Journal of Cystic Fibrosis xxx (xxxx) xxx

Contents lists available at ScienceDirect

Journal of Cystic Fibrosis

journal homepage: www.elsevier.com/locate/jcf

EFFECT OF ELEXACAFTOR/TEZACAFTOR/IVACAFTOR ON ANNUAL RATE OF LUNG FUNCTION DECLINE IN PEOPLE WITH CYSTIC FIBROSIS ☆

Tim Lee [a,*], Gregory S. Sawicki [b], Josje Altenburg [c], Stefanie J. Millar [d], Jessica Morlando Geiger [e], Mark T. Jennings [e], Yiyue Lou [e], Lisa J. McGarry [e], Kate Van Brunt [e], Rachel W. Linnemann [f]

[a] *Leeds Children's Hospital, Leeds, United Kingdom of Great Britain and Northern Ireland United Kingdom*
[b] *Boston Children's Hospital, Boston, MA, United States of America*
[c] *Amsterdam University Medical Centres, Amsterdam, the Netherlands*
[d] *ICON plc, Blue Bell, PA, United States of America*
[e] *Vertex Pharmaceuticals Incorporated, Boston, MA, United States of America*
[f] *Emory University, Atlanta, GA, United States of America*

ARTICLE INFO

Article history:
Received 21 October 2022
Revised 6 December 2022
Accepted 18 December 2022
Available online xxx

Keywords:
Cystic fibrosis
Elexacaftor/tezacaftor/ivacaftor
Cystic fibrosis transmembrane conductance regulator modulator
F508del-CFTR
Lung function

ABSTRACT

Elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) was shown to be safe and efficacious in people with cystic fibrosis (CF) with ≥ 1 *F508del-CFTR* allele in Phase 3 clinical trials. ELX/TEZ/IVA treatment led to improved lung function, with increases in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) and Cystic Fibrosis Questionnaire-Revised respiratory domain score. Here, we evaluated the impact of ELX/TEZ/IVA on the rate of lung function decline over time by comparing changes in $ppFEV_1$ in participants from the Phase 3 trials with a matched group of people with CF from the US Cystic Fibrosis Foundation Patient Registry not eligible for cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapy. Participants treated with ELX/TEZ/IVA had on average no loss of pulmonary function over a 2-year period (mean annualized rate of change in $ppFEV_1$, +0.39 percentage points [95% CI, −0.06 to 0.85]) compared with a 1.92 percentage point annual decline (95% CI, −2.16 to −1.69) in $ppFEV_1$ in untreated controls. ELX/TEZ/IVA is the first CFTR modulator therapy shown to halt lung function decline over an extended time period.

1. Introduction

Progressive lung function decline is a hallmark of cystic fibrosis (CF), with most patients experiencing a decline in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) of 1 to 3 percentage points annually [1]. More rapid decline is associated with more severe CF lung disease and earlier mortality; therefore, preserving lung function is a primary goal of CF clinical care [2,3].

Previous studies indicated that patients treated with the CF transmembrane conductance regulator modulators (CFTRm) ivacaftor (IVA), lumacaftor (LUM)/IVA, and tezacaftor (TEZ)/IVA had reduced rates of lung function decline—47.1%, 41.9%, and 61.5%, respectively—compared with CFTRm-untreated controls [4–6]. A triple combination regimen of elexacaftor (ELX)/TEZ/IVA was shown to be safe and efficacious in patients aged ≥12 years with CF and heterozygous for *F508del-CFTR* and a minimal function mutation (*F*/MF genotypes; Study 445–102) or homozygous for *F508del-CFTR* (*F/F* genotype; Study 445–103) [7,8]. In an extension study, robust and sustained improvements in lung function were seen through 144 weeks of ELX/TEZ/IVA treatment [9].

To further characterize the impact of ELX/TEZ/IVA on lung function decline over time, we compared the annualized rate of change in $ppFEV_1$ in patients treated with ELX/TEZ/IVA with a propensity score–matched historical cohort of CFTRm-untreated controls from the US Cystic Fibrosis Foundation Patient Registry (CFFPR).

☆ Data from this study were presented at the following meeting: 45th Annual European Cystic Fibrosis Conference (ECFS), 8–11 June 2022, Rotterdam, the Netherlands

* Corresponding author: Tim Lee, Clinical Associate Professor, Head of Studies, Postgraduate Programmes in Child Health, University of Leeds, Leeds Regional Paediatric Cystic Fibrosis Centre, A Floor, Clarendon Wing, Leeds Children's Hospital, Great George Street LS1 3EX, United Kingdom, Tel: +44 113 3927125.

E-mail addresses: tim.lee1@nhs.net (T. Lee), Gregory.Sawicki@childrens.harvard.edu (G.S. Sawicki), j.altenburg@amsterdamumc.nl (J. Altenburg), stefaniejmillar@gmail.com (S.J. Millar), Jessica_Morlando@vrtx.com (J.M. Geiger), Mark_Jennings@vrtx.com (M.T. Jennings), Yiyue_Lou@vrtx.com (Y. Lou), Lisa_McGarry@vrtx.com (L.J. McGarry), Kate_VanBrunt@vrtx.com (K. Van Brunt), rachel.linnemann@emory.edu (R.W. Linnemann).

https://doi.org/10.1016/j.jcf.2022.12.009
1569-1993/

Table 1
Demographic and Clinical Characteristics at Baseline.

Characteristic	ELX/TEZ/IVA (N = 468)	Control (N_W = 468; N = 1714)
Age, mean ± SD, years	26.41 ± 10.66	25.77 ± 5.65
Age ≥18 years, n (%)	342 (73.1)	342 (73.1)
Female, n (%)	232 (49.6)	231 (49.4)
Race, n (%)		
White	436 (93.2)	439 (93.7)
Black	4 (0.9)	8 (1.7)
Other	28 (6.0)	22 (4.6)
Ethnicity, n (%)		
Hispanic	20 (4.3)	23 (4.9)
Not Hispanic	426 (91.0)	427 (91.2)
Not reported	22 (4.7)	18 (3.9)
CF-related diabetes, n (%)	158 (33.8)	154 (32.9)
Height-for-age *z*-score, mean ± SD	−0.44 ± 0.97	−0.49 ± 0.53
Weight-for-age *z*-score, mean ± SD	−0.37 ± 0.96	−0.40 ± 0.57
BMI-for-age *z*-score, mean ± SD	−0.24 ± 0.92	−0.24 ± 0.53
BMI, mean ± SD, kg/m^2	21.57 ± 3.17	21.65 ± 1.92
Percent predicted FEV_1, mean ± SD	61.05 ± 15.69	62.60 ± 9.61
Percent predicted FEV_1 group, n (%)		
<40	49 (10.5)	49 (10.5)
40–70	267 (57.1)	267 (57.1)
>70	152 (32.5)	152 (32.5)
Percent predicted FEV_1 decile, mean ± SD	6.57 ± 2.12	6.67 ± 1.16
Percent predicted FVC, mean ± SD	76.51 ± 14.35	77.83 ± 9.26
Percent predicted $FEF_{25–75}$, mean ± SD	37.67 ± 20.66	39.47 ± 11.83
Percent predicted FEV_1/FVC ratio, mean ± SD	78.88 ± 11.01	79.66 ± 6.61
Tobramycin solution for inhalation, n (%)	92 (19.7)	138 (29.4)
Colistin, n (%)	23 (4.9)	26 (5.5)
Aztreonam, n (%)	83 (17.7)	103 (22.0)
Dornase alfa, n (%)	400 (85.5)	407 (87.0)
Acetylcysteine, n (%)	6 (1.3)	8 (1.6)
Oral corticosteroid, n (%)	17 (3.6)	18 (3.9)
Inhaled corticosteroid, n (%)	194 (41.5)	165 (35.2)
Leukotriene modifiers, n (%)	90 (19.2)	105 (22.4)
Hypertonic saline, n (%)	338 (72.2)	342 (73.0)
Azithromycin, n (%)	259 (55.3)	266 (56.8)
MRSA, n (%)	109 (23.3)	136 (29.0)
MSSA, n (%)	152 (32.5)	186 (39.8)
Hemophilus influenzae, n (%)	50 (10.7)	56 (12.0)
Pseudomonas aeruginosa, n (%)	334 (71.4)	326 (69.7)
Alcaligenes, n (%)	53 (11.3)	60 (12.8)
Stenotrophomonas, n (%)	92 (19.7)	99 (21.1)
Aspergillus, n (%)	174 (37.2)	157 (33.6)
Nontuberculosis mycobacterium, n (%)	5 (1.1)	9 (1.9)

BMI: body mass index; CF: cystic fibrosis; ELX/TEZ/IVA: elexacaftor/tezacaftor/ivacaftor; $FEF_{25–75}$: forced expiratory flow at 25% and 75% of pulmonary volume; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; MRSA: methicillin-resistant *Staphylococcus aureus*; MSSA: methicillin-susceptible *Staphylococcus aureus*; N_W: weighted sample size of the control group using the inverse of the number of controls in each matched set to account for one-to-many matching used in the analysis; SD, standard deviation. A match was identified if patients belonged to the same age and $ppFEV_1$ category and were within 0.5 SD of the logit propensity score caliper. Match quality was assessed by calculating the weighted effect sizes of all candidate variables separately as well as by identifying any statistically significant differences; a weighted effect size of <0.20 was deemed acceptable.

2. Methods

Patients who received ELX/TEZ/IVA in the phase 3 clinical studies 445–102 (NCT03525444) and 445–103 (NCT03525548) or open-label extension study 445–105 (NCT03525574) and had ≥3 $ppFEV_1$ measurements over ≥6 months were propensity score matched with up to 5 patients from the CFFPR aged ≥12 years with *F*/MF or *F*/*F* genotypes using methods described in previous studies of IVA, LUM/IVA, and TEZ/IVA [4–6]. Eligibility criteria were applied to the registry population to mimic the clinical trial eligibility criteria. Patients in the US CFFPR were required to be ≥12 years old, have an *F*/MF or *F*/*F* genotype, have no evidence of CFTRm use during either the baseline year or the analysis period, have ≥3 non-missing FEV_1 records spanning ≥6 months through the 2-year follow-up period, and have at least one "stable" encounter in the baseline year with valid nutritional and pulmonary function test data.

Data from 2015 to 2017 were used for *F*/MF controls to avoid possible ELX/TEZ/IVA use in clinical trials or expanded access programs. Data from 2012 to 2014 were used for *F*/*F* controls to avoid LUM/IVA eligibility. Patients treated with ELX/TEZ/IVA with *F*/MF genotypes were matched with CFTRm-untreated patients with *F*/MF genotypes; patients with the *F*/*F* genotype were matched with CFTRm-untreated patients with the *F*/*F* genotype. Two logistic regression models were developed, one for each genotype, which included the same set of candidate variables for propensity score matching known to predict lung function decline and used in prior rate of change analyses [4–6] (**Table S1 and S2**). Backwards stepwise selection was implemented with a statistical significance threshold of 0.20 to identify predictor variables of ELX/TEZ/IVA exposure (ELX/TEZ/IVA patient vs CFFPR control). The two final models with variables identified from backwards stepwise selection were used to generate propensity scores for each patient. A match

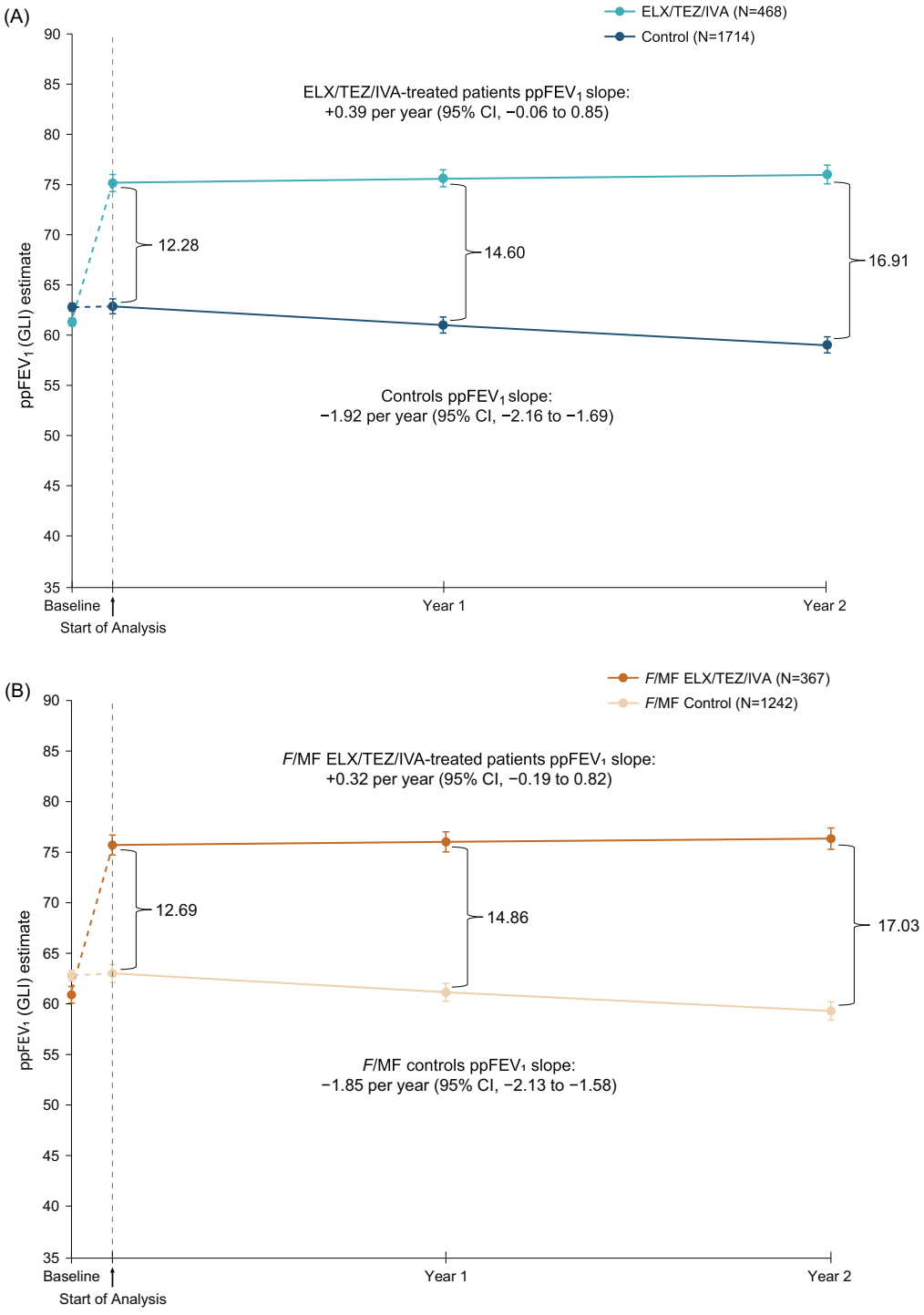

Fig 1. Estimation of the annualized slope for ppFEV$_1$ in (A) all patients with *F*/MF and *F*/*F* genotypes, (B) patients with *F*/MF genotypes, and (C) patients with the *F*/*F* genotype. Start of analysis was defined as >21 days after ELX/TEZ/IVA initiation to remove the acute lung function improvement due to ELX/TEZ/IVA from the calculation of rate of ppFEV$_1$ change. Patients were matched on demographic and clinical characteristics at baseline. Estimation and significance testing were conducted using a mixed model, with random intercepts and slopes for each patient-within-match group and unstructured covariance. The model included fixed effects for treatment group (ELX/TEZ/IVA or control), time, and a treatment-group-by-time interaction. Patients with the *F*/*F* genotype treated with ELX/TEZ/IVA had a 4-week run-in period with TEZ/IVA prior to baseline; patients were matched on the baseline ppFEV$_1$, which reflects the acute benefits of TEZ/IVA. Reduction in the rate of lung function decline is calculated as the percent difference between the ELX/TEZ/IVA-treated and matched control slopes. Because patients treated with ELX/TEZ/IVA had on average no decrease in ppFEV$_1$ over the 2-year period, the reduction in rate of decline is calculated as >100% (120.3%; 95% CI, 96.8%–144.4%). ELX: elexacaftor; *F*/*F*: homozygous for the *F508del-CFTR* mutation; *F*/MF: heterozygous for *F508del-CFTR* and a minimal function mutation; IVA: ivacaftor; ppFEV$_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor.

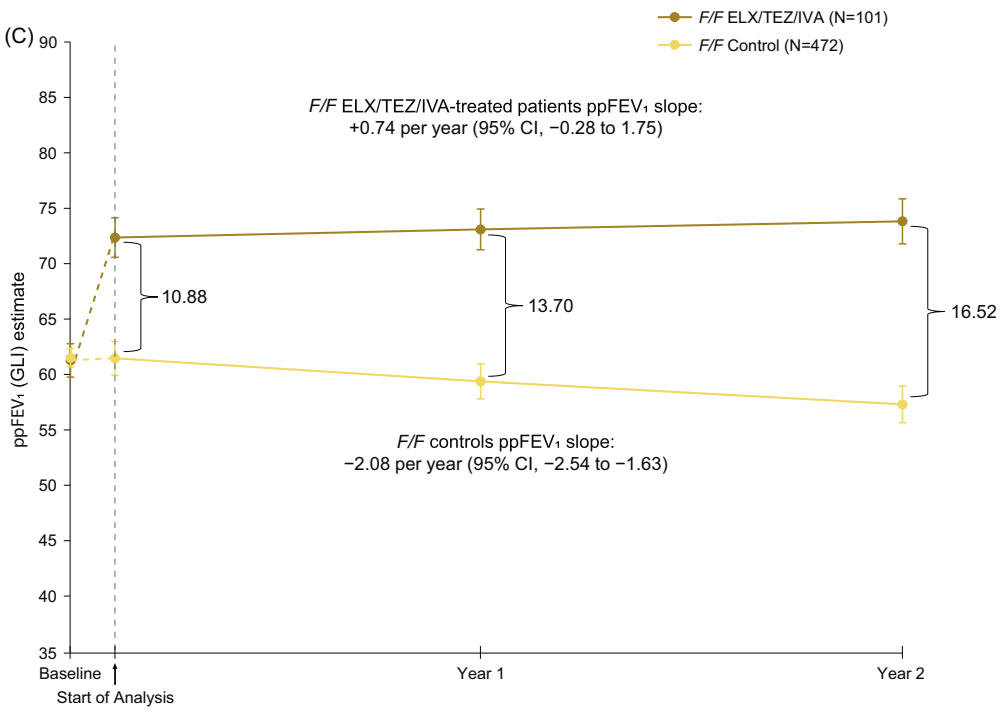

Fig 1. Continued

was identified if patients belonged to the same age and ppFEV$_1$ category and were within 0.5 standard deviations (SD) of the logit propensity score caliper.

The annualized mean rate of change in ppFEV$_1$ was estimated with a mixed model using all available ppFEV$_1$ measures through up to 120 weeks, excluding measures during the first 21 days of ELX/TEZ/IVA to avoid inclusion of acute lung function improvement. The primary analysis included all matched patients with *F/F* or *F*/MF genotypes; subgroup analyses by genotype were also conducted. Estimation and significance testing were conducted using a mixed model, with random intercepts and slopes for each patient-within-match group and unstructured covariance. The model included fixed effects for treatment group (ELX/TEZ/IVA or control), time, and a treatment-group-by-time interaction.

3. Results

3.1. Participant population

A total of 468 patients treated with ELX/TEZ/IVA (n = 367 *F*/MF; n = 101 *F/F*) were matched with 1714 CFTRm-untreated controls (n = 1242 *F*/MF; n = 472 *F/F*). ELX/TEZ/IVA and CFTRm-untreated control groups were well balanced across baseline characteristics after matching; baseline mean ppFEV$_1$ was 61.05 percentage points (SD, 15.69) in the ELX/TEZ/IVA group and 62.60 percentage points (SD, 9.61) in the control group (**Table 1**).

3.2. Annualized rate of change in ppFEV$_1$

Patients treated with ELX/TEZ/IVA had a mean annualized rate of change in ppFEV$_1$ of +0.39 percentage points (95% CI, −0.06 to 0.85) compared with −1.92 percentage points (95% CI, −2.16 to −1.69) in matched controls (mean difference, 2.32 percentage points; P<0.001) (**Fig 1a**). The between-group difference in ppFEV$_1$ was 16.91 percentage points (95% CI, 15.56 to 18.27; P<0.001) at year 2.

For the *F*/MF subgroup, the estimated annualized rate of change in ppFEV$_1$ was +0.32 percentage points (95% CI, −0.19 to 0.82) with ELX/TEZ/IVA compared with −1.85 percentage points (95% CI, −2.13 to −1.58) in CFTRm-untreated controls (mean difference, 2.17 percentage points; P<0.001) (**Fig 1b**). Similarly, for the *F/F* subgroup, the estimated annualized rate of change in ppFEV$_1$ was +0.74 percentage points (95% CI, −0.28 to 1.75) with ELX/TEZ/IVA compared with −2.08 percentage points (95% CI, −2.54 to −1.63) in CFTRm-untreated controls (mean difference, 2.82 percentage points; P<0.001) (**Fig 1c**).

4. Discussion and conclusions

We analyzed rates of lung function decline in patients with *F/F* and *F*/MF genotypes treated with ELX/TEZ/IVA in the pivotal clinical trials compared with CFTRm-untreated matched controls from the CFFPR. While previous studies demonstrated that CFTRm can slow rates of lung function decline [4–6], patients treated with ELX/TEZ/IVA had on average no loss of pulmonary function over a 2-year period (mean annualized rate of change in ppFEV$_1$, +0.39 percentage points) compared with a 1.92 percentage point annual decline in ppFEV$_1$ in CFTRm-untreated controls. Subgroup analyses showed that both genotype groups had on average no loss of ppFEV$_1$ over the 2-year period.

This study has several limitations. The use of noncontemporaneous controls may introduce temporal bias due to changes in clinical care. Although propensity score matching was used to reduce bias by balancing the risk factors for lung function decline between groups, a sensitivity analysis was conducted to evaluate any remaining bias related to the use of noncontemporaneous controls. In this analysis, patients with the *F/F* genotype treated with ELX/TEZ/IVA were matched with the more recent cohort of patients with *F*/MF genotypes (2015–2017); results were consistent with the *F/F*–specific analysis, suggesting limited impact of noncontemporaneous controls (data not shown). Patients with the *F/F* genotype in the ELX/TEZ/IVA trial may have been exposed to CFTRm prior to enrollment and during a 4-week run-in with TEZ/IVA; therefore, baseline characteristics used for matching (e.g., ppFEV$_1$) may reflect benefits of CFTRm treatment. Matching on fac-

tors known to predict future lung function decline was expected to address differences in treatment history; however, this assumption could not be tested. Data on education and insurance were not collected in clinical trials and therefore were not included in the propensity score model. Twenty-one patients with *F*/MF genotypes treated with ELX/TEZ/IVA could not be matched with CFTRm-untreated controls. While these patients were generally younger with more severe disease burden, sensitivity analyses confirmed that their exclusion had no material impact on results. Finally, portions of the open-label extension study that provided data for the current analysis occurred during the COVID-19 global pandemic, when social distancing and mask use likely led to a decline in pulmonary exacerbations [10]; the impact on the estimated rate of change in ppFEV$_1$ in the present analysis is unknown.

ELX/TEZ/IVA is the first CF therapy shown to halt lung function decline over an extended follow-up period of 2 years, suggesting that ELX/TEZ/IVA treatment has a significant impact on the progression and trajectory of CF lung disease.

Funding

This work was supported by Vertex Pharmaceuticals Incorporated.

Conflicts of interest statement

All authors received nonfinancial assistance (assistance with manuscript preparation) from ArticulateScience, LLC, which was funded by Vertex Pharmaceuticals Incorporated. Additional disclosures are as follows: **TL** reports participation on a data safety monitoring board for AlgiPharma outside the submitted word and is a member of the steering committee and protocol review committee for the European Cystic Fibrosis Society (ECFS) Clinical Trial Network. **GSS** reports grants to his institution for clinical trials, consulting fees, and payment or honoraria for a webinar from Vertex Pharmaceuticals. **JA** has nothing further to disclose. **SJM** is a former employee and consultant of ICON plc. ICON plc received payments from Vertex Pharmaceuticals related to the submitted work and received payments, grants, and travel support from various other pharmaceutical, biotechnology, and device companies outside the submitted work. **JMG, MTJ, YY, LJM**, and **KVB** are employees of Vertex Pharmaceuticals and may own stock or stock options in that company. **RWL** reports consulting fees from Vertex Pharmaceuticals; grants to her institution from Vertex Pharmaceuticals and the US Cystic Fibrosis Foundation; and uncompensated participation on advisory boards for Vertex Pharmaceuticals.

Data sharing statement

Vertex is committed to advancing medical science and improving patient health. This includes the responsible sharing of clinical trial data with qualified researchers. Proposals for the use of these data will be reviewed by a scientific board. Approvals are at the discretion of Vertex and will be dependent on the nature of the request, the merit of the research proposed, and the intended use of the data. Please contact CTDS@vrtx.com if you would like to submit a proposal or need more information. The US Cystic Fibrosis Foundation Patient Registry collects and manages its own data and maintains processes for researchers to request summarized data (https://www.cff.org/researchers/patient-registry-data-requests).

CRediT authorship contribution statement

Tim Lee: Investigation, Writing – original draft, Writing – review & editing, Visualization, Supervision. **Gregory S. Sawicki:** Conceptualization, Writing – review & editing, Visualization. **Josje Altenburg:** Conceptualization, Writing – original draft, Writing – review & editing, Visualization. **Stefanie J. Millar:** Conceptualization, Methodology, Software, Validation, Formal analysis, Resources, Data curation, Writing – review & editing. **Jessica Morlando Geiger:** Methodology, Resources, Writing – original draft, Writing – review & editing, Supervision, Project administration. **Mark T. Jennings:** Conceptualization, Methodology, Investigation, Writing – review & editing, Supervision, Project administration. **Yiyue Lou:** Conceptualization, Methodology, Writing – review & editing. **Lisa J. McGarry:** Conceptualization, Methodology, Writing – review & editing, Visualization, Supervision, Project administration. **Kate Van Brunt:** Conceptualization, Methodology, Writing – review & editing, Visualization, Supervision, Project administration. **Rachel W. Linnemann:** Conceptualization, Methodology, Investigation, Writing – review & editing.

Acknowledgments

We thank the patients and their families for participating in the 445–102, 445–103, and 445–105 trials; all site trial investigators and coordinators for their support of the trial sites; the Cystic Fibrosis Foundation for the use of CFFPR data to conduct this study; the patients, care providers, and clinic coordinators at CF centers throughout the United States for their contributions to the CFFPR; Nathan Blow, PhD, of Vertex Pharmaceuticals, who may own stock or stock options in the company, for providing medical writing support under the guidance of the authors; and ArticulateScience, LLC for providing editorial assistance under the guidance of the authors with support from Vertex Pharmaceuticals.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2022.12.009.

References

[1] Liou TG, Elkin EP, Pasta DJ, Jacobs JR, Konstan MW, Morgan WJ, et al. Year–to-year changes in lung function in individuals with cystic fibrosis. J Cyst Fibros 2010;9:250–6.
[2] Konstan MW, Wagener JS. VanDevanter DR. Characterizing aggressiveness and predicting future progression of CF lung disease. J Cyst Fibros 2009;8:S15–19.
[3] Corey M, Edwards L, Levison H, Knowles M. Longitudinal analysis of pulmonary function decline in patients with cystic fibrosis. J Pediatr 1997;131:809–14.
[4] Sawicki GS, McKone EF, Pasta DJ, Millar SJ, Wagener JS, Johnson CA, et al. Sustained benefit from ivacaftor demonstrated by combining clinical trial and cystic fibrosis patient registry data. Am J Respir Crit Care Med 2015;192:836–42.
[5] Konstan MW, McKone EF, Moss RB, Marigowda G, Tian S, Waltz D, et al. Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): a phase 3, extension study. Lancet Respir Med 2017;5:107–18.
[6] Flume PA, Biner RF, Downey DG, Brown C, Jain M, Fischer R, et al. Long-term safety and efficacy of tezacaftor-ivacaftor in individuals with cystic fibrosis aged 12 years or older who are homozygous or heterozygous for Phe508del CFTR (EXTEND): an open-label extension study. Lancet Respir Med 2021;9:733–46.
[7] Middleton PG, Mall MA, Drevinek P, Lands LC, McKone EF, Polineni D, et al. Elexacaftor-Tezacaftor-Ivacaftor for cystic fibrosis with a single Phe508del allele. N Engl J Med 2019;381:1809–19.
[8] Heijerman HGM, McKone EF, Downey DG, Van Braeckel E, Rowe SM, Tullis E, et al. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. Lancet 2019;394:1940–1948.
[9] Griese M, Tullis E, Chilvers M, Fabrizzi B, Jain R, Legg J, et al. Long-term safety and efficacy of elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis and at least one F508del allele: 144-week interim results from an open-label extension study. J Cyst Fibros 2022;21:S99–S100 [abstract 70].
[10] Patel S, Thompson MD, Slaven JE, Sanders DB, Ren CL. Reduction of pulmonary exacerbations in young children with cystic fibrosis during the COVID-19 pandemic. Pediatr Pulmonol 2021;56:1271–3.