figure S1. SIMPLIFY Study Design Schematic**.** Reprinted with permission of the American Thoracic Society. Copyright © 2022 American Thoracic Society.[1] All rights reserved. Annals of the American Thoracic Society is an official journal of the American Thoracic Society.



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118 *Eligibility*

119 **Table S1.** Eligibility Criteria for SIMPLIFY.

Eligibility Criteria at Screening (Week -2)
Eligibility criteria will be evaluated at the Screening visit (Week -2) for each trial in the protocol. Participants that enter the SIMPLIFY Protocol taking only hypertonic saline or only dornase alfa at the time of entry will only be eligible to participate in one trial.
Consent
A. Written informed consent (and assent when applicable) obtained from participant or participant's legal guardian. B. Enrolled in the CF Patient Registry. C. For the 6-week trial duration, willingness to either continue or discontinue daily use of hypertonic saline or dornase alfa (as applicable to Trial A or Trial 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 participants who enter the SIMPLIFY Protocol taking both hypertonic saline and dornase alfa at the time of entry into their first trial: Willingness to be randomized to either Trial A or Trial B.
Demographics
A. Age ≥ 12 years at the Screening Visit.
Disease History
B. Diagnosis of CF. C. 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. D. After interim analysis, if DMC approves, a separate cohort (lower lung function cohort) of approximately 120 participants ≥ 18 years old with FEV_1 % predicted 40 to < 60 % predicted will be enrolled as a separate cohort into Trial A. E. Clinically stable with no significant changes in health status within the 7 days prior to and including the Screening Visit. F. No active smoking or vaping. G. 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
H. 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. I. 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. * J. Ability to tolerate albuterol or levalbuterol (Xopenex). K. 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.
Eligibility Criteria at Randomization (Week 0)
Eligibility criteria will be evaluated prior to randomization at Visit 1 (Week 0) for each trial.

Consent
I. Is willing and able to adhere to the study visit schedule and other protocol requirements.
Disease History
J. No absolute decrease in FEV_1% predicted of ≥ 10% between the Screening Visit and Visit 1 (Week 0).
K. Clinically stable with no significant changes in health status between the Screening Visit and Visit 1 (Week 0).
Concomitant Medications and Treatments
L. 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 (Week 0).
M. More than 70% compliance with submission of daily ePRO questionnaires in the up to 13 days prior to Visit 1 (Week 0).
N. 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 (Week 0).

*For participants with prior participation in SIMPLIFY, participants must continue with assigned use/non-use of therapy in the prior trial or re-establish consistent hypertonic saline and/or dornase alfa therapy prior to entering into the second study. There are no time constraints for re-entering.

Multiple Breath Washout

LCI was determined by nitrogen multiple breath washout (N_2 MBW) according to a standard operating procedure (SOP) using an open circuit, bias flow system (Exhalyzer D®, EcoMedics AG, and Duernten, Switzerland) and collected in device specific software (Spiroware® 3.1 EcoMedics AG). All operators underwent MBW training at the North American MBW core facility in Toronto and were certified for MBW testing prior to study initiation. Participants performed MBW testing in triplicate while watching a video. LCI was defined as the number of lung volume (functional residual capacity) turnovers needed to clear the tracer gas to $1/40^{th}$ of its starting concentration. MBW measurements were transmitted electronically to the Hospital for Sick Children MBW Center via a secure connection for centralized over-reading of the data and analysed using software version 3.3.1 to correct for the previously reported sensor error.[2] Measurements were deemed acceptable when at least 2 measurements per test occasions met quality control criteria.[3]

Blinding and Randomization

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 data coordinating center. Eligible participants in each trial were randomized 1:1 to continue or discontinue therapy using permuted blocks of varying size, stratified by Week 0 $ppFEV_1$ (≥90, <90), treatment combination at screening (single or concurrent use of HS and/or DA), prior study participation (yes/no), and age (≥18 vs < 18). Randomization occurred centrally using the Medidata Rave® RTSM system, a web-based randomization system with randomly generated treatment assignment lists derived for each trial strata by the TDN Coordinating Center and linked to the Medidata Rave® electronic data capture (EDC) system. Only authorized site personnel were given access to the randomization module in EDC. Authorized site personnel entered participant eligibility information and whether or not the participant signed informed consent. If the information entered into the EDC system was consistent with eligibility criteria for the study, the system provided the appropriate authorized site personnel with a randomization assignment for that participant that matched a specific treatment arm.

Data Quality

After data have been entered into the study database, data validation checks were applied on a regular basis. Queries were entered, tracked, and resolved through the EDC system directly. The study database was updated in accordance with the resolved queries. All changes to the study database were documented in an audit trail. Study monitoring was conducted to assess adherence to the protocol, provide site training, and assess data quality via select source document verification. All procedures for the handling and analysis of data are conducted using good computing practices for the handling and analysis of data for clinical trials.

Statistical Analysis

A detailed Statistical Analysis Plan (SAP) was developed and finalized prior to the analysis of study data. Trials were independently analyzed. The SAP outlines all modifications to the analysis plan that deviate from the protocol.

For the purposes of analysis, baseline is defined as Visit 1 (Day 0), unless otherwise specified. All estimates of differences between treatment groups are reported with corresponding 95% confidence intervals from ANOVA models adjusted for randomization strata. Corresponding within-arm estimates of change are least-squares means (LS means, also called estimated marginal means) with weighting proportional to randomization strata frequencies in the corresponding analysis population. The per-protocol (PP) population was used for the primary efficacy analyses, defined in the SAP by criteria including ≥70% adherence to the assigned treatment regimen post-randomization and no *a priori* defined major protocol deviations impacting the primary analysis, with criteria as below:

1. Daily diary completion (“Compliance”)
    a. ≥70% non-missing data
    b. ≥70% non-missing in last 13 days
2. Daily diary responses aligned with randomized treatment (“Adherence”)
    a. to assigned treatment regimen (HS or DA) among non-missing days overall (≥70%)

b. to assigned treatment regimen (HS or DA) among non-missing days in last 13 days (≥70%)
3. No initiation of new acute oral, inhaled, or IV antibiotics for respiratory symptoms
4. Non-missing FEV at Visit 3 (week 6)
5. Given the correct randomization instructions
6. Minimum 70% use of ETI among non-missing days in last 13 days
7. Randomized but determined to be ineligible

Participants could meet more than one criterion for exclusion from the PP population. For participants with multiple PP exclusions, the primary reason included in Figure 1 was determined by chronological order (ie. using the sequence of events in the study). The PP population was used to test for non-inferiority with the intent that this analysis population would result in a more conservative treatment effect (e.g., showing a more *negative* effect with discontinuation) by assuring a population with distinct treatment patterns for which to measure a difference. Sensitivity analyses of the primary and secondary efficacy endpoints were performed on the intent to treat (ITT) population defined as all subjects randomized at Visit 1 (Day 0). Pre-defined subgroup analyses including randomization factors and evaluating age group, sex at birth, genotype, *Pseudomonas aeruginosa* status, and concurrent use of airway clearance therapy were conducted. . Additional subgroup analyses were considered exploratory.

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.[1] Establishment of a NI margin in the context of this study weighted community input about an important reduction in $ppFEV_1$ that would suggest clear negative impact of discontinuation of therapy, given the inexistence of data about the clinical effectiveness of either DA or HS in modulator treated people with CF.

The primary approach to handling missing data was through careful study conduct to prevent loss to follow-up and obtain endpoint data for participants who withdrew from the study.[4] Missing outcome data in the ITT population for additional sensitivity analyses of the primary endpoint and for key secondary endpoints (CRISS, CFQ-R, and LCI) 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 randomization to Week 6. This modification to the control-based mean imputation[5] was pre-specified to assess sensitivity to the missing at random assumption (MAR) under the non-inferiority design. Complete case results in the ITT population, including participants based on availability of non-missing values, are also reported.

To aid in the monitoring of safety, for each trial, the scheduled review following enrollment of 25% and 50% for that trial included a formal evaluation of excess harm as measured by the 6-week change in $ppFEV_1$. In these reviews, the Data Monitoring Committee (DMC) was guided by interim boundaries pre-specified to test for excess harm. For the purposes of each trial in the SIMPLIFY study, excess harm was defined at interim evaluations as a difference between treatment groups in the 6-week change in $ppFEV_1$ for which the upper bound of the associated CI excluded a pre-defined margin of -1.5% (e.g. representing a small and clinically negligible negative effect of withdrawal). This smaller margin was selected for interim monitoring in order to allow for detection of harm near the boundary below the pre-defined NI margin, -3%. The interim evaluations for excess harm during each study were performed using the ITT safety population with Pocock alpha spending adjustment for group sequential testing, a one-sided alpha of 0.025, common standard deviation of 8.4%, and total ITT sample size of 350 allowing for up to 12% attrition from the 400 enrolled. These interim evaluations for excess harm with non-binding stopping rules did not require multiplicity adjustment to control the alpha level of 0.025 for the final test of non-inferiority and had negligible impact on power under the alternative of no difference.

All analyses were performed using SAS (SAS Institute Inc, Cary, NC, 2020) version 9.4), and R (version 4.0.3).[6]

SIMPLIFY Enrollment Progression

In October 2021, the DA trial achieved goal enrollment but was given DMC approval to over-enroll in order to increase data collection of the LCI secondary endpoint, initially impacted by COVID-19 site restrictions. Rather than closing the DA trial, per DMC approval and as permitted in study consent, the study level randomization allocation was altered from 1:1 randomization to subsequently weight randomization of participants on both therapies to the HS trial. By Spring 2022, overall study enrollment was demonstrating increasingly slow enrollment

reflecting both surges in the COVID-19 pandemic and limited remaining eligible patient population to recruit amidst other competing trials and accounting for individuals with CF who had already altered use of the trial therapies. A planned mid-study assessment of the overall (pooled) estimates of the standard deviation of the primary endpoint, the 6-week change in $ppFEV_1$, demonstrated a significantly lower value than included in sample size calculations (<6 as compared to the assumed standard deviation of 8). Thus, ending enrollment for the HS trial just under the original target of 400 participants (with approximately 300 expected in the PP population) was not anticipated to impact study power. Thus, the SIMPLIFY study was closed to enrollment in May 2022 based on feasibility of completing original enrollment targets.

Supplementary Results

Table S2. Overview of compliance to medication reporting and treatment regimen adherence.

	Hypertonic Saline (HS) Trial		Dornase Alfa (DA) Trial	
	Continue N=186	**Discontinue N=184**	**Continue N=237**	**Discontinue N=240**
Daily Medication Use Reporting (Compliance), %				
N	186	184	237	240
Mean (SD)	88.3 (15.02)	91.2 (11.21)	91.2 (12.26)	91.6 (13.43)
≥70% Compliance, n (%) *	150 (80.6%)	153 (83.2%)	208 (87.8%)	214 (89.2%)
Reported Adherence to Assigned Regimen, % †				
N	186	184	237	240
Mean (SD)	98.1 (6.37)	96.1 (14.05)	96.3 (9.66)	97.4 (9.75)
≥70% Adherence, n (%) *	178 (95.7%)	175 (95.1%)	224 (94.5%)	228 (95.0%)
Reported Adherence to ETI, %				
N	186	184	237	240
Mean (SD)	99.6 (1.74)	99.3 (2.73)	99.4 (2.58)	99.5 (2.10)
Reported Adherence to Other Inhaled Therapy (if using), %				
N	156	154	147	148
Mean (SD)	97.5 (6.09)	98.7 (3.76)	96.4 (10.92)	98.5 (4.55)
Reported Adherence to ACT (if using), %				
N	178	174	228	226
Mean (SD)	95.9 (14.43)	96.0 (15.71)	93.5 (19.10)	94.2 (18.51)

* Met ≥70% in both the overall study period (Week 0 to Week 6) and in the last two weeks prior to Week 6.
† Adherence for each participant is defined as Y/X, multiplied by 100, where X is the number of days participant reported on daily medication use and Y is the number of days participant reported following treatment assignment.

Table S3. Baseline and clinical characteristics comparing the ITT and PP populations in the HS trial.

	ITT Population		PP Population	
	Continue N=186	**Discontinue N=184**	**Continue N=140**	**Discontinue N=133**
Sex at Birth				
Male	99 (53.2%)	97 (52.7%)	77 (55.0%)	68 (51.1%)
Female	87 (46.8%)	87 (47.3%)	63 (45.0%)	65 (48.9%)
Age (years)				
N	186	184	140	133
Mean (SD)	22.4 (10.73)	21.7 (10.28)	23.5 (11.34)	21.8 (11.06)
Age Distribution				
≥12 to <18	92 (49.5%)	90 (48.9%)	64 (45.7%)	68 (51.1%)
≥18 to <24	39 (21.0%)	37 (20.1%)	28 (20.0%)	24 (18.0%)
≥24 to <30	18 (9.7%)	32 (17.4%)	15 (10.7%)	22 (16.5%)
≥30	37 (19.9%)	25 (13.6%)	33 (23.6%)	19 (14.3%)
Race				
White	182 (97.8%)	176 (95.7%)	136 (97.1%)	128 (96.2%)
Black or African American	1 (0.5%)	2 (1.1%)	1 (0.7%)	2 (1.5%)
Asian	0 (0%)	1 (0.5%)	0 (0%)	0 (0%)
American Indian or Alaskan Native	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Native Hawaiian or Other Pacific Islander	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Other/Unknown*	3 (1.6%)	5 (2.7%)	3 (2.1%)	3 (2.3%)
Ethnicity				
Hispanic or Latino	6 (3.2%)	14 (7.6%)	6 (4.3%)	11 (8.3%)
Not Hispanic or Latino	180 (96.8%)	170 (92.4%)	134 (95.7%)	122 (91.7%)
Genotype Group				
F508del Homozygous	111 (59.7%)	111 (60.3%)	84 (60.0%)	82 (61.7%)
F508del Heterozygous	72 (38.7%)	71 (38.6%)	53 (37.9%)	51 (38.3%)
Other/Unknown	3 (1.6%)	2 (1.1%)	3 (2.1%)	0 (0%)
FEV_1 (% predicted)				
N	186	184	140	133
Mean (SD)	97.2 (16.50)	96.7 (17.17)	96.8 (17.30)	97.6 (17.55)
FEV_1 (% predicted) Distribution				
<60	1 (0.5%)	1 (0.5%)	1 (0.7%)	1 (0.8%)
≥60 to <70	10 (5.4%)	13 (7.1%)	10 (7.1%)	9 (6.8%)
≥70 to <90	53 (28.5%)	46 (25.0%)	37 (26.4%)	32 (24.1%)
≥90 to <100	33 (17.7%)	45 (24.5%)	26 (18.6%)	31 (23.3%)
≥100	89 (47.8%)	79 (42.9%)	66 (47.1%)	60 (45.1%)
$LCI_{2.5}$ †				
N	47	52	33	33
Mean (SD)	7.8 (2.15)	8.2 (2.56)	7.8 (2.37)	8.1 (2.59)

	ITT Population		PP Population	
	Continue N=186	**Discontinue N=184**	**Continue N=140**	**Discontinue N=133**
Prior Study Enrollee				
	62 (33.3%)	62 (33.7%)	45 (32.1%)	42 (31.6%)
Current Chronic Therapy				
DA	156 (83.9%)	154 (83.7%)	120 (85.7%)	111 (83.5%)
HS	186 (100%)	184 (100%)	140 (100%)	133 (100%)
ETI	186 (100%)	184 (100%)	140 (100%)	133 (100%)
Airway clearance	178 (95.7%)	174 (94.6%)	132 (94.3%)	127 (95.5%)
Inhaled antibiotic (Continuous)	7 (3.8%)	2 (1.1%)	4 (2.9%)	0 (0%)
Inhaled antibiotic (Cycled)	51 (27.4%)	43 (23.4%)	41 (29.3%)	32 (24.1%)
Inhaled antibiotic (Continuous Alternating)	17 (9.1%)	15 (8.2%)	12 (8.6%)	11 (8.3%)
Oral antibiotic	85 (45.7%)	81 (44.0%)	65 (46.4%)	58 (43.6%)
Ibuprofen	8 (4.3%)	15 (8.2%)	8 (5.7%)	11 (8.3%)
Systemic steroids	1 (0.5%)	2 (1.1%)	1 (0.7%)	1 (0.8%)
Previous Modulator Use ‡				
Ivacaftor	8 (4.3%)	1 (0.5%)	6 (4.3%)	1 (0.8%)
Lumacaftor/Ivacaftor	49 (26.3%)	54 (29.3%)	36 (25.7%)	37 (27.8%)
Tezacaftor/Ivacaftor	45 (24.2%)	43 (23.4%)	32 (22.9%)	29 (21.8%)
Positive Microbiology Culture (past year) §				
Pseudomonas aeruginosa	57 (30.6%)	39 (21.2%)	43 (30.7%)	31 (23.3%)
Staphylococcus aureus	118 (63.4%)	137 (74.5%)	89 (63.6%)	105 (78.9%)
Methicillin-resistant staphylococcus aureus	34 (18.3%)	40 (21.7%)	26 (18.6%)	26 (19.5%)
Stenotrophomonas maltophilia	9 (4.8%)	11 (6.0%)	8 (5.7%)	9 (6.8%)
Achromobacter xylosoxidans	1 (0.5%)	2 (1.1%)	0 (0%)	1 (0.8%)
Burkholderia cepacia complex	3 (1.6%)	2 (1.1%)	2 (1.4%)	1 (0.8%)
Haemophilus influenzae	9 (4.8%)	5 (2.7%)	6 (4.3%)	2 (1.5%)
Mycobacterium abscessus	2 (1.1%)	1 (0.5%)	1 (0.7%)	0 (0%)
Mycobacterium avium complex	1 (0.5%)	3 (1.6%)	0 (0%)	0 (0%)

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 S4. Baseline and clinical characteristics comparing the ITT and PP populations in the DA trial.

	ITT Population		PP Population	
	Continue N=237	**Discontinue N=240**	**Continue N=193**	**Discontinue N=199**
Sex at Birth				
Male	117 (49.4%)	127 (52.9%)	96 (49.7%)	101 (50.8%)
Female	120 (50.6%)	113 (47.1%)	97 (50.3%)	98 (49.2%)
Age (years)				
N	237	240	193	199
Mean (SD)	23.2 (11.50)	21.9 (9.19)	23.7 (11.83)	22.1 (9.39)
Age Distribution				
≥12 to <18	108 (45.6%)	110 (45.8%)	85 (44.0%)	89 (44.7%)
≥18 to <24	48 (20.3%)	51 (21.3%)	36 (18.7%)	45 (22.6%)
≥24 to <30	31 (13.1%)	32 (13.3%)	27 (14.0%)	25 (12.6%)
≥30	50 (21.1%)	47 (19.6%)	45 (23.3%)	40 (20.1%)
Race				
White	227 (95.8%)	231 (96.3%)	187 (96.9%)	192 (96.5%)
Black or African American	4 (1.7%)	1 (0.4%)	3 (1.6%)	1 (0.5%)
Asian	1 (0.4%)	0 (0%)	1 (0.5%)	0 (0%)
American Indian or Alaskan Native	0 (0%)	1 (0.4%)	0 (0%)	1 (0.5%)
Native Hawaiian or Other Pacific Islander	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Other/Unknown*	5 (2.1%)	7 (2.9%)	2 (1.0%)	5 (2.5%)
Ethnicity				
Hispanic or Latino	15 (6.3%)	19 (7.9%)	9 (4.7%)	17 (8.5%)
Not Hispanic or Latino	222 (93.7%)	221 (92.1%)	184 (95.3%)	182 (91.5%)
Genotype Group				
F508del Homozygous	140 (59.1%)	129 (53.8%)	115 (59.6%)	105 (52.8%)
F508del Heterozygous	91 (38.4%)	106 (44.2%)	73 (37.8%)	90 (45.2%)
Other/Unknown	6 (2.5%)	5 (2.1%)	5 (2.6%)	4 (2.0%)
FEV_1 (% predicted)				
N	237	240	193	199
Mean (SD)	97.2 (16.32)	96.5 (17.34)	97.0 (16.35)	96.8 (17.40)
FEV_1 (% predicted) Distribution				
<60	3 (1.3%)	1 (0.4%)	3 (1.6%)	1 (0.5%)
≥60 to <70	11 (4.6%)	20 (8.3%)	10 (5.2%)	16 (8.0%)
≥70 to <90	63 (26.6%)	57 (23.8%)	48 (24.9%)	46 (23.1%)
≥90 to <100	51 (21.5%)	53 (22.1%)	42 (21.8%)	42 (21.1%)
≥100	109 (46.0%)	109 (45.4%)	90 (46.6%)	94 (47.2%)
$LCI_{2.5}$ †				
N	61	69	52	55
Mean (SD)	7.9 (1.77)	8.2 (2.73)	8.0 (1.83)	8.5 (2.96)

	ITT Population		PP Population	
	Continue N=237	**Discontinue N=240**	**Continue N=193**	**Discontinue N=199**
Prior Study Enrollee				
	64 (27.0%)	65 (27.1%)	48 (24.9%)	54 (27.1%)
Current Chronic Therapy				
DA	237 (100%)	240 (100%)	193 (100%)	199 (100%)
HS	147 (62.0%)	148 (61.7%)	118 (61.1%)	120 (60.3%)
ETI	237 (100%)	240 (100%)	193 (100%)	199 (100%)
Airway clearance	228 (96.2%)	226 (94.2%)	185 (95.9%)	187 (94.0%)
Inhaled antibiotic (Continuous)	3 (1.3%)	6 (2.5%)	2 (1.0%)	5 (2.5%)
Inhaled antibiotic (Cycled)	50 (21.1%)	56 (23.3%)	44 (22.8%)	50 (25.1%)
Inhaled antibiotic (Continuous Alternating)	25 (10.5%)	23 (9.6%)	20 (10.4%)	21 (10.6%)
Oral antibiotic	103 (43.5%)	104 (43.3%)	84 (43.5%)	88 (44.2%)
Ibuprofen	20 (8.4%)	21 (8.8%)	17 (8.8%)	20 (10.1%)
Systemic steroids	2 (0.8%)	3 (1.3%)	1 (0.5%)	3 (1.5%)
Previous Modulator Use ‡				
Ivacaftor	7 (3.0%)	12 (5.0%)	5 (2.6%)	12 (6.0%)
Lumacaftor/Ivacaftor	69 (29.1%)	62 (25.8%)	58 (30.1%)	52 (26.1%)
Tezacaftor/Ivacaftor	53 (22.4%)	55 (22.9%)	41 (21.2%)	46 (23.1%)
Positive Microbiology Culture (past year) §				
Pseudomonas aeruginosa	63 (26.6%)	66 (27.5%)	55 (28.5%)	57 (28.6%)
Staphylococcus aureus	163 (68.8%)	158 (65.8%)	138 (71.5%)	133 (66.8%)
Methicillin-resistant staphylococcus aureus	56 (23.6%)	54 (22.5%)	44 (22.8%)	46 (23.1%)
Stenotrophomonas maltophilia	19 (8.0%)	9 (3.8%)	17 (8.8%)	9 (4.5%)
Achromobacter xylosoxidans	4 (1.7%)	4 (1.7%)	4 (2.1%)	2 (1.0%)
Burkholderia cepacia complex	4 (1.7%)	4 (1.7%)	4 (2.1%)	4 (2.0%)
Haemophilus influenzae	12 (5.1%)	8 (3.3%)	10 (5.2%)	7 (3.5%)
Mycobacterium abscessus	1 (0.4%)	2 (0.8%)	1 (0.5%)	2 (1.0%)
Mycobacterium avium complex	4 (1.7%)	3 (1.3%)	4 (2.1%)	3 (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.

Figure S2. Difference between the discontinuation and continuation treatment groups in the 6-week change in $ppFEV_1$ among subgroups in the ITT population in the HS trial and DA trial. Treatment differences adjusted for randomization strata. Pre-defined subgroups noted with *.

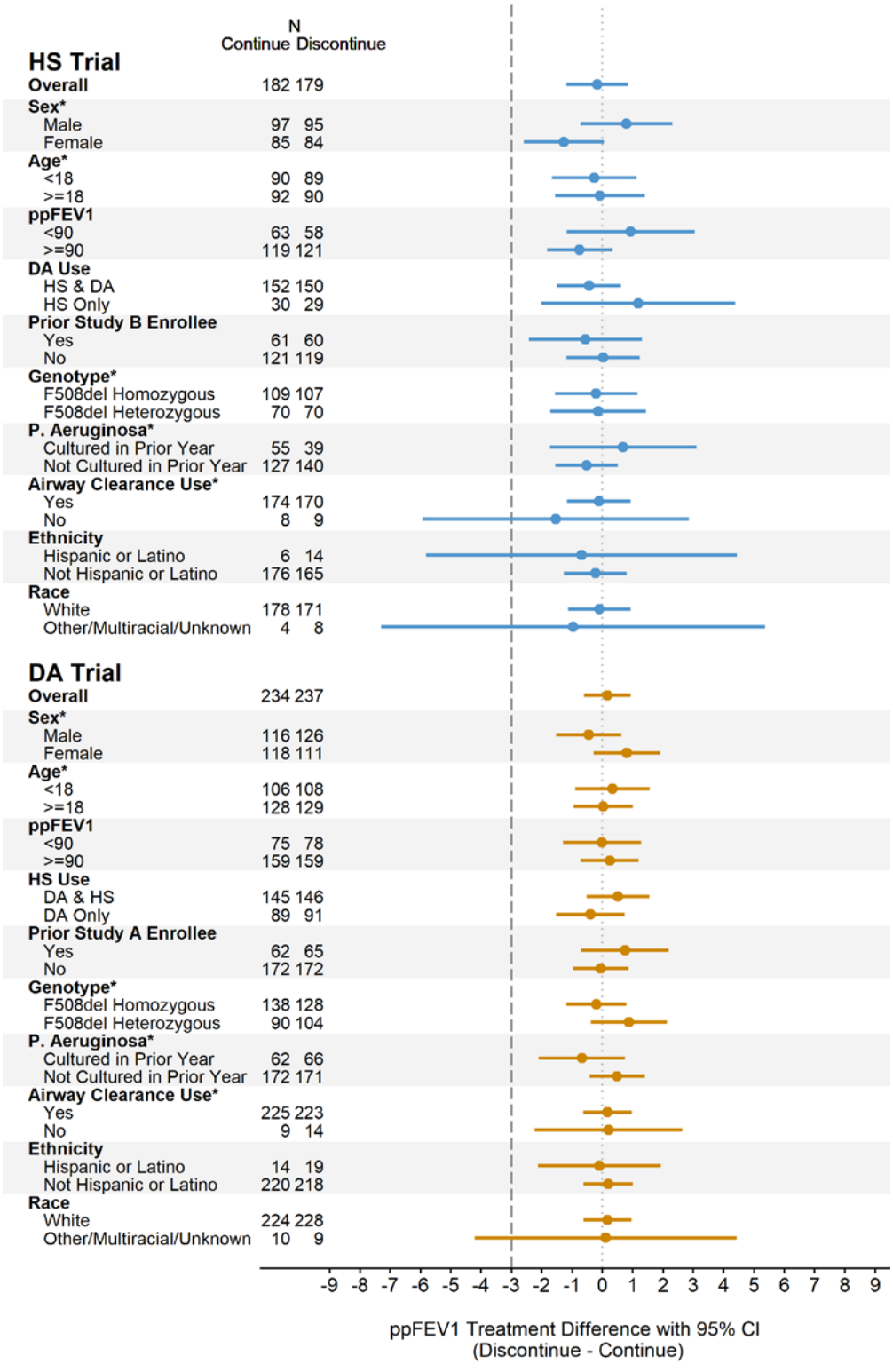


Table S5. Summary of $ppFEV_1$ over time in the PP and ITT populations (HS trial)

		ITT Population (HS Trial)			PP Population (HS Trial)		
Visit	**Statistic**	**Continue N=186**	**Discontinue N=184**	**Difference (Discontinue minus Continue) (95% CI)**	**Continue N=140**	**Discontinue N=133**	**Difference (Discontinue minus Continue) (95% CI)**
Week -2 (Screening)	N (%)	186 (100.0%)	184 (100.0%)		140 (100.0%)	133 (100.0%)	
	Mean (SD)	97.3 (16.49)	96.4 (16.84)	-0.88 (-4.28, 2.53)	97.2 (17.15)	97.4 (17.21)	0.22 (-3.88, 4.31)
Week 0 (Randomization)	N (%)	186 (100.0%)	184 (100.0%)		140 (100.0%)	133 (100.0%)	
	Mean (SD)	97.2 (16.50)	96.7 (17.17)	-0.45 (-3.89, 3.00)	96.8 (17.30)	97.6 (17.55)	0.86 (-3.30, 5.02)
Absolute Change (Week -2 to Week 0)	N (%)	186 (100.0%)	184 (100.0%)		140 (100.0%)	133 (100.0%)	
	Mean (SD)	-0.1 (4.04)	0.3 (3.44)	0.43 (-0.34, 1.20)	-0.4 (3.86)	0.2 (3.63)	0.64 (-0.25, 1.54)
Relative Change (Week -2 to Week 0)	N (%)	186 (100.0%)	184 (100.0%)		140 (100.0%)	133 (100.0%)	
	Mean (SD)	0.0 (4.71)	0.4 (3.87)	0.36 (-0.52, 1.24)	-0.4 (4.44)	0.3 (4.11)	0.64 (-0.38, 1.66)
Week 2 (Visit 2)	N (%)	183 (98.4%)	177 (96.2%)		138 (98.6%)	128 (96.2%)	
	Mean (SD)	97.0 (16.58)	96.2 (17.28)	-0.81 (-4.32, 2.71)	97.2 (17.18)	97.8 (17.42)	0.65 (-3.53, 4.83)
Absolute Change (Week 0 to Week 2)	N (%)	183 (98.4%)	177 (96.2%)		138 (98.6%)	128 (96.2%)	
	Mean (SD)	0.0 (3.67)	-0.4 (3.78)	-0.38 (-1.15, 0.40)	0.6 (2.94)	0.3 (3.66)	-0.24 (-1.04, 0.57)
Relative Change (Week 0 to Week 2)	N (%)	183 (98.4%)	177 (96.2%)		138 (98.6%)	128 (96.2%)	
	Mean (SD)	0.1 (3.98)	-0.3 (4.18)	-0.39 (-1.23, 0.46)	0.7 (3.29)	0.5 (4.12)	-0.22 (-1.12, 0.69)
Difference in Absolute Changes (Week 0 to Week 2 minus Week -2 to Week 0)	N (%)	183 (98.4%)	177 (96.2%)		138 (98.6%)	128 (96.2%)	
	Mean (SD)	0.1 (6.57)	-0.7 (6.07)	-0.79 (-2.10, 0.52)	1.0 (5.56)	0.1 (6.07)	-0.89 (-2.30, 0.52)
Week 6 (Visit 3)	N (%)	182 (97.8%)	179 (97.3%)		140 (100.0%)	133 (100.0%)	
	Mean (SD)	96.8 (18.00)	96.2 (17.28)	-0.57 (-4.23, 3.08)	96.9 (17.74)	97.5 (17.10)	0.56 (-3.59, 4.71)
Absolute Change (Week 0 to Week 6)	N (%)	182 (97.8%)	179 (97.3%)		140 (100.0%)	133 (100.0%)	
	Mean (SD)	-0.4 (5.68)	-0.5 (3.98)	-0.17 (-1.19, 0.84)	0.1 (3.64)	-0.2 (4.10)	-0.30 (-1.22, 0.63)

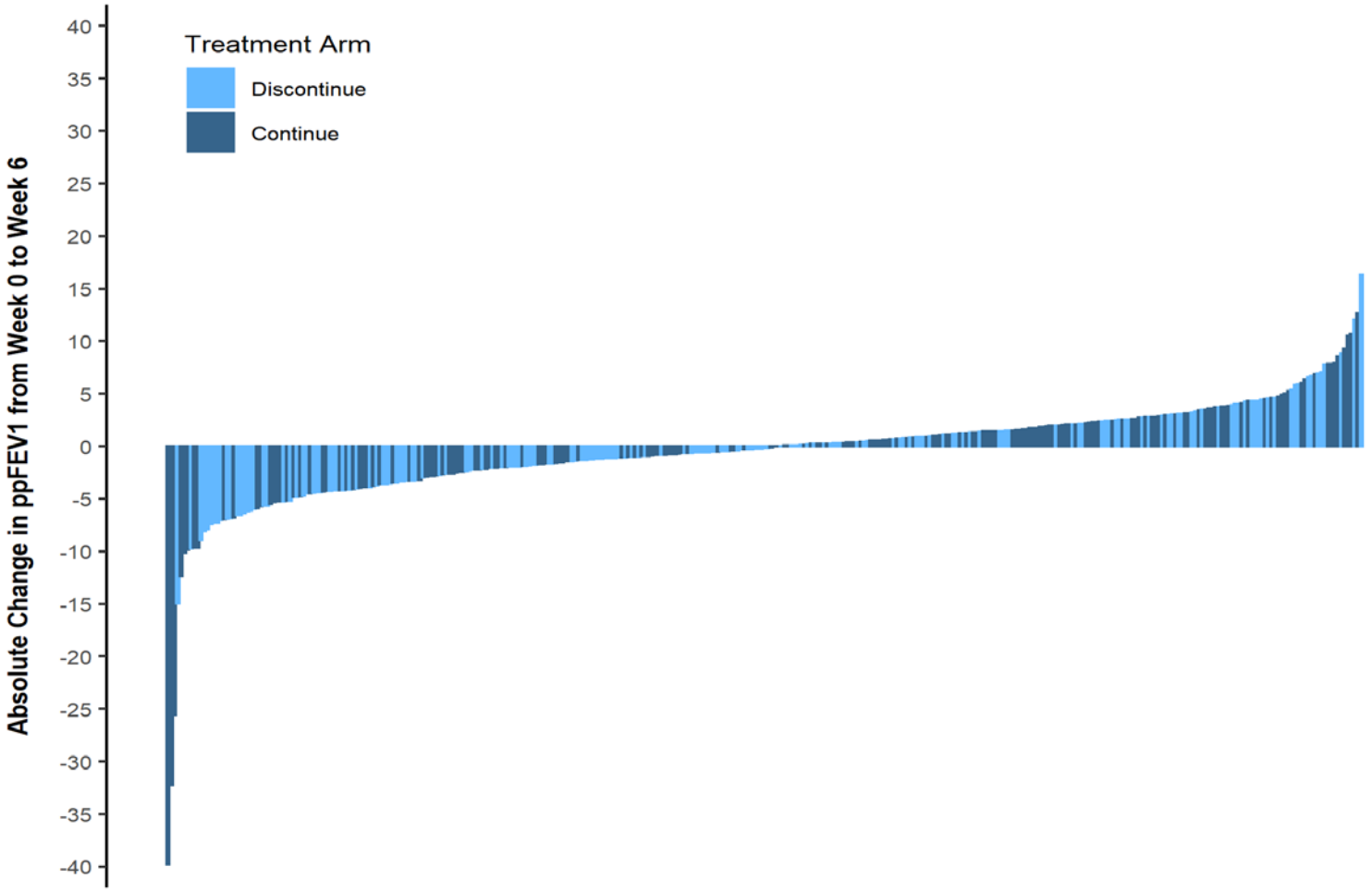
		ITT Population (HS Trial)			PP Population (HS Trial)		
Visit	**Statistic**	**Continue N=186**	**Discontinue N=184**	**Difference (Discontinue minus Continue) (95% CI)**	**Continue N=140**	**Discontinue N=133**	**Difference (Discontinue minus Continue) (95% CI)**
Relative Change (Week 0 to Week 6)	N (%)	182 (97.8%)	179 (97.3%)		140 (100.0%)	133 (100.0%)	
	Mean (SD)	-0.5 (6.36)	-0.5 (4.31)	-0.01 (-1.13, 1.11)	0.1 (3.85)	0.0 (4.39)	-0.12 (-1.11, 0.87)

Table S6. Summary of $ppFEV_1$ over time in the PP and ITT populations (DA trial).

		ITT Population (DA Trial)			PP Population (DA Trial)		
Visit	**Statistic**	**Continue N=186**	**Discontinue N=184**	**Difference (Discontinue minus Continue) (95% CI)**	**Continue N=140**	**Discontinue N=133**	**Difference (Discontinue minus Continue) (95% CI)**
Week -2 (Screening)	N (%)	237 (100.0%)	240 (100.0%)		193 (100.0%)	199 (100.0%)	
	Mean (SD)	97.0 (16.20)	96.5 (17.17)	-0.58 (-3.59, 2.42)	97.0 (16.10)	96.6 (17.16)	-0.46 (-3.76, 2.85)
Week 0 (Randomization)	N (%)	237 (100.0%)	240 (100.0%)		193 (100.0%)	199 (100.0%)	
	Mean (SD)	97.2 (16.32)	96.5 (17.34)	-0.70 (-3.73, 2.33)	97.0 (16.35)	96.8 (17.40)	-0.17 (-3.52, 3.18)
Absolute Change (Week -2 to Week 0)	N (%)	237 (100.0%)	240 (100.0%)		193 (100.0%)	199 (100.0%)	
	Mean (SD)	0.2 (4.00)	0.0 (3.24)	-0.12 (-0.78, 0.54)	0.0 (3.79)	0.2 (3.11)	0.28 (-0.40, 0.97)
Relative Change (Week -2 to Week 0)	N (%)	237 (100.0%)	240 (100.0%)		193 (100.0%)	199 (100.0%)	
	Mean (SD)	0.2 (4.38)	0.1 (3.45)	-0.16 (-0.87, 0.55)	0.0 (4.07)	0.3 (3.32)	0.28 (-0.46, 1.02)
Week 2 (Visit 2)	N (%)	230 (97.0%)	236 (98.3%)		189 (97.9%)	196 (98.5%)	
	Mean (SD)	97.6 (16.21)	96.1 (17.73)	-1.45 (-4.54, 1.64)	97.1 (16.22)	96.5 (17.83)	-0.67 (-4.09, 2.74)
Absolute Change (Week 0 to Week 2)	N (%)	230 (97.0%)	236 (98.3%)		189 (97.9%)	196 (98.5%)	
	Mean (SD)	0.2 (3.91)	-0.1 (3.60)	-0.30 (-0.99, 0.38)	0.1 (3.96)	-0.1 (3.67)	-0.15 (-0.92, 0.61)
Relative Change (Week 0 to Week 2)	N (%)	230 (97.0%)	236 (98.3%)		189 (97.9%)	196 (98.5%)	
	Mean (SD)	0.3 (3.87)	-0.2 (3.83)	-0.40 (-1.10, 0.30)	0.2 (3.90)	-0.1 (3.91)	-0.27 (-1.05, 0.51)
Difference in Absolute Changes (Week 0 to Week 2 minus Week -2 to Week 0)	N (%)	230 (97.0%)	236 (98.3%)		189 (97.9%)	196 (98.5%)	
	Mean (SD)	0.0 (6.33)	-0.1 (5.49)	-0.09 (-1.17, 0.99)	0.1 (6.14)	-0.2 (5.51)	-0.33 (-1.50, 0.84)
Week 6 (Visit 3)	N (%)	234 (98.7%)	237 (98.8%)		193 (100.0%)	199 (100.0%)	
	Mean (SD)	97.3 (16.36)	96.4 (17.36)	-0.86 (-3.92, 2.19)	96.8 (16.39)	97.0 (17.30)	0.20 (-3.15, 3.54)
Absolute Change (Week 0 to Week 6)	N (%)	234 (98.7%)	237 (98.8%)		193 (100.0%)	199 (100.0%)	
	Mean (SD)	-0.1 (4.37)	0.0 (4.10)	0.17 (-0.60, 0.93)	-0.2 (4.37)	0.2 (3.69)	0.37 (-0.44, 1.17)
Relative Change (Week 0 to Week 6)	N (%)	234 (98.7%)	237 (98.8%)		193 (100.0%)	199 (100.0%)	
	Mean (SD)	-0.1 (4.54)	0.1 (4.38)	0.19 (-0.62, 0.99)	-0.1 (4.51)	0.3 (3.97)	0.40 (-0.45, 1.24)

Figure S3. Individual changes in the 6-week change in ppFEV$_1$ for the (A) ITT and (B) PP populations (HS trial).

A) In the Continue and Discontinue arms, respectively, 153/182 (84%) and 147/179 (82%) of participants had a Week 6 ppFEV$_1$ within 5% of their baseline value (i.e., ppFEV$_1$ change between -5 and 5%).



B) In the Continue and Discontinue arms, respectively, 118/140 (84%) and 107/133 (80%) of participants had a Week 6 ppFEV$_1$ within 5% of their baseline value (i.e., ppFEV$_1$ change between -5 and 5%).

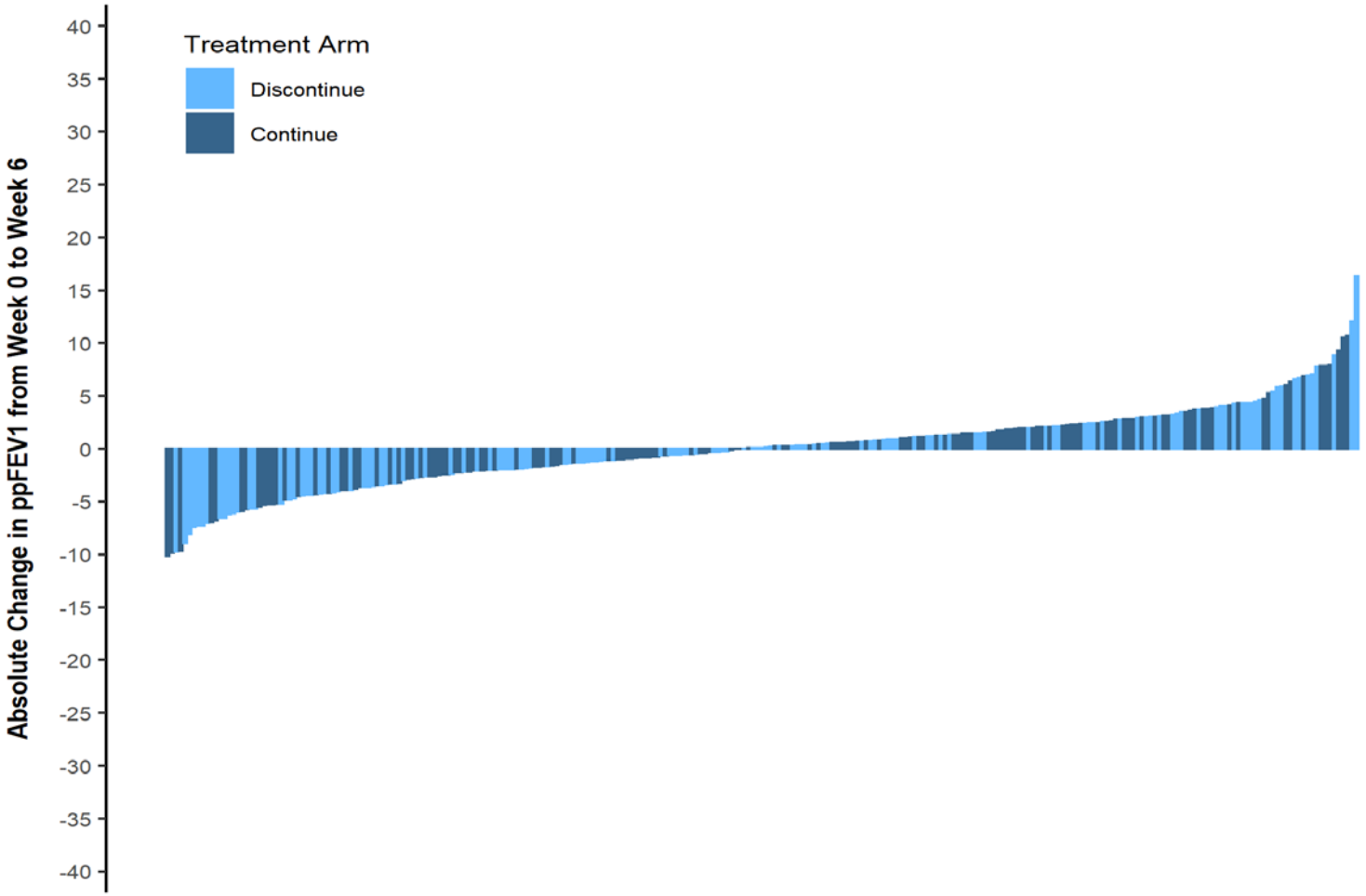
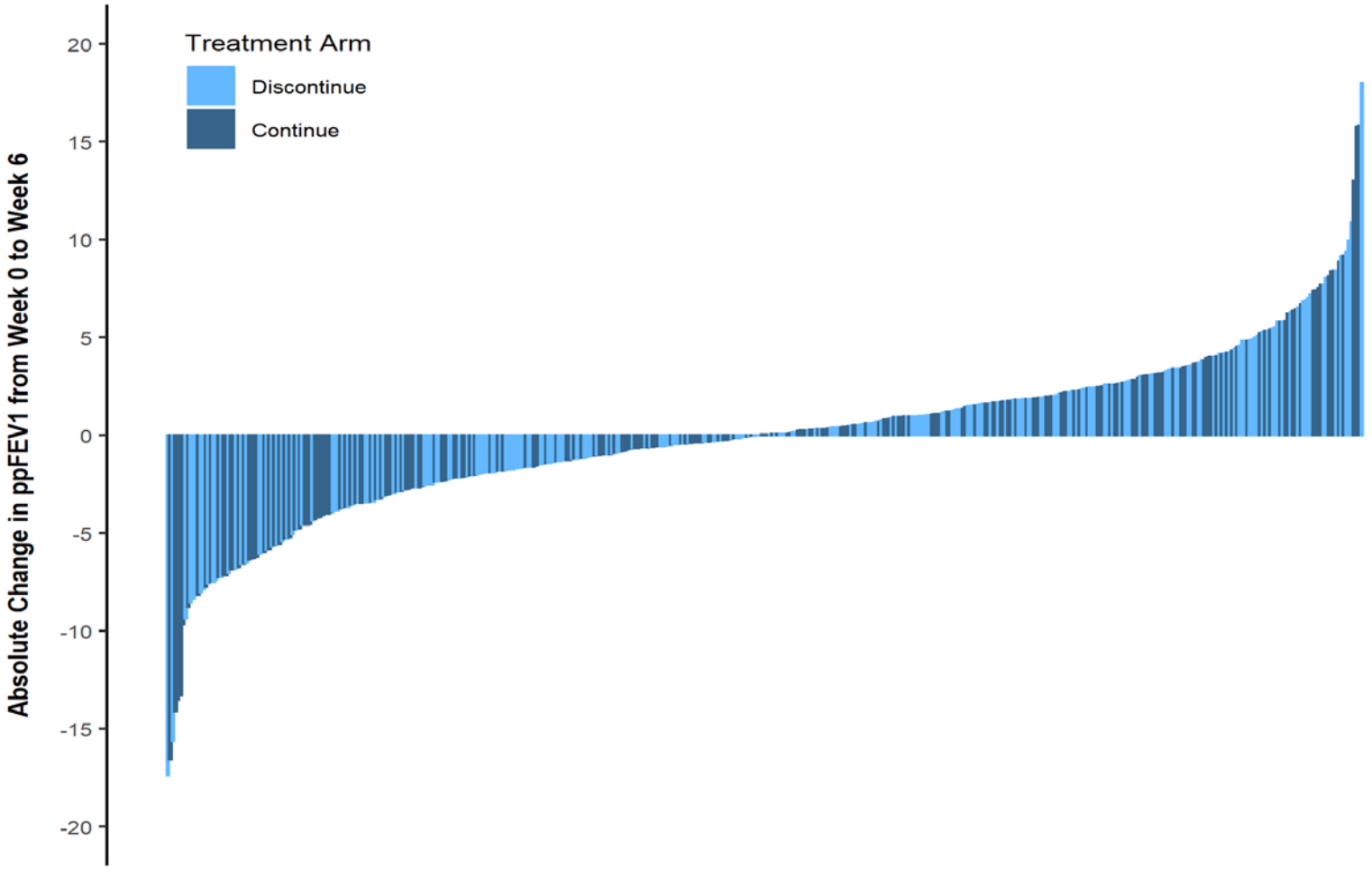


Figure S4. Individual changes in the 6-week change in $ppFEV_1$ for the (A) ITT and (B) PP populations (DA trial).

A) In the Continue and Discontinue arms, respectively, 187/234 (80%) and 192/237 (81%) of participants had a Week 6 $ppFEV_1$ within 5% of their baseline value (i.e., $ppFEV_1$ change between -5 and 5%).



B) In the Continue and Discontinue arms, respectively, 155/193 (80%) and 165/199 (83%) of participants had a Week 6 ppFEV$_1$ within 5% of their baseline value (i.e., ppFEV$_1$ change between -5 and 5%).

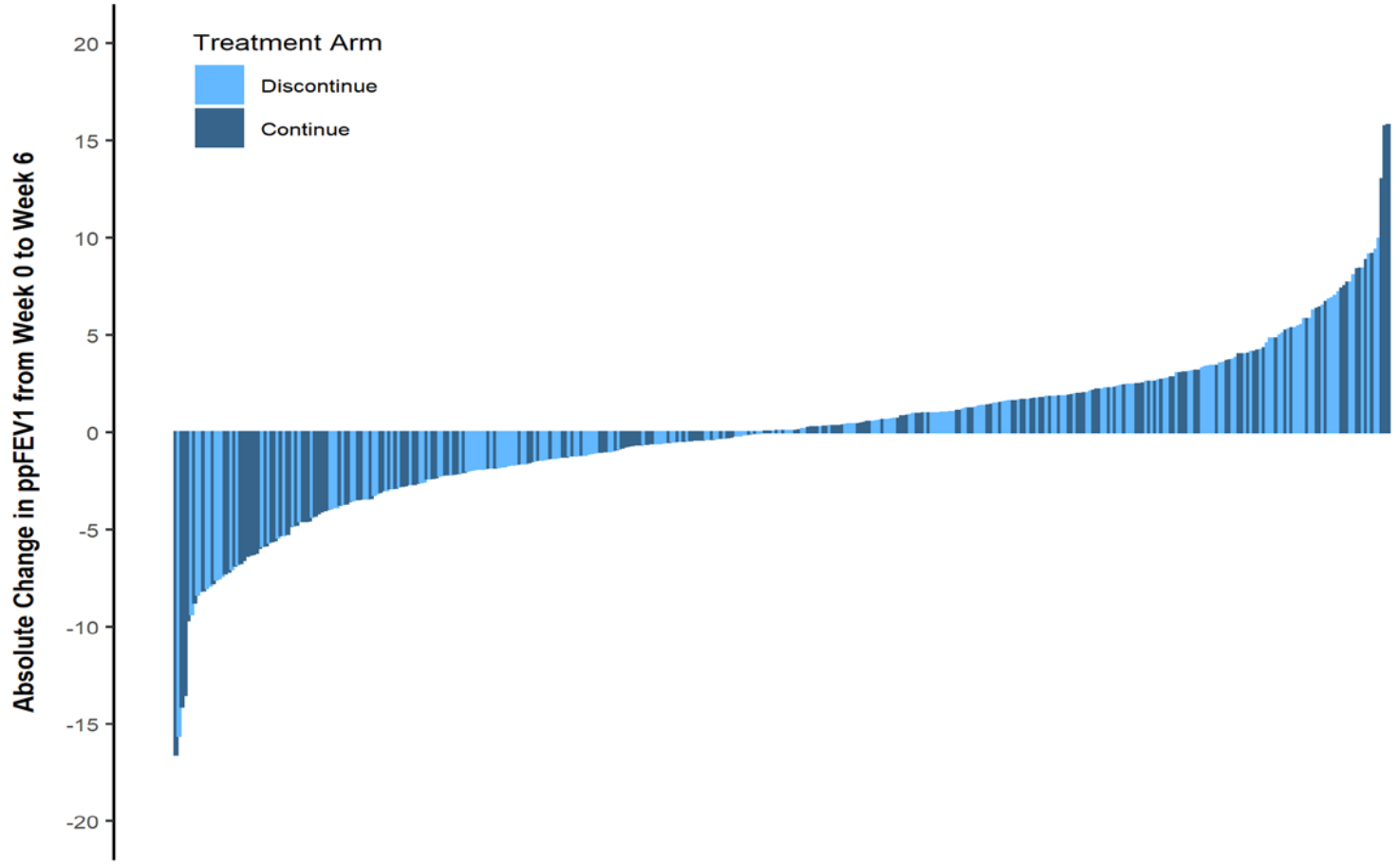


Table S7. Comparison of demographic and baseline characteristics among ITT and PP populations in the overall HS trial and in the sub-cohort for whom $LCI_{2.5}$ was available at baseline.

	Overall (HS Trial)		LCI Subset (HS Trial)	
	ITT Population N=370	**PP Population N=273**	**ITT Population N=99**	**PP Population N=66**
Sex at Birth				
Male	196 (53.0%)	145 (53.1%)	47 (47.5%)	28 (42.4%)
Female	174 (47.0%)	128 (46.9%)	52 (52.5%)	38 (57.6%)
Age (years)				
N	370	273	99	66
Mean (SD)	22.0 (10.50)	22.7 (11.22)	19.9 (9.49)	20.4 (10.51)
Age Distribution				
≥12 to <18	182 (49.2%)	132 (48.4%)	60 (60.6%)	40 (60.6%)
≥18 to <24	76 (20.5%)	52 (19.0%)	18 (18.2%)	10 (15.2%)
≥24 to <30	50 (13.5%)	37 (13.6%)	10 (10.1%)	7 (10.6%)
≥30	62 (16.8%)	52 (19.0%)	11 (11.1%)	9 (13.6%)
Race				
White	358 (96.8%)	264 (96.7%)	98 (99.0%)	66 (100%)
Black or African American	3 (0.8%)	3 (1.1%)	0 (0.0%)	0 (0.0%)
Asian	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
American Indian or Alaskan Native	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Native Hawaiian or Other Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other/Unknown*	8 (2.2%)	6 (2.2%)	1 (1.0%)	0 (0.0%)
Ethnicity				
Hispanic or Latino	20 (5.4%)	17 (6.2%)	6 (6.1%)	4 (6.1%)
Not Hispanic or Latino	350 (94.6%)	256 (93.8%)	93 (93.9%)	62 (93.9%)
Genotype Group				
F508del Homozygous	222 (60.0%)	166 (60.8%)	66 (66.7%)	44 (66.7%)
F508del Heterozygous	143 (38.6%)	104 (38.1%)	32 (32.3%)	21 (31.8%)
Other/Unknown	5 (1.4%)	3 (1.1%)	1 (1.0%)	1 (1.5%)
FEV_1 (% predicted)				
N	370	273	99	66
Mean (SD)	97.0 (16.82)	97.2 (17.40)	100.5 (15.53)	100.3 (16.40)
FEV_1 (% predicted) Distribution				
<60	2 (0.5%)	2 (0.7%)	0 (0.0%)	0 (0.0%)
≥60 to <70	23 (6.2%)	19 (7.0%)	3 (3.0%)	3 (4.5%)
≥70 to <90	99 (26.8%)	69 (25.3%)	21 (21.2%)	14 (21.2%)
≥90 to <100	78 (21.1%)	57 (20.9%)	23 (23.2%)	16 (24.2%)
≥100	168 (45.4%)	126 (46.2%)	52 (52.5%)	33 (50.0%)
$LCI_{2.5}$ †				
N	99	66	99	66

	Overall (HS Trial)		LCI Subset (HS Trial)	
	ITT Population N=370	**PP Population N=273**	**ITT Population N=99**	**PP Population N=66**
Mean (SD)	8.0 (2.37)	7.9 (2.47)	8.0 (2.37)	7.9 (2.47)
Prior Study Enrollee				
	124 (33.5%)	87 (31.9%)	37 (37.4%)	22 (33.3%)
Current Chronic Therapy				
DA	310 (83.8%)	231 (84.6%)	81 (81.8%)	54 (81.8%)
HS	370 (100%)	273 (100%)	99 (100%)	66 (100%)
ETI	370 (100%)	273 (100%)	99 (100%)	66 (100%)
Airway clearance	352 (95.1%)	259 (94.9%)	97 (98.0%)	65 (98.5%)
Inhaled antibiotic (Continuous)	9 (2.4%)	4 (1.5%)	2 (2.0%)	1 (1.5%)
Inhaled antibiotic (Cycled)	94 (25.4%)	73 (26.7%)	19 (19.2%)	11 (16.7%)
Inhaled antibiotic (Continuous Alternating)	32 (8.6%)	23 (8.4%)	8 (8.1%)	7 (10.6%)
Oral antibiotic	166 (44.9%)	123 (45.1%)	51 (51.5%)	34 (51.5%)
Ibuprofen	23 (6.2%)	19 (7.0%)	4 (4.0%)	4 (6.1%)
Systemic steroids	3 (0.8%)	2 (0.7%)	0 (0.0%)	0 (0.0%)
Previous Modulator Use ‡				
Ivacaftor	9 (2.4%)	7 (2.6%)	3 (3.0%)	3 (4.5%)
Lumacaftor/Ivacaftor	103 (27.8%)	73 (26.7%)	35 (35.4%)	25 (37.9%)
Tezacaftor/Ivacaftor	88 (23.8%)	61 (22.3%)	26 (26.3%)	18 (27.3%)
Positive Microbiology Culture (past year) §				
Pseudomonas aeruginosa	96 (25.9%)	74 (27.1%)	21 (21.2%)	18 (27.3%)
Staphylococcus aureus	255 (68.9%)	194 (71.1%)	73 (73.7%)	49 (74.2%)
Methicillin-resistant staphylococcus aureus	74 (20.0%)	52 (19.0%)	21 (21.2%)	12 (18.2%)
Stenotrophomonas maltophilia	20 (5.4%)	17 (6.2%)	5 (5.1%)	5 (7.6%)
Achromobacter xylosoxidans	3 (0.8%)	1 (0.4%)	1 (1.0%)	0 (0.0%)
Burkholderia cepacia complex	5 (1.4%)	3 (1.1%)	0 (0.0%)	0 (0.0%)
Haemophilus influenzae	14 (3.8%)	8 (2.9%)	4 (4.0%)	1 (1.5%)
Mycobacterium abscessus	3 (0.8%)	1 (0.4%)	0 (0.0%)	0 (0.0%)
Mycobacterium avium complex	4 (1.1%)	0 (0.0%)	1 (1.0%)	0 (0.0%)

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 S8. Comparison of demographic and baseline characteristics among ITT and PP populations in the overall DA trial and in the sub-cohort for whom $LCI_{2.5}$ was available at baseline.

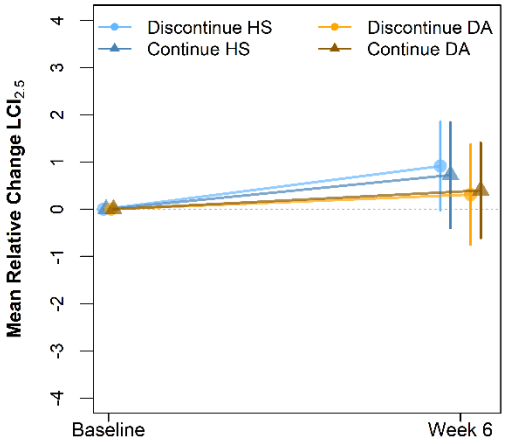
	Overall (DA Trial)		LCI Subset (DA Trial)	
	ITT Population N=477	**PP Population N=392**	**ITT Population N=130**	**PP Population N=107**
Sex at Birth				
Male	244 (51.2%)	197 (50.3%)	67 (51.5%)	54 (50.5%)
Female	233 (48.8%)	195 (49.7%)	63 (48.5%)	53 (49.5%)
Age (years)				
N	477	392	130	107
Mean (SD)	22.6 (10.41)	22.9 (10.68)	20.5 (8.59)	21.0 (9.15)
Age Distribution				
≥12 to <18	218 (45.7%)	174 (44.4%)	71 (54.6%)	55 (51.4%)
≥18 to <24	99 (20.8%)	81 (20.7%)	27 (20.8%)	23 (21.5%)
≥24 to <30	63 (13.2%)	52 (13.3%)	16 (12.3%)	14 (13.1%)
≥30	97 (20.3%)	85 (21.7%)	16 (12.3%)	15 (14.0%)
Race				
White	458 (96.0%)	379 (96.7%)	127 (97.7%)	106 (99.1%)
Black or African American	5 (1.0%)	4 (1.0%)	0 (0.0%)	0 (0.0%)
Asian	1 (0.2%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
American Indian or Alaskan Native	1 (0.2%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
Native Hawaiian or Other Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other/Unknown*	12 (2.5%)	7 (1.8%)	3 (2.3%)	1 (0.9%)
Ethnicity				
Hispanic or Latino	34 (7.1%)	26 (6.6%)	7 (5.4%)	5 (4.7%)
Not Hispanic or Latino	443 (92.9%)	366 (93.4%)	123 (94.6%)	102 (95.3%)
Genotype Group				
F508del Homozygous	269 (56.4%)	220 (56.1%)	86 (66.2%)	69 (64.5%)
F508del Heterozygous	197 (41.3%)	163 (41.6%)	43 (33.1%)	37 (34.6%)
Other/Unknown	11 (2.3%)	9 (2.3%)	1 (0.8%)	1 (0.9%)
FEV_1 (% predicted)				
N	477	392	130	107
Mean (SD)	96.8 (16.83)	96.9 (16.87)	99.9 (15.19)	99.5 (15.26)
FEV_1 (% predicted) Distribution				
<60	4 (0.8%)	4 (1.0%)	0 (0.0%)	0 (0.0%)
≥60 to <70	31 (6.5%)	26 (6.6%)	4 (3.1%)	4 (3.7%)
≥70 to <90	120 (25.2%)	94 (24.0%)	27 (20.8%)	22 (20.6%)
≥90 to <100	104 (21.8%)	84 (21.4%)	30 (23.1%)	23 (21.5%)
≥100	218 (45.7%)	184 (46.9%)	69 (53.1%)	58 (54.2%)
$LCI_{2.5}$ †				
N	130	107	130	107
Mean (SD)	8.1 (2.32)	8.2 (2.47)	8.1 (2.32)	8.2 (2.47)

	Overall (DA Trial)		LCI Subset (DA Trial)	
	ITT Population N=477	**PP Population N=392**	**ITT Population N=130**	**PP Population N=107**
Prior Study Enrollee				
	128 (27.0%)	102 (26.0%)	30 (23.1%)	23 (21.5%)
Current Chronic Therapy				
DA	477 (100%)	392 (100%)	130 (100%)	107 (100%)
HS	295 (61.8%)	238 (60.7%)	79 (60.8%)	65 (60.7%)
ETI	477 (100%)	392 (100%)	130 (100%)	107 (100%)
Airway clearance	454 (95.2%)	372 (94.9%)	125 (96.2%)	103 (96.3%)
Inhaled antibiotic (Continuous)	9 (1.9%)	7 (1.8%)	1 (0.8%)	1 (0.9%)
Inhaled antibiotic (Cycled)	106 (22.2%)	94 (24.0%)	28 (21.5%)	25 (23.4%)
Inhaled antibiotic (Continuous Alternating)	48 (10.1%)	41 (10.5%)	10 (7.7%)	8 (7.5%)
Oral antibiotic	207 (43.4%)	172 (43.9%)	68 (52.3%)	55 (51.4%)
Ibuprofen	41 (8.6%)	37 (9.4%)	14 (10.8%)	12 (11.2%)
Systemic steroids	5 (1.0%)	4 (1.0%)	2 (1.5%)	2 (1.9%)
Previous Modulator Use ‡				
Ivacaftor	19 (4.0%)	17 (4.3%)	3 (2.3%)	3 (2.8%)
Lumacaftor/Ivacaftor	131 (27.5%)	110 (28.1%)	40 (30.8%)	36 (33.6%)
Tezacaftor/Ivacaftor	108 (22.6%)	87 (22.2%)	31 (23.8%)	26 (24.3%)
Positive Microbiology Culture (past year) §				
Pseudomonas aeruginosa	129 (27.0%)	112 (28.6%)	32 (24.6%)	29 (27.1%)
Staphylococcus aureus	321 (67.3%)	271 (69.1%)	93 (71.5%)	76 (71.0%)
Methicillin-resistant staphylococcus aureus	110 (23.1%)	90 (23.0%)	33 (25.4%)	23 (21.5%)
Stenotrophomonas maltophilia	28 (5.9%)	26 (6.6%)	9 (6.9%)	9 (8.4%)
Achromobacter xylosoxidans	8 (1.7%)	6 (1.5%)	1 (0.8%)	1 (0.9%)
Burkholderia cepacia complex	8 (1.7%)	8 (2.0%)	2 (1.5%)	2 (1.9%)
Haemophilus influenzae	20 (4.2%)	17 (4.3%)	9 (6.9%)	8 (7.5%)
Mycobacterium abscessus	3 (0.6%)	3 (0.8%)	1 (0.8%)	1 (0.9%)
Mycobacterium avium complex	7 (1.5%)	7 (1.8%)	1 (0.8%)	1 (0.9%)

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.

Figure S5. (A) Unadjusted mean relative changes from baseline in $LCI_{2.5}$. Bars indicate standard errors. (B) Estimated differences between the discontinuation and continuation arms in the 6-week relative change in the cohort for whom $LCI_{2.5}$ was available among the primary PP population and ITT population with and without imputation to account for missing data. Treatment differences adjusted for randomization strata.

(A)



(B)

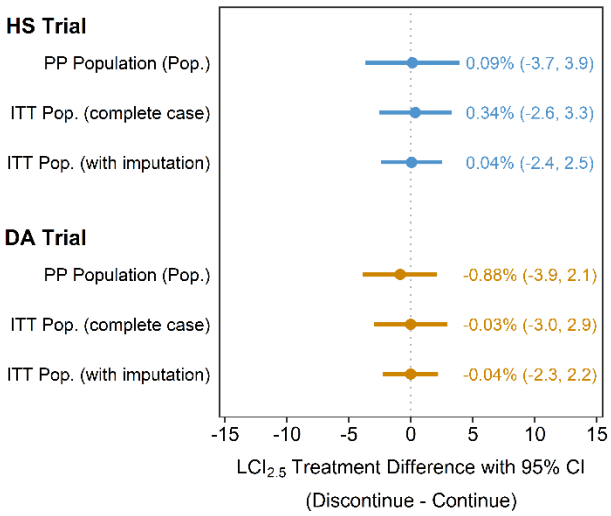
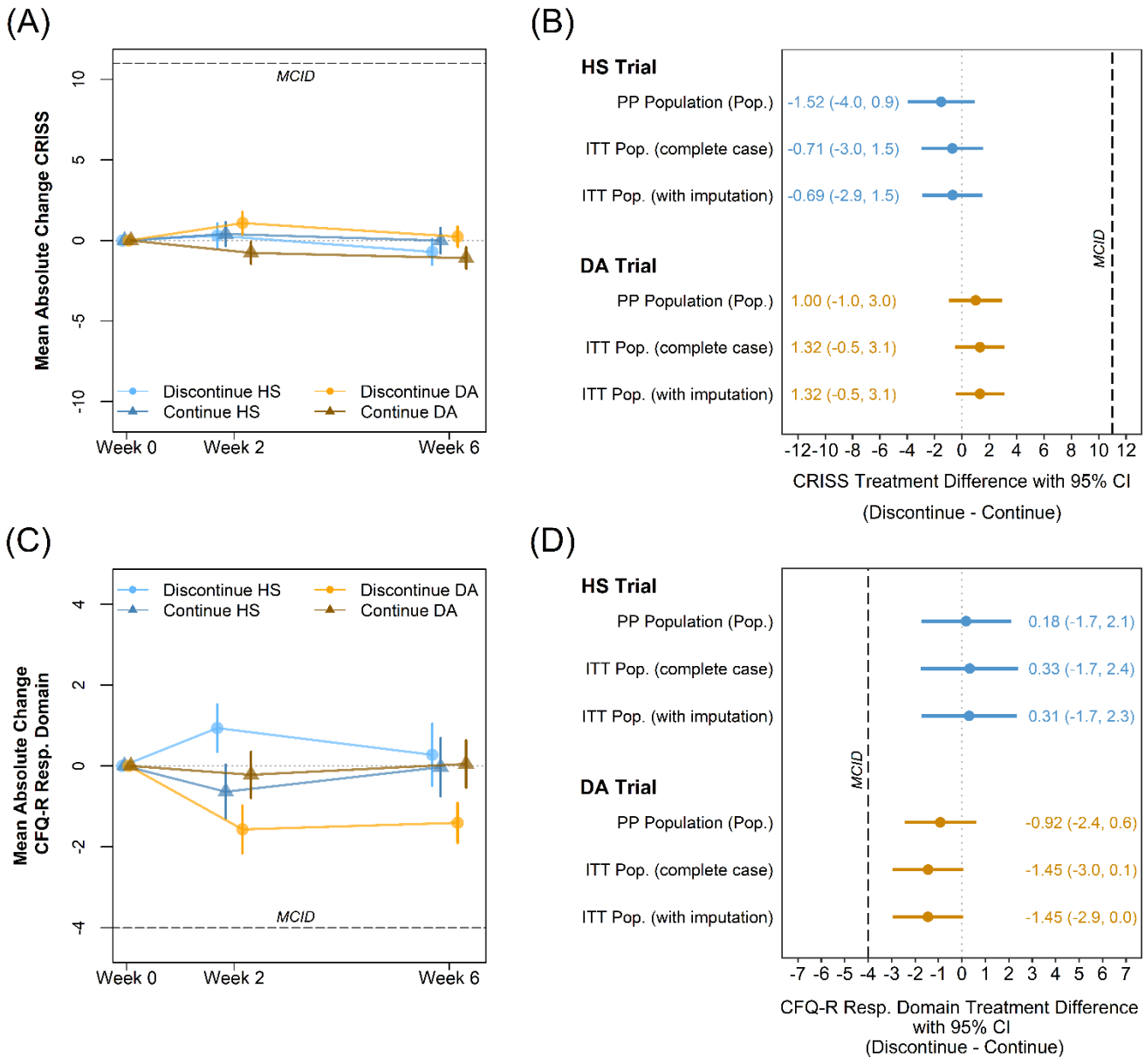


Figure S6. Unadjusted mean changes from baseline in (A) CRISS and (C) CFQ-R across the entire study cohort. Bars indicate standard errors. Estimated differences between the discontinuation and continuation arms in the 6-week change in (B) CRISS and (D) CFQ-R among the primary PP population and ITT population with and without imputation to account for missing data. Treatment differences adjusted for randomization strata.



Mean (median; interquartile range [IQR]) CRISS and CFQ-R Respiratory Domain scores at Week 0 were 11.5 (14; 0–23) and 94.1 (100; 88.9–100) in the HS trial and 12.0 (14; 0–23) and 95.0 (100; 94.4–100) in the DA trial, respectively.

Table S9. Overview of secondary outcomes including exacerbations, hospitalizations and acute antibiotic use (HS Trial)

	Hypertonic Saline (HS) Trial		
	Continue N=186	**Discontinue N=184**	**Adjusted OR * (95% CI)**
Participants initiating acute antibiotics, n (%)	9 (4.8%)	11 (6.0%)	1.27 (0.5, 3.1)
Participants with at least one protocol-defined PEx, n (%)	3 (1.6%)	1 (0.5%)	0.33 (0.0, 2.6)
Participants with at least one hospitalization, n (%)	1 (0.5%)	2 (1.1%)	2.14 (0.2, 47.1)

PEx= Pulmonary exacerbation;* Odds ratio (OR) estimates from logistic regression models adjusted for randomization strata.

Table S10. Overview of secondary outcomes including exacerbations, hospitalizations and acute antibiotic use (DA Trial)

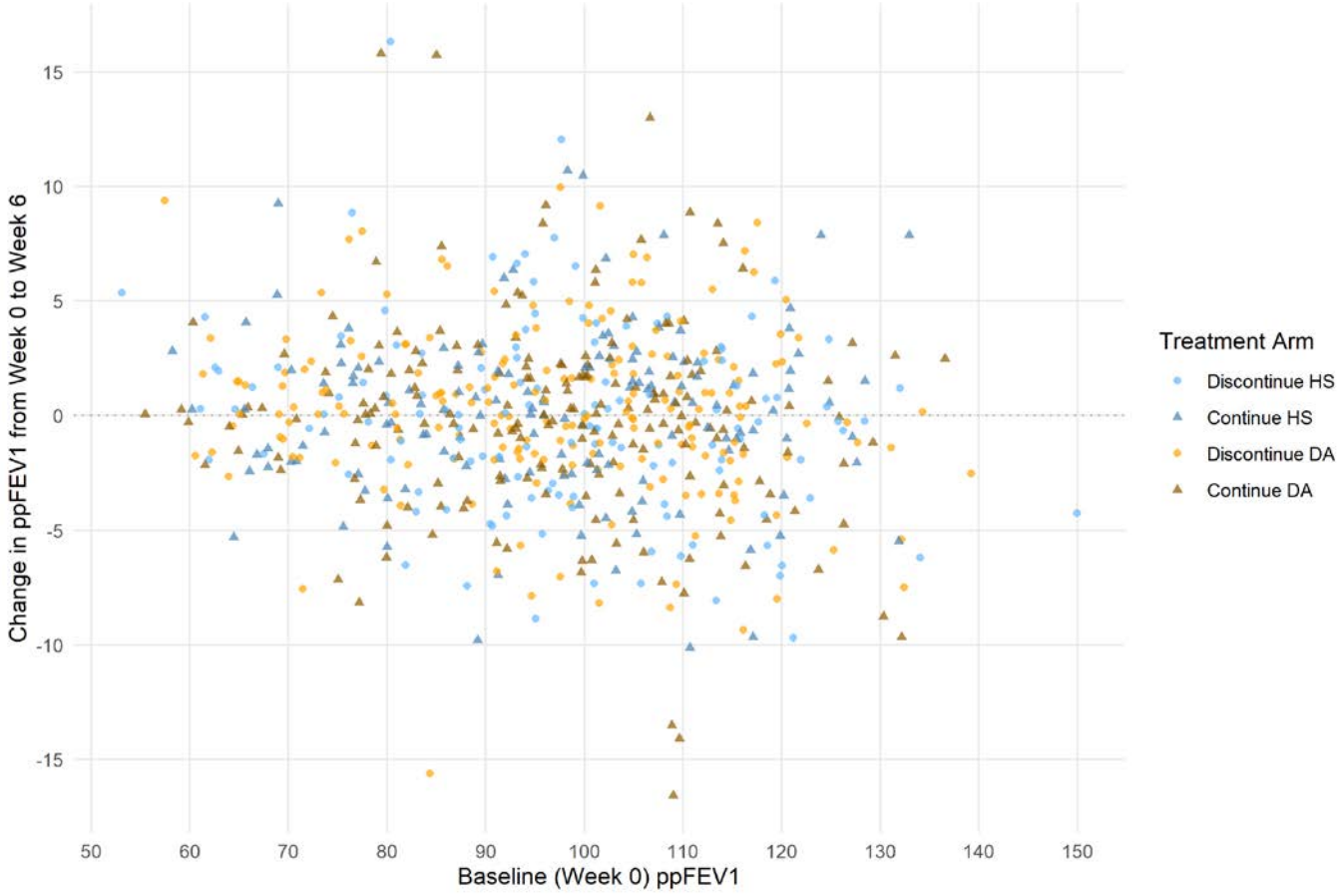
	Dornase Alfa (DA) Trial		
	Continue N=237	**Discontinue N=240**	**Adjusted OR * (95% CI)**
Participants initiating acute antibiotics, n (%)	8 (3.4%)	14 (5.8%)	1.78 (0.7, 4.5)
Participants with at least one protocol-defined PEx, n (%)	2 (0.8%)	4 (1.7%)	2.02 (0.4, 14.8)
Participants with at least one hospitalization, n (%)	0 (0.0%)	0 (0.0%)	-

* Odds ratio (OR) estimates from logistic regression models adjusted for randomization strata.

Table S11. Post-hoc summary of respiratory adverse events by baseline $ppFEV_1$.

	Hypertonic Saline (HS) Trial		Dornase Alfa (DA) Trial	
	Continue N=186	**Discontinue N=184**	**Continue N=237**	**Discontinue N=240**
All Participants, N	186	184	237	240
Participants with at least one respiratory AE, n (%)	22 (11.8%)	30 (16.3%)	24 (10.1%)	47 (19.6%)
$ppFEV_1$ <70%, N	11	14	14	21
Participants with at least one respiratory AE, n (%)	1 (9.1%)	5 (35.7%)	1 (7.1%)	7 (33.3%)
$ppFEV_1$ ≥70 to <90%, N	53	46	63	57
Participants with at least one respiratory AE, n (%)	8 (15.1%)	5 (10.9%)	9 (14.3%)	13 (22.8%)
$ppFEV_1$ ≥90 to <100%, N	33	45	51	53
Participants with at least one respiratory AE, n (%)	5 (15.2%)	12 (26.7%)	7 (13.7%)	10 (18.9%)
$ppFEV_1$ ≥100%, N	89	79	109	109
Participants with at least one respiratory AE, n (%)	8 (9.0%)	8 (10.1%)	7 (6.4%)	17 (15.6%)

Figure S7. Post-hoc descriptive display of baseline ppFEV$_1$ by 6-week change in ppFEV$_1$ by treatment arm and trial in the PP population.



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