Short Communication

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

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A B S T R A C T

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.

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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 [ppFEV1]), 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],...
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 ppFEV1 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 ppFEV1 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 ppFEV1 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: 0.3, 1.8) for Digestive Symptoms to 13.5 points (95% CI: 9.7, 17.3) 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 [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.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study</th>
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<tbody>
<tr>
<td></td>
<td>445-102 (F/M/F genotypes)</td>
</tr>
<tr>
<td></td>
<td>PBO (N = 203)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>98 (48.3)</td>
</tr>
<tr>
<td>Age at baseline, mean (SD), years</td>
<td>26.8 (11.3)</td>
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<tr>
<td>Age group at screening, n (%)</td>
<td>60 (29.6)</td>
</tr>
<tr>
<td>≥12 to &lt;18 years</td>
<td>143 (70.4)</td>
</tr>
<tr>
<td>ppFEV1, mean (SD)</td>
<td>61.3 (15.5)</td>
</tr>
<tr>
<td>CFQ-R non-RD scores, mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Physical Functioning</td>
<td>76.4 (21.6)</td>
</tr>
<tr>
<td>Vitality</td>
<td>63.8 (18.3)</td>
</tr>
<tr>
<td>Emotional Functioning</td>
<td>80.2 (16.7)</td>
</tr>
<tr>
<td>Body Image</td>
<td>77.2 (23.5)</td>
</tr>
<tr>
<td>Eating Problems</td>
<td>89.1 (17.5)</td>
</tr>
<tr>
<td>Treatment Burden</td>
<td>61.4 (20.2)</td>
</tr>
<tr>
<td>Health Perceptions</td>
<td>64.2 (20.1)</td>
</tr>
<tr>
<td>Weight</td>
<td>74.1 (31.7)</td>
</tr>
<tr>
<td>Digestive Symptoms</td>
<td>83.4 (16.9)</td>
</tr>
<tr>
<td>Role Functioning</td>
<td>83.3 (15.2)</td>
</tr>
<tr>
<td>Social Functioning/School</td>
<td>68.8 (17.9)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>CFQ-R domain</th>
<th>Study</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>445-102 (F/M/F genotypes)</td>
</tr>
<tr>
<td></td>
<td>PBO (N = 203)</td>
</tr>
<tr>
<td>Physical Functioning</td>
<td>–3.3 (–5.0, –1.5)</td>
</tr>
<tr>
<td>Vitality</td>
<td>–5.3 (–7.2, –3.3)</td>
</tr>
<tr>
<td>Emotional Functioning</td>
<td>–0.9 (–2.2, 0.4)</td>
</tr>
<tr>
<td>Body Image</td>
<td>0.4 (–1.5, 2.3)</td>
</tr>
<tr>
<td>Eating Problems</td>
<td>–2.4 (–4.0, –0.8)</td>
</tr>
<tr>
<td>Treatment Burden</td>
<td>–2.0 (–3.6, –0.3)</td>
</tr>
<tr>
<td>Health Perceptions</td>
<td>–4.4 (–6.6, –2.3)</td>
</tr>
<tr>
<td>Weight</td>
<td>0.1 (–3.4, 3.5)</td>
</tr>
<tr>
<td>Digestive Symptoms</td>
<td>–0.4 (–2.3, 1.4)</td>
</tr>
<tr>
<td>Role Functioning</td>
<td>–2.4 (–4.1, –0.8)</td>
</tr>
<tr>
<td>Social Functioning/School Functioning</td>
<td>–1.3 (–2.8, 0.2)</td>
</tr>
</tbody>
</table>

Cl, confidence interval; CFQ-R, Cystic Fibrosis Questionnaire—Revised; ELX, exelacaftor; F/F, homozygous for the CFTR F508del mutation; F/M, heterozygous for the CFTR F508del mutation and a minimal function CFTR mutation; IVA, ivacaftor; PBO, placebo; ppFEV1, percentage predicted forced expiratory volume in 1 second; RD, respiratory domain; SD, standard deviation; TEZ, tezacaftor.

* Through Week 24.

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 Insmde, 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/M genotype) 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/M, 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.

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References


