Journal of Cystic Fibrosis xxx (xxxx) xxx

Contents lists available at ScienceDirect

Journal of Cystic Fibrosis

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

Short Communication

Non-respiratory health-related quality of life in people with cystic fibrosis receiving elexacaftor/tezacaftor/ivacaftor

Isabelle Fajac[a], Cori Daines[b], Isabelle Durieu[c], Jennifer L. Goralski[d], Harry Heijerman[e], Christiane Knoop[f], Christof Majoor[g], Bote G. Bruinsma[h], Samuel Moskowitz[h], Valentin Prieto-Centurion[h], Kate Van Brunt[h], Yaohua Zhang[h], Alexandra Quittner[i,*]

[a] *APHP.Centre–Université de Paris, Paris, France*
[b] *University of Arizona, Banner University Medical Center, Tucson, AZ, US*
[c] *Hospices Civils de Lyon, Adult Cystic Fibrosis Centre, Université de Lyon, France*
[d] *Division of Pulmonary and Critical Care Medicine, University of North Carolina, Chapel Hill, NC, US*
[e] *University Medical Center Utrecht, Utrecht, the Netherlands*
[f] *Department of Chest Medicine, Hôpital Erasme, Brussels, Belgium*
[g] *Department of Respiratory Medicine, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, the Netherlands*
[h] *Vertex Pharmaceuticals Incorporated, Boston, MA, USA*
[i] *Behavioral Health Systems Research, 2460 Tigertail Avenue, Miami, FL 33139, US*

ARTICLE INFO

Article history:
Received 12 May 2022
Revised 1 August 2022
Accepted 26 August 2022
Available online xxx

Keywords:
Cystic fibrosis
Elexacaftor/tezacaftor/ivacaftor
CFQ-R
Quality of life

ABSTRACT

Elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) was shown to be safe and efficacious in people with cystic fibrosis (CF) heterozygous for *F508del* and a minimal function mutation (*F*/MF) or homozygous for *F508del* (*F*/*F*) in two pivotal Phase 3 trials, significantly improving percentage predicted forced expiratory volume in 1 second, Cystic Fibrosis Questionnaire–Revised, Respiratory Domain (CFQ-R RD) scores, and sweat chloride concentration. Here, we analyzed the 11 non-respiratory domains (non-RDs) of the CFQ-R, which assess general health-related quality of life (i.e., Physical Functioning, Role Functioning, Vitality, Health Perceptions, Emotional Functioning, and Social Functioning) and quality of life impacted by CF (i.e., Body Image, Eating Problems, Treatment Burden, Weight, and Digestive Symptoms), for participants in these two Phase 3 trials. ELX/TEZ/IVA treatment led to higher scores in all CFQ-R non-RDs, with improvements in most domains compared with control treatments. These findings demonstrate that ELX/TEZ/IVA improves a range of CF-specific symptoms and general functioning and well-being.

1. Introduction

Pivotal Phase 3 clinical trials [1,2] in people heterozygous for the cystic fibrosis (CF) transmembrane conductance regulator (*CFTR*) *F508del* mutation and a minimal function *CFTR* mutation (F/MF; Study 445-102 [NCT03525444]) or homozygous for *F508del* (*F*/*F*; Study 445-103 [NCT03525548]) led to the 2019 approval in the US of the CFTR modulator regimen elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA). ELX/TEZ/IVA treatment significantly improved lung function (assessed by percentage predicted forced expiratory volume in 1 second [$ppFEV_1$]), CFTR function (assessed by sweat chloride concentration), and respiratory symptoms (assessed by Cystic Fibrosis Questionnaire–Revised, Respiratory Domain [CFQ-R RD] score) [1,2]. Initially indicated for people with CF aged ≥12 years with ≥1 *F508del* mutation [3],

Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; CFQ-R, Cystic Fibrosis Questionnaire–Revised; ELX, elexacaftor; FEV_1, forced expiratory volume in 1 second; *F*/*F*, homozygous for the *F508del-CFTR* mutation; *F*/MF, heterozygous for the *F508del-CFTR* mutation and a minimal function *CFTR* mutation; HRQoL, health-related quality of life; IVA, ivacaftor; LS, least squares; PBO, placebo; $ppFEV_1$, percentage predicted forced expiratory volume in 1 second; q12h, every 12 h; qd, once daily; RD, respiratory domain; SD, standard deviation; TEZ, tezacaftor.

* Corresponding author.
E-mail addresses: isabelle.fajac@parisdescartes.fr (I. Fajac), cdaines@arizona.edu (C. Daines), isabelle.durieu@chu-lyon.fr (I. Durieu), jennifer_goralski@med.unc.edu (J.L. Goralski), H.G.M.Heijerman@umcutrecht.nl (H. Heijerman), christiane.knoop@erasme.ulb.ac.be (C. Knoop), maj00rcj@gmail.com (C. Majoor), Bote_Bruinsma@vrtx.com (B.G. Bruinsma), sam.moskowitz1@gmail.com (S. Moskowitz), Valentin_Prieto-Centurion@vrtx.com (V. Prieto-Centurion), Kate_VanBrunt@vrtx.com (K. Van Brunt), Yaohua_Zhang@vrtx.com (Y. Zhang), aquittner0202@gmail.com (A. Quittner).

https://doi.org/10.1016/j.jcf.2022.08.018

ELX/TEZ/IVA has now been approved in the US, Europe, and some other regions for children aged 6 through 11 years [4,5].

The CFQ-R is a validated CF-specific patient-reported outcome instrument that examines disease-related symptoms and health-related quality of life (HRQoL) in people with CF [6]. In both pivotal ELX/TEZ/IVA Phase 3 trials, participants had clinically significant improvements in CFQ-R RD score versus controls, with increases exceeding the established minimal clinically important difference of four points [1,2]. Initial results from the PROMISE study in people with CF aged ≥12 years with ≥1 *F508del* mutation showed that improvements in CFQ-R RD score and lung function seen in clinical trials are mirrored in real-world settings [7].

Beyond the assessment of respiratory symptoms, the CFQ-R also measures 11 non-RDs, which extend quality-of-life measures to general aspects of HRQoL and to those aspects specifically impacted by CF. Here, we report results for the CFQ-R non-RDs from participants in the ELX/TEZ/IVA pivotal Phase 3 studies.

2. Methods

2.1. Eligibility criteria

Both studies enrolled participants aged ≥12 years with a $ppFEV_1$ of 40–90% inclusive at screening and stable CF as judged by investigators.

2.2. Study design

Study 445-102 was a 24-week, placebo-controlled trial that enrolled participants with *F*/MF genotypes. Randomization was stratified by age (<18 vs. ≥18 years), sex, and $ppFEV_1$ severity (<70% vs. ≥70%) during a 4-week screening period. Participants received either 1) ELX 200 mg once daily (qd), TEZ 100 mg qd, and IVA 150 mg every 12 h (q12h) or 2) placebo with the same dosing schedule, in a 1:1 ratio.

Study 445-103 was a 4-week, active-controlled trial that enrolled participants with the *F*/*F* genotype. Randomization was stratified by age (<18 vs. ≥18 years) at screening and $ppFEV_1$ severity (<70% vs. ≥70%) determined during a 4-week run-in period. To ensure a stable on-treatment baseline, participants received TEZ 100 mg qd and IVA 150 mg q12h during the run-in period. Participants then received either 1) ELX 200 mg qd, TEZ 100 mg qd, and IVA 150 mg q12h or 2) TEZ 100 mg qd and IVA 150 mg q12h, in a 1:1 ratio.

2.3. CFQ-R outcomes

Absolute change in CFQ-R domain score from baseline was evaluated over 24 weeks in Study 445-102 and over 4 weeks in Study 445-103. At relevant study visits, participants completed the child or adolescent/adult version of the CFQ-R, as appropriate. The child version comprises 35 items across eight domains capturing self-assessment of Body Image, Digestive Symptoms, Eating Problems, Emotional Functioning, Physical Functioning, Respiratory Symptoms, Social Functioning/School Functioning, and Treatment Burden. The adult version includes additional domains assessing Vitality, Health Perceptions, Weight, and Functioning—totaling 50 items [6]. For each item, responses are on a four-point Likert scale for frequency (always, often, sometimes, never), intensity (great deal, somewhat, a little, not at all), or true/false (very true, somewhat true, somewhat false, very false). Items in each domain were summed, and domain scores were standardized to a 0-100 scale; higher scores indicate more favorable functional status or fewer symptoms as reported by the patient [6]. The reported outcomes reflect pooled analysis of data from both the child and adolescent/adult versions in which the respective domains of each group are analyzed. A minimal clinically important difference has only been defined for the Respiratory Domain of the CFQ-R.

2.4. Statistical analysis

A mixed-effects model for repeated measures was used to calculate change from baseline in CFQ-R domain scores with ELX/TEZ/IVA versus placebo or versus TEZ/IVA, according to each study's design. No adjustment for multiplicity was performed; therefore, reported *P* values are considered nominal.

3. Results

3.1. Participant population

In total, 403 participants were randomized in Study 445-102 (placebo [$n = 203$]; ELX/TEZ/IVA [$n = 200$]) and 107 participants in Study 445-103 (TEZ/IVA [$n = 52$]; ELX/TEZ/IVA [$n = 55$]). For each study, baseline demographics, clinical characteristics, and CFQ-R non-RD scores were similar across treatment groups (Table 1).

3.2. Efficacy

Participants with *F*/MF genotypes treated with ELX/TEZ/IVA had increases from baseline in all 11 CFQ-R non-RD scores, ranging from 2.1 points (95% CI: 0.2, 3.9) for Digestive Symptoms to 13.2 points (95% CI: 9.8, 16.6) for Weight (Table 2). An analysis of treatment differences showed ELX/TEZ/IVA treatment led to greater improvements in all CFQ-R non-RD scores, except Digestive Symptoms, compared with placebo (nominal $P < 0.05$; Fig. 1a).

Participants with the *F*/*F* genotype also had increases from baseline in all 11 CFQ-R non-RD scores, ranging from 1.1 points (95% CI: −3.1, 5.2) for Digestive Symptoms to 9.9 points (95% CI: 6.2, 13.5) for Physical Functioning (Table 2). An analysis of treatment differences showed ELX/TEZ/IVA treatment led to greater improvements in 7 of 11 CFQ-R non-RD scores compared with TEZ/IVA (nominal $P < 0.05$; Fig. 1b).

4. Discussion and conclusions

Previous population-level analyses in children and adults with CF found little change in CFQ-R domain scores over a 12-month period and stable physical domains over a nearly 2-year period [8,9]. In contrast, the current analysis of CFQ-R non-RD scores from participants treated with ELX/TEZ/IVA in two Phase 3 pivotal studies demonstrated numerical increases in all domains, with greater improvements from baseline compared with control groups in the majority of domains. Previously reported results from these trials showed significantly greater increases in CFQ-R RD scores with ELX/TEZ/IVA treatment relative to control groups, exceeding the established minimal clinically important difference of 4 points (20.2 [Study 445-102] and 17.4 [Study 445-103] points) [1,2]. These data demonstrate that ELX/TEZ/IVA treatment improves CF disease symptoms and HRQoL in people with CF with *F*/MF or *F*/*F* genotypes.

Some limitations of this study should be considered. First, the duration of Study 445-103 was limited to 4 weeks. However, previous randomized controlled trials of CFTR modulators have shown improvements in lung function and respiratory symptoms at ≤4 weeks that were sustained over ≥24 weeks of treatment [10–13]. Additionally, a post hoc analysis of CFQ-R non-RDs from a 24-week Phase 3b study in people with CF aged ≥12 years with the *F*/*F* genotype found that 9 of 11 CFQ-R non-RD scores improved with ELX/TEZ/IVA treatment versus TEZ/IVA [14]. Interestingly, one of the domains that showed no improvement with ELX/TEZ/IVA treatment was Digestive Symptoms, consistent with results reported

Table 1
Baseline demographics, clinical characteristics, and CFQ-R non-RD scores.

Characteristic	Study			
	445-102 (*F*/MF genotypes)		445-103 (*F*/*F* genotype)	
	PBO ($N = 203$)	ELX/TEZ/IVA ($N = 200$)	TEZ/IVA ($N = 52$)	ELX/TEZ/IVA ($N = 55$)
Female, n (%)	98 (48.3)	96 (48.0)	28 (53.8)	31 (56.4)
Age at baseline, mean (SD), years	26.8 (11.3)	25.6 (9.7)	27.9 (10.8)	28.8 (11.5)
Age group at screening, n (%)				
≥12 to <18 years	60 (29.6)	56 (28.0)	14 (26.9)	16 (29.1)
≥18 years	143 (70.4)	144 (72.0)	38 (73.1)	39 (70.9)
$ppFEV_1$, mean (SD)	61.3 (15.5)	61.6 (15.0)	60.2 (14.4)	61.6 (15.4)
CFQ-R non-RD scores, mean (SD)				
Physical Functioning	76.4 (21.6)	76.5 (21.7)	76.3 (24.5)	75.2 (24.0)
Vitality	63.8 (18.3)	62.8 (17.1)	60.6 (19.9)	61.4 (17.6)
Emotional Functioning	80.2 (16.7)	82.0 (16.0)	80.3 (17.8)	82.1 (14.7)
Body Image	77.2 (23.5)	78.8 (22.1)	86.1 (21.9)	80.0 (20.7)
Eating Problems	89.1 (17.5)	90.0 (17.9)	90.0 (16.8)	89.1 (19.8)
Treatment Burden	61.4 (20.2)	59.2 (19.2)	58.5 (21.5)	59.4 (20.4)
Health Perceptions	64.2 (20.1)	63.5 (20.5)	61.6 (23.2)	63.5 (20.3)
Weight	74.1 (31.7)	74.4 (31.0)	81.8 (28.3)	78.2 (33.0)
Digestive Symptoms	83.4 (16.9)	83.1 (18.1)	80.3 (22.7)	83.0 (18.5)
Role Functioning	83.3 (15.2)	81.7 (17.5)	79.0 (17.2)	80.4 (19.9)
Social Functioning/School Functioning	68.8 (17.9)	70.5 (17.0)	73.5 (16.3)	67.9 (17.7)

CFQ-R, Cystic Fibrosis Questionnaire–Revised; ELX, elexacaftor; *F*/*F*, homozygous for the CFTR *F508del* mutation; *F*/MF, heterozygous for the CFTR *F508del* mutation and a minimal function CFTR mutation; IVA, ivacaftor; PBO, placebo; $ppFEV_1$, percentage predicted forced expiratory volume in 1 second; RD, respiratory domain; SD, standard deviation; TEZ, tezacaftor.

Table 2
Mean absolute change in CFQ-R non-RD scores from baseline by treatment group.

CFQ-R domain	LS mean absolute change (95% CI), points			
	Study			
	445-102 (*F*/MF genotypes)*		445-103 (*F*/*F* genotype)[a]	
	PBO ($N = 203$)	ELX/TEZ/IVA ($N = 200$)	TEZ/IVA ($N = 52$)	ELX/TEZ/IVA ($N = 55$)
Physical Functioning	−3.3 (−5.0, −1.5)	9.2 (7.4, 11.0)	−1.9 (−5.7, 1.9)	9.9 (6.2, 13.5)
Vitality	−5.3 (−7.2, −3.3)	7.9 (6.0, 9.7)	−3.6 (−8.4, 1.2)	8.9 (4.4, 13.4)
Emotional Functioning	−0.9 (−2.2, 0.4)	2.5 (1.1, 3.8)	1.1 (−1.3, 3.4)	2.9 (0.6, 5.1)
Body Image	0.4 (−1.5, 2.3)	4.2 (2.4, 6.1)	−0.2 (−3.2, 2.8)	2.2 (−0.7, 5.1)
Eating Problems	−2.4 (−4.0, −0.8)	2.5 (0.9, 4.1)	−0.4 (−4.4, 3.5)	6.4 (2.6, 10.3)
Treatment Burden	−2.0 (−3.6, −0.3)	4.9 (3.2, 6.5)	0.3 (−3.5, 4.2)	3.7 (0.0, 7.4)
Health Perceptions	−4.4 (−6.6, −2.3)	12.6 (10.5, 14.7)	−0.5 (−4.9, 3.8)	9.0 (4.9, 13.1)
Weight	0.1 (−3.4, 3.5)	13.2 (9.8, 16.6)	−5.0 (−11.3, 1.2)	7.5 (1.6, 13.3)
Digestive Symptoms	−0.4 (−2.3, 1.4)	2.1 (0.2, 3.9)	0.2 (−4.1, 4.4)	1.1 (−3.1, 5.2)
Role Functioning	−2.4 (−4.1, −0.8)	4.4 (2.8, 6.0)	0.8 (−2.8, 4.5)	6.8 (3.4, 10.2)
Social Functioning/School Functioning	−1.3 (−2.8, 0.2)	4.6 (3.1, 6.1)	1.5 (−1.6, 4.5)	6.9 (3.9, 9.8)

CI, confidence interval; CFQ-R, Cystic Fibrosis Questionnaire–Revised; ELX, elexacaftor; *F*/*F*, homozygous for the CFTR *F508del* mutation; *F*/MF, heterozygous for the CFTR *F508del* mutation and a minimal function CFTR mutation; IVA, ivacaftor; LS, least squares; PBO, placebo; TEZ, tezacaftor.
* Through Week 24.
[a] At Week 4.

here. A recent prospective cohort study of 43 patients treated with ELX/TEZ/IVA for 3 months did show increases from baseline in all non-RD scores; however, the study lacked a control comparator [15]. Further studies will be required to understand the impact of ELX/TEZ/IVA treatment on the Digestive Symptoms domain of the CFQ-R. Second, because the analysis of CFQ-R non-RD scores was not controlled for multiplicity, *P* values are considered nominal. Finally, unlike the RD, a minimal clinically important difference has not been established for non-RDs, thus limiting clinical interpretation.

In conclusion, ELX/TEZ/IVA treatment extends clinical benefit beyond previously reported improvements in lung function, respiratory symptoms, and CFTR function to broad benefits in patient-reported disease-related symptoms and general functioning and well-being. These results further the understanding of the patient-relevant treatment benefits of ELX/TEZ/IVA.

Declaration of Competing Interest

IF reports grants and personal fees from Vertex during the conduct of the study. **KVB**, **BGB**, **VP-C**, and **YZ** are employees of Vertex and may own stock or stock options in the company. **SMM** was an employee at Vertex Pharmaceuticals at the time of the study. **HH** reports personal fees from Vertex, Gilead, Horizon, PTC, and Chiesi and serves on advisory boards for Vertex and PTC, outside the submitted work. SM has a patent pending for Methods of Treatment for Cystic Fibrosis, a patent pending for Methods of Treatment of Cystic Fibrosis, and a patent pending for Pharmaceutical Compositions for Treating Cystic Fibrosis. **AQ** reports consulting fees from Vertex and Insmed, outside of the submitted work. **CD**, **ID**, **JG**, **CK**, and **CM** have no disclosures to report.

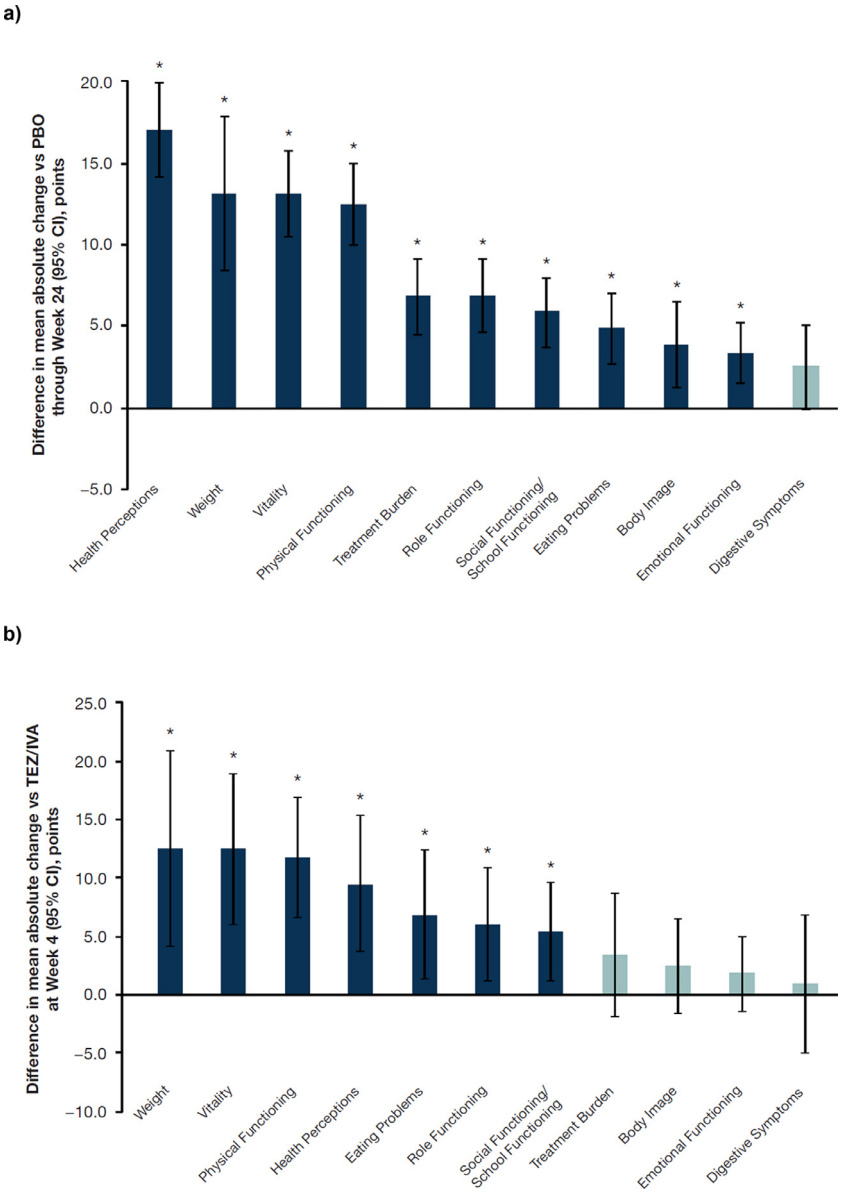

Fig. 1. Difference in mean absolute change in CFQ-R non-RD scores from baseline in a) Study 445-102 ELX/TEZ/IVA versus placebo at Week 24 (*F*/MF genotypes) and b) Study 445-103 ELX/TEZ/IVA versus TEZ/IVA at Week 4 (*F*/*F* genotype).
CFQ-R, Cystic Fibrosis Questionnaire–Revised; ELX, elexacaftor; *F*/*F*, homozygous for the CFTR *F508del* mutation; *F*/MF, heterozygous for the CFTR *F508del* mutation and a minimal function CFTR mutation; IVA, ivacaftor; PBO, placebo; RD, respiratory domain; TEZ, tezacaftor.
* Nominal $P < 0.05$.

Acknowledgments

Editorial coordination and support were provided by Wayne Dunlap, PhD, of Vertex Pharmaceuticals Incorporated. Editorial assistance was provided by Lee Kempster, PhD, of MediTech Media (UK), under the guidance of the authors and was supported by Vertex Pharmaceuticals Incorporated.

Funding

This work was supported by Vertex Pharmaceuticals Incorporated.

References

[1] 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.
[2] 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;394:1940–8.
[3] Vertex Pharmaceuticals Inc. TRIKAFTA® (elexacaftor, tezacaftor and ivacaftor tablets; ivacaftor tablets), co-packaged for oral use. Summary of product characteristics. 2019.
[4] Vertex Pharmaceuticals Inc. Trikafta® (elexacaftor/tezacaftor/ivacaftor) [package insert]. Boston, MA. Revised 10/2021.
[5] European Pharmaceutical Review. Kaftrio® with ivacaftor approved by EC to treat children with cystic fibrosis. 2022.
[6] Quittner AL, Sawicki GS, McMullen A, Rasouliyan L, Pasta DJ, Yegin A, et al. Erratum to: psychometric evaluation of the cystic fibrosis questionnaire-revised in a national, US sample. Qual Life Res 2012;21:1279–90.
[7] Nichols DP, Paynter AC, Heltshe SL, Donaldson SH, Frederick CA, Freedman SD, et al. Clinical effectiveness of elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis. Am J Respir Crit Care Med 2021.
[8] Sawicki GS, Rasouliyan L, McMullen AH, Wagener JS, McColley SA, Pasta DJ, et al. Longitudinal assessment of health-related quality of life in an observational cohort of patients with cystic fibrosis. Pediatr Pulmonol 2011;46:36–44.
[9] Dill EJ, Dawson R, Sellers DE, Robinson WM, Sawicki GS. Longitudinal

trends in health-related quality of life in adults with cystic fibrosis. Chest 2013;144:981–9.
[10] Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Drevinek P, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. N Engl J Med 2011;365:1663–72.
[11] Wainwright CE, Elborn JS, Ramsey BW, Marigowda G, Huang X, Cipolli M, et al. Lumacaftor-ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. N Engl J Med 2015;373:220–31.
[12] Taylor-Cousar JL, Munck A, McKone EF, van der Ent CK, Moeller A, Simard C, et al. Tezacaftor–ivacaftor in patients with cystic fibrosis homozygous for Phe508del. N Engl J Med 2017;377:2013–23.
[13] Daines CL, Tullis E, Costa S, Linneman RW, Mall MA, McKone EF, et al. Long-term safety and efficacy of elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis and at least one F508del allele: 96-week interim results from an open-label extension study Poster Presented at the 35th Annual North American Cystic Fibrosis Conference (virtual); 2021. November 2-5.
[14] Sutharson S, McKone EF, Downey DG, Duckers J, MacGregor G, Tullis E, et al. Efficacy and safety of elexacaftor plus tezacaftor plus ivacaftor versus tezacaftor plus ivacaftor in people with cystic fibrosis homozygous for F508del-CFTR: a 24-week, multicentre, randomised, double-blind, active-controlled, phase 3b trial. Lancet Respir Med 2022;10:267–77.
[15] DiMango E, Spielman DB, Overdevest J, Keating C, Francis SF, Dansky D, et al. Effect of highly effective modulator therapy on quality of life in adults with cystic fibrosis. Int Forum Allergy Rhinol 2021;11:75–8.