

Clinical Effectiveness of Elexacaftor/Tezacaftor/Ivacaftor in People with Cystic Fibrosis

A Clinical Trial

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Abstract

Rationale: The cystic fibrosis (CF) modulator drug, elexacaftor/tezacaftor/ivacaftor (ETI), proved highly effective in controlled clinical trials for individuals with at least one F508del allele, which occurs in at least 85% of people with CF.

Objectives: PROMISE is a postapproval study to understand the broad effects of ETI through 30 months' clinical use in a more diverse U.S. patient population with planned analyses after 6 months.

Methods: Prospective, observational study in 487 people with CF age 12 years or older with at least one F508del allele starting ETI for the first time. Assessments occurred before and 1, 3, and 6 months into ETI therapy. Outcomes included change in percent predicted FEV₁ (ppFEV₁), sweat chloride concentration, body mass index (BMI), and self-reported respiratory symptoms.

Measurements and Main Results: Average age was 25.1 years, and 44.1% entered the study using tezacaftor/ivacaftor or lumacaftor/ivacaftor, whereas 6.7% were using ivacaftor, consistent with F508del homozygosity and G551D allele,

respectively. At 6 months into ETI therapy, ppFEV₁ improved 9.76 percentage points (95% confidence interval [CI], 8.76 to 10.76) from baseline, cystic fibrosis questionnaire–revised respiratory domain score improved 20.4 points (95% CI, 18.3 to 22.5), and sweat chloride decreased −41.7 mmol/L (95% CI, −43.8 to −39.6). BMI also significantly increased. Changes were larger in those naive to modulators but substantial in all groups, including those treated with ivacaftor at baseline.

Conclusions: ETI by clinical prescription provided large improvements in lung function, respiratory symptoms, and BMI in a diverse population naive to modulator drug therapy, using existing two-drug combinations, or using ivacaftor alone. Each group also experienced significant reductions in sweat chloride concentration, which correlated with improved ppFEV₁ in the overall study population.

Clinical trial registered with www.clinicaltrials.gov (NCT NCT04038047).

Keywords: cystic fibrosis; clinical trial; elexacaftor/tezacaftor/ivacaftor; PROMISE; modulators

(Received in original form August 27, 2021; accepted in final form November 16, 2021)

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Am J Respir Crit Care Med Vol 205, Iss 5, pp 529–539, Mar 1, 2022

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Originally Published in Press as DOI: 10.1164/rccm.202108-1986OC on November 16, 2021

Internet address: www.atsjournals.org

At a Glance Commentary

Scientific Knowledge on the

Subject: Elexaftor/tezacaftor/ivacaftor (ETI) is a modulator drug shown to provide substantial health benefits and improved cystic fibrosis transmembrane conductance regulator function in controlled clinical trials. This combination drug is effective in a large majority of people with cystic fibrosis and represents a milestone advance in managing this disease.

What This Study Adds to the

Field: PROMISE is a postapproval, real-world, observational study to understand the effects of ETI in clinical use in the United States. We find similar substantial improvements across a range of clinical outcomes, which set a new benchmark for modulator drug therapy and highlight the anticipated positive impact of ETI in the management and care of this disease.

Cystic fibrosis (CF) is an autosomal recessive genetic disease resulting in life-shortening, multiorgan system dysfunction. Since the discovery of the CF transmembrane conductance regulator (*CFTR*) gene, a collective effort has been underway to correct the basic cellular defect. A major contribution has been the advent of *CFTR* modulators, small molecules that either correct protein misfolding and

misprocessing or improve channel gating to enhance apical anion transport (e.g., chloride and bicarbonate) (1–3). By partially restoring channel function, *CFTR* modulators improve a range of clinical outcomes, but effects vary depending on the underlying *CFTR* mutations, modulator combination used, and individual clinical characteristics.

Until recently, the benchmark for highly effective *CFTR* modulator therapy was ivacaftor in people with CF (PwCF) who have G551D or other *CFTR* gating mutations (2). The biological and clinical effects of restoring *CFTR* function with ivacaftor have been substantial (4–9). Observational and patient registry studies, including the G551D Observational Trial (GOAL), demonstrated long-term clinical benefits and reduced mortality at the population level, but ivacaftor is highly effective as a monotherapy in less than 10% of all PwCF (4, 5, 10–13). Recently, the three-drug combination elexacaftor/tezacaftor/ivacaftor (ETI) was approved for individuals with at least one F508del allele. F508del is the most common CF mutation worldwide; thus, ETI has the potential to treat at least 85% of PwCF, underscoring its impact on CF care and prognosis. Randomized controlled trials of ETI demonstrated improvements in lung function, respiratory symptoms, risk of acute pulmonary exacerbations, and weight gain that met or exceeded those measured in the prior ivacaftor studies (14, 15), although its use in clinical practice and effects beyond endpoints necessary for clinical registration have not been widely reported.

Since regulatory approval in late 2019, ETI use has become widespread in the United States, raising intense interest in the clinical effects beyond outcomes measured in controlled trials. A deeper understanding of

the biological and clinical impacts of *CFTR* correction in a broader array of patients will also support the goal of realizing highly effective *CFTR*-directed therapy for all PwCF.

Here we present results from the PROMISE study (NCT04038047); a CF Foundation-supported postapproval observational study of 487 participants age at least 12 years old initiating ETI therapy (16). Participants were assessed before starting ETI and are being followed for 30 months of drug use. The results presented are a preplanned analysis of the primary clinical outcomes after at least 6 months of ETI to determine its performance as a sustained clinical therapy and describe unique effects of ETI relevant to clinical care and the emerging CF landscape.

Methods

Study Design and Population

The PROMISE study is a prospective observational study that was described previously (16). Eligible participants were at least 12 years of age and had at least one copy of F508del and the intent to initiate ETI by the participant's physician. Key exclusion criteria (see Table E1 in the online supplement) included use of ETI within 180 days of baseline, new chronic therapy initiation, or treatment for nontuberculous mycobacterial infection within 28 days of baseline, and initiation of acute antibiotics or systemic corticosteroids within 14 days of baseline. Participants enrolled and completed a baseline study visit before initiating ETI. Three subsequent visits occurred at 1, 3, and 6 months after initiating therapy. Additional 18- and 30-month study visits are planned.

A complete list of PROMISE Study Group members can be found in the online supplement.

Supported by the Cystic Fibrosis Foundation. Additional programmatic funding that supported this research was provided by the National Institute of Diabetes and Digestive and Kidney Diseases (P30DK072482 [S.M.R. and G.M.S.]) and NHLBI (P30DK089507 [D.P.N.], R35HL135816 [S.M.R.], UL1TR003096 [S.M.R.], UL1 TR002535 [S.D.S.], K24HL14166 [L.R.H.], and K08HL138153 [G.M.S.]). Funding agencies had no role in the design, management, data collection, analyses, or interpretation of the data or in the writing of the manuscript or the decision to submit for publication. The views expressed in this publication are those of the authors and not necessarily those of the Cystic Fibrosis Foundation or NIH.

Author Contributions: Study concept, design, and initiation: D.P.N., S.M.R., S.L.H., J.P.C., J.M.V.D., and M.H.K. Statistical analysis and advisement: A.C.P., S.L.H., and M.H.K. Analyses and interpretation of data: all authors. First drafting of manuscript: D.P.N., S.M.R., A.C.P., and S.L.H. Critical revisions and intellectual content: all authors. The PROMISE Study Group consists of key study team members at the central coordinating center and all lead investigators and research coordinators who are responsible for ethical board approval, participant recruitment, and conduct at local study sites.

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This article has a related editorial.

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

Site personnel were allowed to conduct the 6-month study visit outside the protocol-allowed window of 180 days after ETI initiation \pm 14 days when necessary owing to the coronavirus disease (COVID-19) pandemic (17). Remote collection for certain procedures was implemented in response to the uncertain impact of the COVID-19 pandemic in an effort to mitigate against missing data, but the present analysis does not include any data collected at home for this purpose (e.g., home spirometry).

A core set of clinical assessments was conducted in all participants at each visit: spirometry, height, weight, and completion of the respiratory domain of the cystic fibrosis questionnaire-revised (CFQ-R RD) administered using electronic personal devices (18). Sweat chloride was collected at baseline and at 1- and 6-month visits. CFQ-R RDs were administered electronically within predefined windows when in-person visits were delayed because of the pandemic. Spirometry was performed according to the American Thoracic Society standards, and percent predicted FEV₁ (ppFEV₁) and FVC (ppFVC) were calculated using Global Lung Initiative Equations (19, 20). Body mass index (BMI) *z*-scores were calculated for participants younger than 18 years at baseline using the Center for Disease Control reference equations. Significant protocol adaptations were made in response to the COVID-19 pandemic (*see* the online supplement), but the impact on the core outcomes through 6 months was minor. Use of ETI was recorded at each visit by participant self-report.

PROMISE is organized into several organ system-based substudies (16). Outcomes from substudies will be reported separately. The target sample of at least 400 participants overall was chosen to allow for adequate enrollment into the various substudies without creating an impractically burdensome procedure load for each participant or study site. A sample of 400 participants provides more than 95% power to detect changes in ppFEV₁ (estimated mean change, 6; SD, 10) and sweat chloride (estimated mean change, -50 ; SD, 22) as large as or larger (and with comparable variance) than those observed in the GOAL study of PwCF and the G551D mutation receiving ivacaftor alone (5). The study was registered at ClinicalTrials.gov (NCT04038047), and institutional review board approval was granted at participating sites.

Statistical Analysis

Clinical outcomes and change are presented using summary statistics and paired *t* tests with 95% confidence intervals (CI) at each time point. The primary outcomes are the change in sweat chloride and ppFEV₁ at 6 and 30 months (30 months to be reported later). Sample size was determined based on the cumulative needs of the substudy efforts, as previously described, providing adequate power for the core clinical outcome measures reported here (16). In addition to the overall cohort, change statistics were calculated for strata defined by baseline modulator use before initiating ETI (none, ivacaftor monotherapy, or corrector-potentiator combination treatment [i.e., lumacaftor/ivacaftor or tezacaftor/ivacaftor]). *P* values for chronic medication use were generated using McNemar's exact test. For exploratory univariate testing of effect modification by demographic characteristics, ANOVA tests determined whether there was a difference in the change from baseline to 6 months. False discovery rate in these exploratory tests was controlled using the Benjamini-Hochberg method, with a false discovery rate threshold of 5% within each outcome (21). Mean baseline values and change scores are revealed in each stratum if a significant association existed after correction. All analyses were performed with SAS version 9.4 and R version 4.1 (22).

Results

Study Population and Follow-Up

A total of 489 participants were enrolled at 56 U.S. CF Foundation Therapeutics Development Network sites between November 2019 and May 2020. Two participants were found to be ineligible after enrollment and were withdrawn, leaving 487 participants in the analysis population. Seven participants did not initiate ETI and withdrew before the 1-month visit (Figure E1). Participants were on average 25.1 years old (range, 11.6–64.6), 51% female at birth (*n* = 246), 94% Caucasian (*n* = 457), 6% Hispanic (*n* = 30), and 48% F508del homozygous. At baseline, participants were either not on a CFTR modulator (50.9%), on a two-drug CFTR modulator combination (lumacaftor/ivacaftor or tezacaftor/ivacaftor, 44.1%), or on ivacaftor alone (6.7%) (Table 1); prior modulator use corresponded with indication by underlying CFTR genotype.

The COVID-19 pandemic impacted in-person research conduct, and therefore study visit completion was 86%, 40%, and 89% at 1, 3, and 6 months after starting ETI, respectively (17). More than 94% of 1-month visits were completed before March 11, 2020, when the World Health Organization declared a global pandemic and effects on in-person visits began. The 3-month study visits occurred during the greatest limitations to in-person research conduct. In response to these challenges, the allowable timeframe to complete the 6-month visit was extended. This greatly improved completion at this time point but extended median time from ETI initiation to 222 days (range, 142–416) (Figure E2). Mean changes in lung function and sweat chloride concentration were similar between the 1-month time point, largely completed before the pandemic, and the 3- and 6-month visits conducted during the pandemic (Table 2 and Table E4). When comparing changes from baseline in ppFEV₁, sweat chloride, CFQ-R RD, and BMI between participants completing the 6-month study visit on time versus those for whom visits were delayed beyond the \pm 14-day window, no meaningful differences were observed. Of those completing a visit, the numbers reporting not using ETI at 1, 3, and 6 months were 4 (0.9%), 3 (1.5%), and 9 (2.1%), respectively.

Changes in Clinical Outcomes

Improvements from baseline to 6 months occurred in all outcome measures in the overall study population and in each subgroup defined by baseline modulator use before starting ETI (Figure 1 and Table 2). Lung function measured by ppFEV₁ improved in the entire cohort by an average of 9.8 percentage points (95% CI, 8.8 to 10.8 points). The largest average changes in ppFEV₁ were in those previously using no modulator (10.8; 95% CI, 9.3 to 12.4) or a two-drug combination (9.2; 95% CI, 7.8 to 10.7). The subgroup entering the study on ivacaftor had an average of 6.1 (95% CI, 3.3 to 8.9) increase in ppFEV₁ at 6 months (Table 2). Similarly, average sweat chloride changes were largest among the two-drug (-43.4 mmol/L; 95% CI, -46.4 to -40.4) and no-modulator subgroups (-43.2 ; 95% CI, -46.2 to -40.1), but still substantially improved in the ivacaftor subgroup (-23.9 ; 95% CI, -31.0 to -16.8).

Respiratory signs or symptoms of illness decreased from baseline to 6 months, with a mean 20.4-point (95% CI, 18.3 to 22.5

Table 1. Demographics and Baseline Characteristics

	Total (n = 487)	Modulator Use at Baseline*		
		None (n = 238)	Iva (n = 34)	Two-Drug (n = 215)
Age, yr	25.1 (10.7)	24.7 (10.8)	27.4 (12.9)	25.1 (10.1)
Sex at birth, female	246 (50.5%)	120 (50.4%)	15 (44.1%)	111 (51.6%)
Race				
White	457 (93.8%)	219 (92.0%)	33 (97.1%)	205 (95.3%)
Black or African American	12 (2.5%)	8 (3.4%)	0 (0.0%)	4 (1.9%)
Asian	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
American Indian or Alaska Native	1 (0.2%)	1 (0.4%)	0 (0.0%)	0 (0.0%)
Native Hawaiian or other Pacific Islander	1 (0.2%)	1 (0.4%)	0 (0.0%)	0 (0.0%)
More than one race	13 (2.7%)	6 (2.5%)	1 (2.9%)	6 (2.8%)
Other or unknown	3 (0.6%)	3 (1.3%)	0 (0.0%)	0 (0.0%)
Hispanic or Latino	30 (6.2%)	18 (7.6%)	2 (5.9%)	10 (4.7%)
ppFEV ₁	80.5 (22.7)	80.2 (23.2)	79.3 (20.8)	81.1 (22.5)
ppFEV ₁ (by group)				
<65	130 (26.7%)	64 (26.9%)	10 (29.4%)	56 (26.0%)
65–90	161 (33.1%)	76 (31.9%)	9 (26.5%)	76 (35.3%)
>90	196 (40.2%)	98 (41.2%)	15 (44.1%)	83 (38.6%)
Weight, kg (age ≥18)	65.6 (13.6)	64.6 (12.5)	67.7 (11.5)	66.4 (15.1)
Weight percentile (age <18)	52.9 (29.2)	50.8 (29.8)	57.2 (27.8)	54.6 (29.0)
BMI, kg/m ² (age ≥18)	23.1 (4.0)	22.8 (3.9)	23.5 (2.7)	23.5 (4.3)
BMI Percentile (age <18)	56.0 (26.5)	53.8 (27.9)	65.1 (24.5)	57.1 (25.1)
Genotype group				
F508del homozygous	236 (48.5%)	27 (11.3%)	0 (0.0%)	209 (97.2%)
F508del heterozygous (MF [†])	195 (40.0%)	192 (80.7%)	0 (0.0%)	3 (1.4%)
F508del heterozygous (G551D)	35 (7.2%)	2 (0.8%)	33 (97.1%)	0 (0.0%)
F508del heterozygous (other)	21 (4.3%)	17 (7.1%)	1 (2.9%)	3 (1.4%)

Definition of abbreviations: BMI = body mass index; Iva = ivacaftor monotherapy; MF = minimal function; ppFEV₁ = percent predicted FEV₁; two-drug = tezacaftor/iva or lumacaftor/iva.

*Most recent modulator used within 90 days of the baseline visit.

[†]MF mutation defined by the VX-445-102 study eligibility list (15).

points) improvement in the CFQ-R RD score in the entire cohort. BMI also improved significantly, with a 6-month mean increase from baseline of 1.2 kg/m² in adults and 0.3 z-score in adolescents. Improvements in BMI and CFQ-R RD were similar between baseline modulator subgroups (Table 2).

At the 6-month visit, the overall mean ppFEV₁ improved to 90.9 in the study cohort with mean age of 25 years (Table 2). Mean sweat chloride was 45.7 mmol/L, mean CFQ-R RD was 90.5 of a maximum 100 points, and mean BMI was 24.5 kg/m² (0.5 z-score in adolescents). The 6-month absolute values across these outcomes were similar among subgroups apart from sweat chloride, which was lower (23.9 mmol/L) in the subgroup previously treated with ivacaftor (i.e., those with F508del and a gating or residual function mutation) (Figure 2 and Table 2). Increasing numbers of participants reached the maximum possible score for CFQ-R RD. Among 302 subjects who completed the questionnaire at 6 months, 32% had the maximum possible CFQ-R RD score of 100, and an additional 50% had a

score above 80. Large improvements in CFQ-R RD scores occurred even in those starting with relatively low lung function (<65 ppFEV₁) at baseline (Figure 3).

Participants were encouraged to continue baseline medications through at least the 6-month study visit to better understand the impacts of ETI. In addition to routine collection of concomitant medications, self-reported use of four common chronic therapies was specifically queried at each visit. At the 6-month visit, the proportion using dornase alfa decreased by 6%, hypertonic saline by 9.8%, azithromycin by 9.1%, and inhaled antibiotics by 34% relative to baseline (Table 3). Changes in medication use did not significantly differ between subgroups based on modulator use before ETI.

Correlation between Change in Sweat Chloride and ppFEV₁

Prior studies with CFTR modulators have only shown correlation between clinical outcome measures and CFTR function measured by sweat chloride if considering

extended observation periods (i.e., >12 mo) or if combining multiple studies (4, 23). In our study, a correlation between changes in ppFEV₁ and sweat chloride was observed over the first 6 months of ETI. In the entire study population, each additional 10-point decrease from baseline in sweat chloride was associated with an additional 0.89-point increase in ppFEV₁ (Pearson $r = -0.19$; $P < 0.005$) (Figure 4).

Outcomes and Baseline Demographics

Table E2 indicates effect modification of sex on sweat chloride change at 6 months, with larger improvements among females. As with previous work on CFTR modulators, weight and change in sweat chloride were marginally correlated (Figure E5) (24, 25). An exploratory analysis of post-ETI sweat chloride with sex, weight, and CFTR genotype as covariates showed that the association between sweat chloride and sex was significant even when adjusting for weight, but the association with weight was not significant after adjusting for sex (Figure

Table 2. Clinical Outcomes and Change from Baseline by Visit, Stratified by Baseline Modulator Use

Outcome	Visit		Baseline Modulator Use*				
			All	None	Iva	Two-Drug	
ppFEV ₁	Baseline	<i>n</i>	487	238	34	215	
		Mean ± SD	80.5 ± 22.7	80.2 ± 23.2	79.3 ± 20.8	81.1 ± 22.5	
	1 mo	<i>n</i> [<i>n</i> chg.] [†]	412 [412]	198 [198]	32 [32]	182 [182]	
		Mean ± SD	88.5 ± 22.6	88.5 ± 22.7	84.6 ± 24.1	89.1 ± 22.2	
	3 mo	Change	+8.80	+10.10	+5.55	+7.96	
		CI (chg.)	(8.01 to 9.59)	(8.93 to 11.26)	(3.24 to 7.86)	(6.78 to 9.13)	
		<i>n</i> [<i>n</i> chg.] [†]	190 [190]	94 [94]	11 [11]	85 [85]	
		Mean ± SD	87.6 ± 23.1	88.4 ± 22.8	74.7 ± 23.9	88.3 ± 23.2	
		Change	+10.31	+12.57	+3.94	+8.63	
		CI (chg.)	(8.99 to 11.63)	(10.55 to 14.59)	(1.24 to 6.65)	(6.85 to 10.40)	
	6 mo	<i>n</i> [<i>n</i> chg.] [†]	356 [356]	166 [166]	24 [24]	166 [166]	
		Mean ± SD	90.9 ± 21.5	91.0 ± 20.8	87.5 ± 21.9	91.3 ± 22.2	
Change		+9.76	+10.84	+6.14	+9.21		
CI (chg.)		(8.76 to 10.76)	(9.32 to 12.35)	(3.34 to 8.94)	(7.76 to 10.66)		
ppFVC		Baseline	<i>n</i>	487	238	34	215
			Mean ± SD	91.9 ± 18.2	92.1 ± 18.4	93.2 ± 19.0	91.4 ± 17.8
	1 mo	<i>n</i> [<i>n</i> chg.] [†]	412 [412]	198 [198]	32 [32]	182 [182]	
		Mean ± SD	96.9 ± 16.3	97.3 ± 15.8	94.6 ± 18.3	96.9 ± 16.5	
	3 mo	Change	+5.95	+6.94	+2.52	+5.48	
		CI (chg.)	(5.21 to 6.69)	(5.82 to 8.06)	(0.50 to 4.54)	(4.40 to 6.56)	
		<i>n</i> [<i>n</i> chg.] [†]	190 [190]	94 [94]	11 [11]	85 [85]	
		Mean ± SD	96.9 ± 17.1	97.9 ± 16.8	91.0 ± 18.3	96.6 ± 17.4	
		Change	+7.50	+9.22	+3.48	+6.12	
		CI (chg.)	(6.34 to 8.66)	(7.44 to 10.99)	(0.87 to 6.09)	(4.51 to 7.74)	
	6 mo	<i>n</i> [<i>n</i> chg.] [†]	356 [356]	166 [166]	24 [24]	166 [166]	
		Mean ± SD	98.8 ± 16.1	99.2 ± 15.7	97.7 ± 19.2	98.5 ± 16.1	
Change		+6.93	+7.60	+3.85	+6.71		
CI (chg.)		(6.03 to 7.83)	(6.20 to 9.00)	(1.27 to 6.44)	(5.43 to 7.99)		
Sweat chloride, mmol/L		Baseline	<i>n</i>	462	221	33	208
			Mean ± SD	88.0 ± 18.4	95.6 ± 12.8	52.6 ± 23.0	85.6 ± 15.2
	1 mo	<i>n</i> [<i>n</i> chg.] [†]	399 [387]	187 [180]	30 [29]	182 [178]	
		Mean ± SD	49.1 ± 19.6	57.3 ± 17.9	25.3 ± 15.0	44.5 ± 17.2	
	6 mo	Change	-38.95	-39.15	-25.31	-40.97	
		CI (chg.)	(-40.60 to -37.29)	(-41.68 to -36.62)	(-31.43 to -19.19)	(-43.17 to -38.76)	
		<i>n</i> [<i>n</i> chg.] [†]	383 [369]	174 [165]	31 [30]	178 [174]	
		Mean ± SD	45.7 ± 21.2	53.5 ± 19.6	26.2 ± 20.4	41.5 ± 19.5	
		Change	-41.70	-43.15	-23.92	-43.40	
		CI (chg.)	(-43.80 to -39.60)	(-46.21 to -40.09)	(-31.03 to -16.81)	(-46.38 to -40.41)	
	CFQ-R RD	Baseline	<i>n</i>	410	205	23	182
			Mean ± SD	70.3 ± 18.2	69.1 ± 18.5	71.0 ± 18.9	71.4 ± 17.9
1 mo		<i>n</i> [<i>n</i> chg.] [†]	380 [342]	187 [170]	28 [22]	165 [150]	
		Mean ± SD	82.7 ± 15.0	82.2 ± 14.8	83.3 ± 17.8	83.3 ± 14.7	
3 mo		Change	+12.54	+12.81	+10.35	+12.55	
		CI (chg.)	(10.32 to 14.76)	(9.53 to 16.09)	(0.52 to 20.19)	(9.37 to 15.74)	
		<i>n</i> [<i>n</i> chg.] [†]	352 [319]	166 [154]	27 [21]	159 [144]	
		Mean ± SD	87.5 ± 13.5	87.2 ± 13.2	87.9 ± 15.2	87.7 ± 13.7	
		Change	+16.95	+17.97	+14.81	+16.16	
		CI (chg.)	(14.76 to 19.13)	(15.00 to 20.95)	(5.75 to 23.87)	(12.69 to 19.63)	
6 mo		<i>n</i> [<i>n</i> chg.] [†]	302 [273]	144 [137]	25 [18]	133 [118]	
		Mean ± SD	90.5 ± 11.3	90.1 ± 12.2	91.8 ± 11.4	90.7 ± 10.4	
	Change	+20.39	+22.51	+18.52	+18.22		
	CI (chg.)	(18.28 to 22.50)	(19.47 to 25.54)	(7.63 to 29.40)	(15.22 to 21.22)		
	BMI [‡] , adults, kg/m ²	Baseline	<i>n</i>	326	157	24	145
			Mean ± SD	23.1 ± 4.0	22.8 ± 3.9	23.5 ± 2.7	23.5 ± 4.3
1 mo		<i>n</i> vis. [<i>n</i> chg.]	272 [272]	128 [128]	22 [22]	122 [122]	
		Mean ± SD	23.7 ± 4.2	23.4 ± 4.2	23.8 ± 3.1	24.0 ± 4.3	
3 mo		Change	+0.42	+0.47	+0.39	+0.37	
		CI (chg.)	(0.33 to 0.50)	(0.34 to 0.59)	(0.11 to 0.68)	(0.25 to 0.49)	
		<i>n</i> vis. [<i>n</i> chg.]	136 [136]	65 [65]	10 [10]	61 [61]	
		Mean ± SD	24.1 ± 3.8	23.9 ± 3.8	23.5 ± 2.7	24.4 ± 3.9	
		Change	+0.85	+1.08	+0.86	+0.62	
		CI (chg.)	(0.68 to 1.03)	(0.85 to 1.30)	(-0.05 to 1.76)	(0.34 to 0.90)	
6 mo		<i>n</i> vis. [<i>n</i> chg.]	268 [268]	121 [121]	22 [22]	125 [125]	
		Mean ± SD	24.5 ± 4.6	24.2 ± 4.6	24.6 ± 3.2	24.8 ± 4.7	
	Change	+1.24	+1.31	+1.28	+1.17		
	CI (chg.)	(1.05 to 1.44)	(1.01 to 1.61)	(0.47 to 2.09)	(0.89 to 1.44)		
	BMI, peds [§] (z-score)	Baseline	<i>n</i>	159	80	10	69
			Mean ± SD	0.2 ± 0.9	0.1 ± 0.9	0.5 ± 0.7	0.2 ± 0.8
1 mo		<i>n</i> [<i>n</i> chg.] [†]	140 [140]	70 [70]	10 [10]	60 [60]	
		Mean ± SD	0.3 ± 0.8	0.2 ± 0.9	0.5 ± 0.7	0.3 ± 0.8	

(Continued)

Table 2. (Continued)

Outcome	Visit		Baseline Modulator Use*			
			All	None	Iva	Two-Drug
3 mo		Change	+0.11	+0.11	+0.05	+0.12
		CI (chg.)	(0.07 to 0.15)	(0.05 to 0.18)	(-0.07 to 0.18)	(0.08 to 0.16)
		n [n chg.] [†]	55 [55]	28 [28]	2 [2]	25 [25]
6 mo		Mean ± SD	0.3 ± 0.7	0.0 ± 0.8	-0.5 ± 0.4	0.6 ± 0.5
		Change	+0.24	+0.28	+0.14	+0.20
		CI (chg.)	(0.15 to 0.33)	(0.12 to 0.45)	(-1.92 to 2.19)	(0.11 to 0.29)
		n [n chg.] [†]	139 [139]	67 [67]	10 [10]	62 [62]
		Mean ± SD	0.5 ± 0.8	0.5 ± 0.8	0.7 ± 0.9	0.4 ± 0.8
		Change	+0.30	+0.37	+0.20	+0.23
		CI (chg.)	(0.22 to 0.37)	(0.24 to 0.50)	(-0.06 to 0.45)	(0.14 to 0.31)

Definition of abbreviations: BMI = body mass index; CFQ-R RD = Cystic Fibrosis Questionnaire–Revised, Respiratory Domain; chg. = change; CI = confidence interval; Iva = ivacaftor monotherapy; n vis. = number of participants attending the study visit; ppFEV₁ = percent predicted FEV₁; ppFVC = percent predicted FVC; two-drug = lumacaftor/iva or tezacaftor/iva.

*Prior use of modulators defined as any use within 90 days of the baseline measurement.

[†][n chg.] is the number of participants contributing to the change estimate (having both baseline and follow-up measured).

[‡]Pregnant participants were excluded from analyses of BMI.

[§]z-scores are based on Centers for Disease Control and Prevention percentiles.

E5). CFQ-R RD changes were, on average, larger among older and female participants who generally reported more symptoms of CF lung disease before starting ETI (Table E2). All groups subdivided by sex, age, or prior modulator use reported similar, near-maximum post-ETI scores (Figure 2 and Table E2). There were no identified interactions between ppFEV₁ change and age, sex, ethnicity, or race. A stratification by baseline ppFEV₁ (Table E5) shows significant improvements in each baseline lung function group. Owing to the study design, this breakdown cannot be used to demonstrate a

ceiling effect (a reduction in change at high baseline levels) for ppFEV₁.

CFTR Genotype Representation

Participants with one F508del allele had a wide variety of second CFTR mutations. Changes in ppFEV₁ and sweat chloride are shown in Figure E3 for mutations other than G551D/F508del or F508del/F508del if present in at least six individuals in PROMISE. Mean sweat chloride values after starting ETI are also provided for groups containing data from at least three participants in Figure E4. PROMISE

included 11 individuals with F508del plus one of the mutations added to the U.S. Food and Drug Administration (FDA)-approved label indication based largely on *in vitro* testing for improved CFTR function (26). These 11 individuals had a greater mean reduction in sweat chloride from baseline compared with a group identified as having F508del plus a mutation not expected to respond to ETI (i.e., a minimal function allele) (difference, 13.4 mmol/L; 95% CI, 2.4–24.3) (Table E3). Changes in ppFEV₁ were not significantly different between

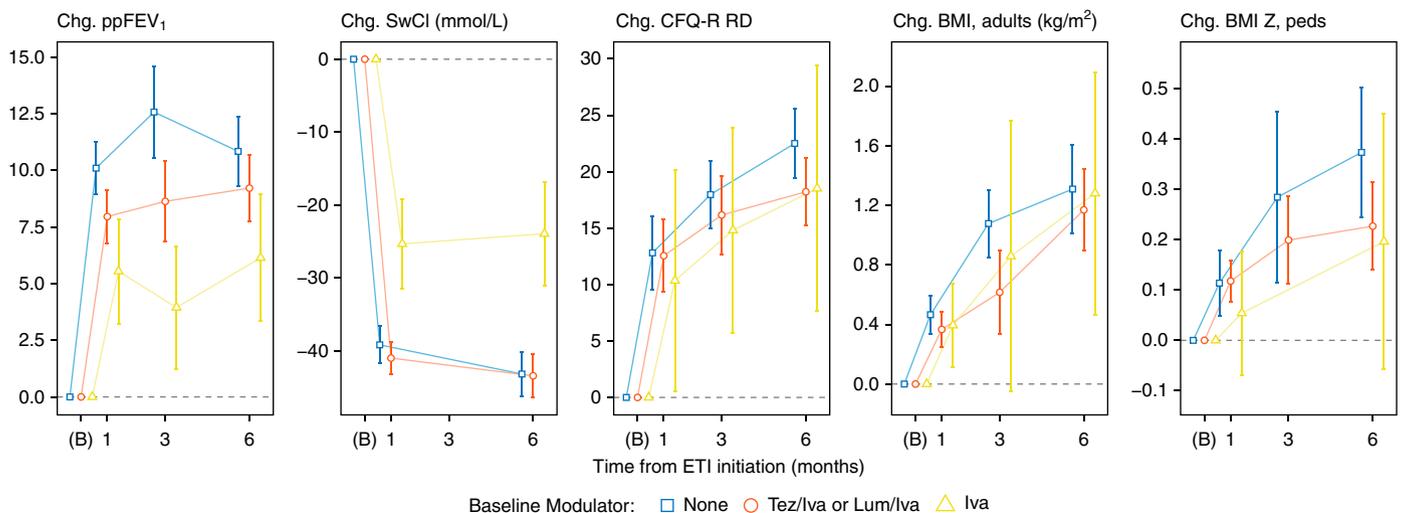


Figure 1. Changes from baseline with 95% confidence intervals, stratified by cystic fibrosis transmembrane conductance regulator modulator use at baseline (iva = ivacaftor monotherapy). Times of observation are pre-elaxaftor/tezacaftor/ivacaftor baseline (B) and planned visit times. Participants who were pregnant at a visit were excluded from analyses of body mass index (BMI). Confidence intervals with five or fewer participants are not shown, and low follow-up at 3 months requires additional caution in interpretation (see Table 2). CFQ-R RD = Cystic Fibrosis Questionnaire–Revised, Respiratory Domain; Chg. = change; ETI = elaxaftor/tezacaftor/ivacaftor; Lum = lumacaftor; ppFEV₁ = percent predicted FEV₁; SwCl = sweat chloride; Tez = tezacaftor.

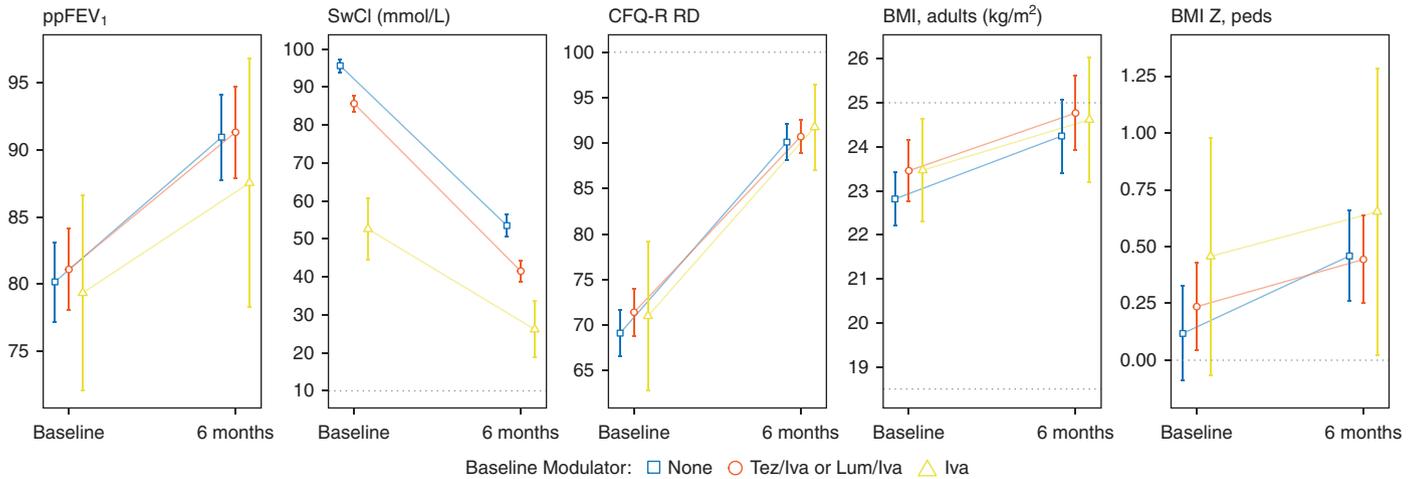


Figure 2. Cross-sectional estimates and 95% confidence intervals of outcomes, stratified by cystic fibrosis transmembrane conductance regulator modulator use at baseline (iva = ivacaftor monotherapy). Times shown are baseline and the 6-month post-elaxaftor/tezacaftor/ivacaftor visit. Participants who were pregnant at a visit ($n = 2$ at baseline; $n = 7$ at 6 mo) were excluded from analyses of body mass index (BMI). Dotted lines show limits of the instrument (sweat chloride [SwCl] and Cystic Fibrosis Questionnaire–Revised, Respiratory Domain [CFQ-R RD]) or thresholds (BMI 25 for overweight, BMI 18 for underweight, and BMI z-score 0 for median). Lum = lumacaftor; ppFEV₁ = percent predicted FEV₁; Tez = tezacaftor.

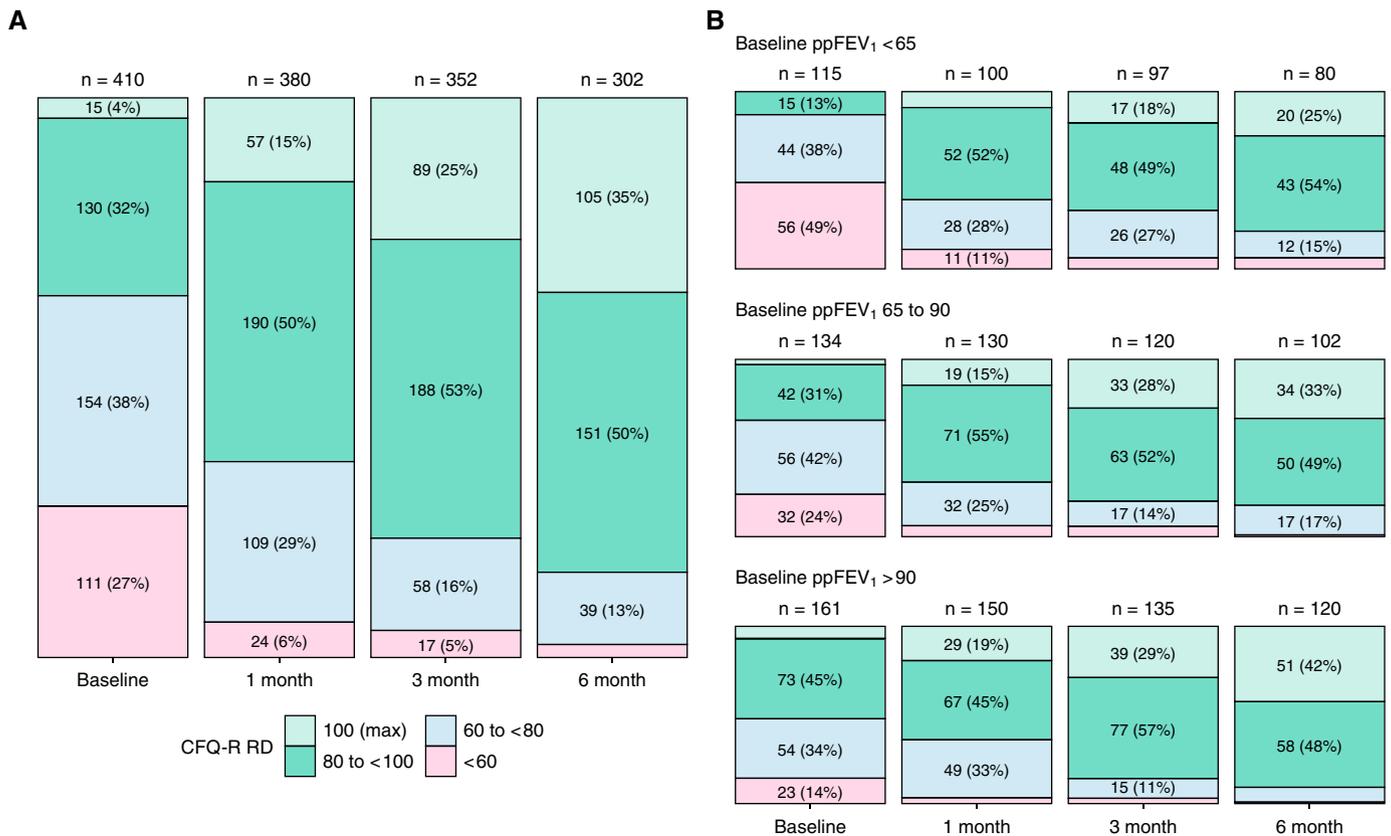


Figure 3. (A) Cystic Fibrosis Questionnaire–Revised, Respiratory Domain (CFQ-R RD) with participants grouped into categories at each visit. The top category (100, light green) represents the maximum achievable score, which a substantial number of participants obtained 6 months after elaxaftor/tezacaftor/ivacaftor initiation. Labels are omitted for categories with too few participants. (B) The same plot split into categories based on baseline percent predicted FEV₁ (ppFEV₁). The trend toward the maximum score was observed at each level of baseline lung function, with higher proportions in the high baseline lung function cohort reporting maximal CFQ-R RD at 6 months.

Table 3. Use of Four Chronic Daily Medications Assessed at Each Visit by Self-Report

Outcome	Visit	Using/Observed (%)	P Value
Inhaled antibiotics	Baseline	248/486 (51.0)	—
	1 mo	186/417 (44.6)	—
	3 mo	97/195 (49.7)	—
	6 mo	145/429 (33.8)	<0.005
Azithromycin	Baseline	238/486 (49.0)	—
	1 mo	206/417 (49.4)	—
	3 mo	94/195 (48.2%)	—
	6 mo	191/429 (44.5%)	0.01
Hypertonic saline	Baseline	368/486 (75.7%)	—
	1 mo	308/417 (73.9%)	—
	3 mo	148/195 (75.9%)	—
	6 mo	293/429 (68.3%)	<0.005
Dornase alfa	Baseline	424/486 (87.2%)	—
	1 mo	365/417 (87.5%)	—
	3 mo	166/195 (85.1%)	—
	6 mo	350/429 (81.6%)	<0.005

these groups. Those with two minimal function mutations of particular interest owing to their prevalence and unique properties (W1282X, N1303K) were compared with the same comparator group (Table E3) as an exploratory analysis (27–29). No significant differences in change in sweat chloride or ppFEV₁ were found, though available numbers of participants were small.

Discussion

This planned 6-month analysis of the PROMISE study enabled two important questions to be addressed: How does ETI drug therapy perform during clinical use, and what additional impacts of ETI can be identified that may be relevant to clinical care or future research priorities? We found clear evidence of substantial improvement in clinical outcomes among nearly 500 individuals despite a broad range of baseline demographic and other characteristics, including lung function, genotype, and prior CFTR modulator use (Table 2). The overall average improvement in ppFEV₁ at 6 months was nearly 10%, the largest magnitude in a large observational study among PwCF. This occurred despite CFTR modulator use by the majority of participants at the time of enrollment (47% entered on two-drug combinations and 7% on ivacaftor) (Table 2). For comparison, the mean 6-month ppFEV₁ improvement after starting ivacaftor to target the *G551D* mutation was

6.7% in the GOAL study, which enrolled a modulator-naïve but similar population with respect to baseline age and lung function (5).

Lung function improved after initiating ETI therapy regardless of preexisting CFTR modulator use, which was closely associated with underlying CFTR genotype and generally consistent with drug indication (Table 1). Each subgroup, defined by modulator use before starting ETI (and associated genotype), had a baseline ppFEV₁ between 79% and 81% (Table 2) and reached an average ppFEV₁ near or above 90% predicted by 6 months (Figure 2). Even the substantially sized subset ($n = 196$) of those at or above 90% predicted at baseline (an exclusion criteria for the phase 3 trials) achieved a mean improvement of 6.5 ppFEV₁ (Table E5). In this study, those below 65% predicted at baseline had a mean improvement of 12.2 ppFEV₁ by 6 months into ETI therapy, and others have reported significant clinical improvement with ETI in people with even more advanced lung disease (30, 31). A high degree of CFTR functional improvement was achieved, as reflected by an overall mean reduction in sweat chloride of 45.7 mmol/L at 6 months, with all subgroups improving to a mean sweat chloride value below 60 mmol/L. Perhaps consequently, daily respiratory signs and symptoms significantly decreased with ETI therapy. At baseline, 36% of participants reported a CFQ-R RD score of at least 80 points, and 4% reported the maximum score of 100. After steady improvement, 85% had scores of at least 80, and 35% reported the

maximum score of 100 by 6 months, suggesting many subjects resolved chronic respiratory symptoms. Given the substantial number of PwCF who reported a maximum score, it is possible that the CFQ-R RD may no longer be a dynamic endpoint for future studies enrolling people already treated with ETI. Substantial gains in CFQ-R RD were observed even when baseline ppFEV₁ was less than 65% (Figure 3) (32). The mean overall improvement in this symptom score at 6 months was over 20 points compared with 7.4 points in GOAL, which had a similar open-label design that may bias self-reporting of respiratory symptoms (5, 18). For context, the minimal clinically important change in the CFQ-R RD has been identified as 4 points (18).

BMI also increased to an average of 24.5 kg/m² among adults at 6 months and 65th percentile among adolescents and continued to increase even after changes in outcomes like sweat chloride and ppFEV₁ had largely plateaued. These results suggest that goals for calorie supplementation may need to be reconsidered in many PwCF after starting ETI as chronic therapy (33). Future evaluation of BMI beyond 6 months of

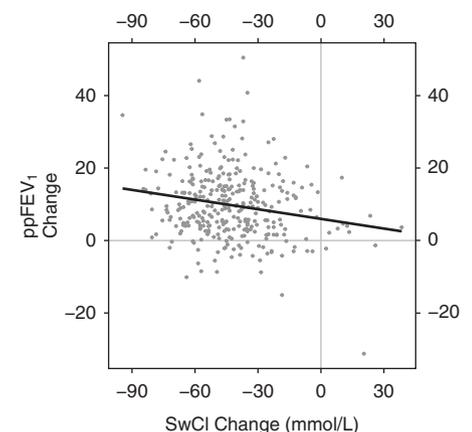


Figure 4. Correlation between the change in percent predicted FEV₁ (ppFEV₁) and the change in sweat chloride (mmol/L) from baseline to 6 months (visit 4). Pearson correlation coefficient is -0.19 ($P < 0.005$). The dark line shows the equivalent linear regression fit, indicating that each additional 10-point decrease in sweat chloride (SwCl) is associated with a mean 0.89 greater change in ppFEV₁ from baseline to 6 months after elaxafor/tezacaftor/ivacaftor initiation. This correlation remains significant if the influential points at (17, -31) and (-95, 35) are excluded, or if Spearman's rank-based association statistic is substituted for the Pearson correlation statistic.

modulator therapy, body composition, and related endocrine and gastrointestinal outcomes planned within PROMISE will be of particular importance to better understand BMI trajectories, emergence of overweight/obesity, and the relationships of BMI with these additional outcomes.

Participants transitioning from ivacaftor to ETI, representing those with highly responsive CFTR gating mutations (97% had F508del/G551D), achieved the lowest sweat chloride concentration reported to date in response to modulator drug therapy. The group ($n = 34$) had a baseline mean sweat chloride on ivacaftor indicative of substantial drug response (52.6 mmol/L), but this value fell to 23.9 mmol/L at the 6-month visit after transitioning to ETI. This is below even the indeterminate range as a diagnostic test for CFTR dysfunction (34) and recapitulates recent clinical trial data in this population (35). Those entering the study on ivacaftor also experienced clinically meaningful and statistically significant improvements in ppFEV₁, BMI, and respiratory symptoms when transitioning to ETI, supporting the benefit of drug-induced CFTR modulation even when CFTR function is already in the intermediate range.

In contrast to similar prior studies of CFTR modulator drugs, we observed a statistically significant correlation between change in sweat chloride and ppFEV₁ (Figure 4) (5, 23, 36). We hypothesize that three factors contributed to this finding in the PROMISE study: 1) the large effect sizes caused by ETI; 2) the heterogeneity of the cohort by genotype and prior CFTR modulator use, increasing the spectrum of observed responses; and 3) the large sample size (37). This connection between restoration of CFTR function (i.e., change in sweat chloride) and clinical impact (i.e., improved FEV₁, among other measures) supports the notion that sustained improvements in CFTR function with ongoing drug use will be associated with long-term clinical benefit, as observed with longer observation and natural history studies of ivacaftor therapy (4, 9, 38–40). Given the comparative 6-month findings of ETI in this study and ivacaftor in GOAL, we are particularly interested in monitoring this as the PROMISE study progresses. The strength of correlation between changes in sweat chloride and ppFEV₁ in this study was modest, and additional work will be

needed to better understand the use of sweat chloride as an indicator of clinical benefit, especially in individuals or small populations (41–43). It is important to recognize that small changes in sweat chloride did not preclude substantial improvement in clinical outcomes (Figure 4).

This was the first opportunity to consider the effects of ETI in those with CFTR mutations that the FDA has subsequently approved for ETI use without an F508del allele based on *in vitro* testing (26). A group of 11 such individuals with no prior modulator exposure who had one of these mutations in combination with F508del had an average sweat chloride improvement of -53.0 mmol/L, 13.4 mmol/L larger than those with F508del and a mutation known to not respond to ETI (Table E3). These data support that ETI can improve CFTR function in individuals when targeting these mutations identified through *in vitro* testing. It is unknown whether ETI would be more or less effective in the absence of an F508del allele. We also acknowledge that the average changes in ppFEV₁ were not statistically significantly greater than the F508del/minimal function group in this small, heterogeneous population.

Females experienced approximately 10 mmol/L greater reduction in sweat chloride compared with males, despite similar baseline values. An analysis of the subjects treated with ivacaftor in GOAL identified a similar association, in addition to noting an association between weight and change in sweat chloride (24). The association between sex and change in sweat chloride in our study remained even when adjusting for weight, and the biological basis for this observation is unclear (24, 25). In addition, 11 female participants were found to be pregnant during the study. Increased pregnancy rates associated with highly effective CFTR modulator use is an important consideration in the lives of PwCF, and we expect the need for further attention to reproductive and sexual health (44–46).

The safety of ETI was not assessed in this study, but we observed low self-reported discontinuation rates, consistent with clinical trials. Although participants were encouraged to maintain all other chronic medications through 6 months, significant reductions in use of supportive therapies,

and in particular inhaled antibiotics, occurred by the 6-month visit (Table 3). Monitoring further changes in medication use and the association with clinical status will be important to understanding the future treatment landscape (47, 48). Changes in inhaled antibiotics may be particularly relevant, as ivacaftor use has been associated with reduced detection of *Pseudomonas aeruginosa* and some other pathogens in clinical respiratory cultures (4, 13, 39, 49). Microbiological changes are the focus of a substudy of PROMISE and are being carefully assessed through prospective, serial sputum collection.

In summary, the clinical results through 6 months of this prospective observational study find robust health benefits of ETI in real-world practice that are similar to those found in controlled clinical trials. Compared with prior similar studies in CF, these results set a new benchmark for highly effective modulator drug therapy (5). The full range of potential biological and clinical effects of ETI are important to understand; several organ-specific substudies focused on translational and clinical outcomes will follow. Similarly, a study in those aged 6–11 years is forthcoming concurrent with FDA label extension in younger patients. The measured health status of PROMISE participants at 6 months into ETI therapy demonstrates how daily morbidity has dramatically improved for those for whom ETI is indicated and available.

Certain limitations exist in these analyses, including the potential influence of the COVID-19 pandemic that contributed to a number of missing or delayed study visits at the 3- and 6-month time points (Figure E2). We compared the 6-month changes in outcomes between those completing the study visits by the end of the predefined window and those completing the visits late owing to the pandemic. We found no meaningful differences and overlapping 95% CIs for ppFEV₁, sweat chloride, CFQ-R RD, and BMI (data not shown). It is fortunate that response to ETI occurs soon after starting drug therapy and that a large majority of the 1-month study visits were completed before pandemic-related restrictions began, though it is possible that our results were still affected. Completion of this study through at least 30 months of ETI will better characterize long-term

outcomes and provide a robust understanding of the durability of these early health improvements—hopefully in a time with less need for social distancing. This study is collecting concomitant medications used, including antibiotics, but is not systematically capturing predefined pulmonary exacerbation events in real time. This decision, along with the relatively short timeframe reported in this first phase and potential impact of social distancing on risk of exacerbations, led us to

postpone our analyses of antibiotic use until the end of the study. In addition, in the evaluation of mutations added to the United States Prescribing Information for approved drug use but not yet reported clinically, participants had at least one responsive F508del allele, which also contributed to their sweat chloride response. Despite these limitations, we are encouraged to find that ETI was broadly effective in individuals, including many who would not meet eligibility criteria for the randomized controlled

trials that led to drug approval, and we hope that data from this study will support ongoing work to realize highly efficacious CFTR-directed therapy for all PwCF. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank the many people with cystic fibrosis and research teams across the United States who made this study possible.

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