Safety and Efficacy of Elvecactor/Tezacaftor/Ivacaftor for Two or More F508del Alleles: Interim Results of an Open-Label Phase 3 Clinical Trial

To the Editor:

Cystic fibrosis (CF) is caused by mutations in the CFTR (CF transmembrane conductance regulator) gene (1). The most common CFTR mutation in populations of European descent is F508del, with up to 90% of people with CF (pwCF) having one or more F508del alleles (2–4).

Two pivotal phase 3 studies of a triple-combination regimen consisting of small-molecule CFTR modulators elvecactor (ELX)/tezacaftor (TEZ)/ivacaftor (IVA) showed unprecedented clinical efficacy in pwCF 12 years old or older heterozygous for the F508del-CFTR mutation and a minimal function mutation (F/MF; an MF mutation results in either no CFTR protein or a CFTR protein that does not respond to IVA and TEZ/IVA in vitro) or homozygous for F508del (F/F) (5–7). ELX/TEZ/IVA was generally safe and well tolerated in both studies (5, 6).

Eligible participants from both pivotal phase 3 studies could elect to participate in an ongoing, phase 3, open-label extension (OLE) study to evaluate the long-term safety and efficacy of ELX/TEZ/IVA. We report the results of an interim analysis of the OLE performed after the last ongoing participant had completed the Week 24 visit. Final results from this study will be published after study completion. These interim results have been accepted for oral presentation (8).

Results

A total of 506 participants received ELX/TEZ/IVA in this study (n = 399 F/MF; n = 107 F/F). Participant demographics were similar to those observed in the pivotal studies (5, 6). A total of 471 (93.1%) participants experienced AEs (Table 1); AE rates in the ELX/TEZ/IVA arm of the larger, longer F/MF pivotal study, which was the primary source of phase 3 safety data, are provided for comparison (5, 9). The majority of participants had mild or moderate AEs that were similar to those observed in the pivotal studies (5, 6). The most common AEs included infections (PEx) (49.6 per 100 participant-years), cough (44.3), and oropharyngeal pain (25.7). A total of 80 (15.8%) participants experienced serious AEs (exposure-adjusted rate, 27.5 per 100 participant-years), with infective PEx of CF, hemoptysis, and distal intestinal obstruction syndrome as the more common events. Seven participants (1.4%) had AEs resulting in treatment...
discontinuation; these AEs included liver events ($n = 4$), depression ($n = 1$), rash ($n = 1$), and tinnitus and contusion ($n = 1$ [in the same participant]). AEs of elevated transaminases occurred in 36 (7.1%) participants, and laboratory elevations in alanine aminotransferase or aspartate aminotransferase >3×, >5×, and >8× the upper limit of normal occurred in 32 (6.3%), 11 (2.2%), and 3 (0.6%) participants, respectively.

Key efficacy and PD data from the OLE and parent studies are provided in Figure 1. In F/MF participants, the mean absolute changes from baseline (95% confidence interval [CI]) in ppFEV$_1$ at

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**Table 1. Adverse Events**

| Event | OLE Study ($N = 506$; Mean Duration of Exposure: 37.2 wk) | F/MF Pivotal Study* ELX/TEZ/IVA Arm ($n = 202$; Mean Duration of Exposure: 23.6 wk) |
|-------|----------------------------------------------------------|------------------------------------------------------------------|
| | Participants with AEs [$n$ [%]] | Event Rate per 100 Participant-Years | Participants with AEs [$n$ [%]] | Event Rate per 100 Participant-Years |
| Any AE | 471 (93.1) | 739.9 | 188 (93.1) | 1,096.0 |
| AEs by maximum severity | | | | |
| Mild | 180 (35.6) | ND | 67 (33.2) | ND |
| Moderate | 238 (47.0) | ND | 102 (50.5) | ND |
| Severe | 51 (10.1) | ND | 19 (9.4) | ND |
| Life-threatening† | 2 (0.4) | ND | 0 | ND |
| AEs leading to treatment discontinuation | 7 (1.4) | 3.3 | 2 (1.0) | 3.0 |
| AEs leading to treatment interruption | 29 (5.7) | 13.7 | 19 (9.4) | 26.0 |
| AEs leading to death | 0 | 0 | 0 | 0 |
| Most common AEs in the OLE study (occurring in $\geq 10\%$ of participants) | | | | |
| Infective pulmonary exacerbation of CF | 127 (25.1) | 49.6 | 44 (21.8) | 64.9 |
| Cough | 118 (23.3) | 44.3 | 34 (16.8) | 38.9 |
| Oropharyngeal pain | 74 (14.6) | 25.7 | 20 (9.9) | 27.0 |
| Nasopharyngitis | 69 (13.6) | 21.6 | 22 (10.9) | 30.0 |
| Headache | 66 (13.0) | 24.9 | 35 (17.3) | 48.9 |
| Sputum increased | 63 (12.5) | 20.6 | 40 (19.8) | 46.9 |
| Upper respiratory tract infection | 60 (11.9) | 18.3 | 24 (11.9) | 30.0 |
| Fatigue | 51 (10.1) | 16.3 | 9 (4.5) | 9.0 |
| SAEs‡ | 80 (15.8) | 27.5 | 28 (13.9) | 36.9 |
| Most common SAEs (occurring in $\geq 1\%$ of participants) | | | | |
| Infective pulmonary exacerbation of CF | 42 (8.3) | 12.2 | 11 (5.4) | 12.0 |
| Hemoptysis | 5 (1.0) | 1.5 | 2 (1.0) | 2.0 |
| Distal intestinal obstruction syndrome | 5 (1.0) | 1.5 | 1 (0.5) | 1.0 |
| Any rash event | 50 (9.9) | 15.8 | 22 (10.9) | 30.0 |
| SAEs | 1 (0.2) | 0.3 | 3 (1.5) | 3.0 |
| Leading to treatment interruption | 5 (1.0) | 1.3 | 4 (2.0) | 4.0 |
| Leading to treatment discontinuation | 1 (0.2) | 0.3 | 1 (0.5) | 1.0 |
| ALT or AST increase‡ | | | | |
| $>3\times$ to $\leq 5\times$ ULN | 21 (4.2) | ND | 11 (5.4) | ND |
| $>5\times$ to $<8\times$ ULN | 8 (1.6) | ND | 2 (1.0) | ND |
| $>8\times$ ULN | 3 (0.6) | ND | 3 (1.5) | ND |
| Elevated transaminase AEs‡ | | | | |
| Any AEs | 36 (7.1) | 16.5 | 22 (10.9) | 42.9 |
| SAEs | 2 (0.4) | 1.0 | 0 | 0 |
| Leading to treatment interruption | 11 (2.2) | 5.1 | 2 (1.0) | 3.0 |
| Leading to treatment discontinuation | 3 (0.6) | 1.5 | 0 | 0 |

**Definition of abbreviations**: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CF = cystic fibrosis; ELX = elexacaftor; F/MF = heterozygous for the F508del-CFTR mutation and a minimal function CFTR mutation; IVA = ivacaftor; ND = not determined; OLE = open-label extension; SAE = serious adverse event; TEZ = tezacaftor; ULN = upper limit of normal.

*Some of the data from the F/MF pivotal study were previously published (5) but are provided here for comparison.

†The life-threatening AEs were a suicide attempt and a pulmonary hemorrhage.

‡In the placebo arm of the F/MF pivotal study, 8 (4.0%) participants had an elevated transaminase AE. Laboratory elevations in ALT or AST of $>3\times$ to $<5\times$ ULN, $>5\times$ to $<8\times$ ULN, and $>8\times$ ULN were seen in 8 (4.0%), 1 (0.5%), and 2 (1.0%) participants, respectively.
**Figure 1.** Mixed-effects model for repeated measures analysis of absolute change from baseline in FEV₁ % predicted (ppFEV₁), sweat chloride (SwCl), body mass index (BMI), and Cystic Fibrosis Questionnaire-Revised respiratory domain (CFQ-R RD) by visit. The graphed data represent the least squares mean (SE) absolute change from parent study baseline by mixed-effects model for repeated measures at each visit. The data labels on each plot represent the least squares mean (95% confidence interval) absolute change from parent study baseline and the number of evaluable participants for that visit. For participants heterozygous for the F508del-CFTR mutation and a minimal function CFTR mutation (F/MF) (5), the data labels correspond with the Week 24 visit of the open-label extension. For participants homozygous for the F508del-CFTR mutation (F/F) (6), the data labels correspond with the Week 4 visit of the F/F pivotal study and the Week 24 visit of the open-label extension. For participants treated with ELX/TEZ/IVA or placebo (PBO), the white shaded portion of the graph corresponds to the F/F pivotal study and the gray shaded portion of the graph corresponds to the OLE.

- **SwCl**: Sweat Chloride
- **BMI**: Body Mass Index
- **CFQ-R RD**: Cystic Fibrosis Questionnaire-Revised respiratory domain
- **ppFEV₁**: Percentage predicted forced expiratory volume in 1 second

Baseline for SwCl and CFQ-R RD were assessed through Week 24 in all participants. The ppFEV₁ were assessed through Week 24 in participants with the F/F genotype. For participants with F/MF genotypes, n = 203 for those who received placebo in the 24-week F/MF pivotal study and n = 196 for those treated with eluxacaftor (ELX)/TEZ/IVA. For participants with the F/F genotype, n = 52 for those treated with TEZ/IVA and n = 55 for those treated with ELX/TEZ/IVA in the 4-week F/F pivotal study. OLE = open-label extension; PBO = placebo.
Week 24 were 14.9 (13.5–16.3) and 14.3 (12.9–15.7) percentage points in those who had been in the respective placebo (n = 189) or ELX/TEZ/IVA (n = 180) groups in the F/MF pivotal study. Among F/MF participants, the estimated PEx event rate per 48 weeks (95% CI) was 0.30 (0.24–0.39) (n = 403). In F/F participants, the mean absolute changes from baseline (95% CI) in ppFEV1 at Week 36 were 12.8 (10.1–15.4) and 11.9 (9.3–14.5) percentage points in those who had been in the TEZ/IVA (n = 49) or ELX/TEZ/IVA (n = 51) groups, respectively, in the F/F pivotal study. Among F/F participants, the estimated PEx event rate per 48 weeks (95% CI) was 0.30 (0.20–0.45) (n = 107). Efficacy in these and all other secondary endpoints tested was comparable with and maintained from parent studies.

Discussion
Safety results from this interim analysis were consistent with the initial 24-week placebo-controlled F/MF pivotal study, with similar or lower exposure-adjusted event rates observed in the OLE (Table 1) (5). ELX/TEZ/IVA was generally safe and well tolerated. Most AEs were consistent with common manifestations of CF and were not treatment limiting (3, 10). In participants who received ELX/TEZ/IVA in parent studies, improvements in efficacy and PD measures, including ppFEV1, SwCl concentration, BMI, CFQ-R RD score, and PEx event rate, were maintained or continued to improve further over 24 weeks (F/MF genotypes) or 36 weeks (F/F genotype) of additional treatment. These results validate the durability of ELX/TEZ/IVA efficacy responses, with no emerging safety concerns. Among participants who had received placebo or TEZ/IVA in the respective parent studies, initiation of ELX/TEZ/IVA rapidly led to marked improvements in these efficacy measures that were consistent with the results seen in the ELX/TEZ/IVA arms of those parent studies. Thus, the results of this combined-group interim analysis demonstrate the safety and sustained efficacy of long-term ELX/TEZ/IVA treatment in pwCF 12 years old or older with one or more F508del alleles.

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Pulmonary Arterial Hypertension Caused by AhR Signal Activation Protecting against Colitis

To the Editor:

Accumulating evidence indicates that AhR (aryl hydrocarbon receptor) ligands are crucial mediators of host health and disease. The Chinese herbal medicine Qing-Dai contains high levels of AhR ligands and has shown to induce remission of ulcerative colitis (UC) (1). A recent nationwide randomized placebo-controlled trial demonstrated that 8 weeks of Qing-Dai (0.5–2.0 g/d) intake showed effectiveness as treatment for UC (2). However, Qing-Dai has been associated with pulmonary arterial hypertension (PAH) as a potentially serious side effect (3). A Japanese nationwide survey demonstrated that Qing-Dai was used in 877 (1.8%) out of 49,320 patients with UC, and 11 patients with PAH who had a history of regularly taking Qing-Dai were reported (4). Despite the clinical importance of Qing-Dai in the field of UC, the cause-and-effect association between AhR signal activation by Qing-Dai and the development of PAH has not been fully elucidated. Therefore, we conducted a reverse translational study (from bedside back to the bench) to investigate whether Qing-Dai induces PAH experimentally. Importantly, if Qing-Dai is critically involved in the pathogenesis of PAH, it could be possible to establish a novel animal model of PAH, which might be generally used as an AhR ligand-inducing model of PAH.

All animal studies were performed in strict accordance with the recommendations of the Guide for the Care and Use of Laboratory Animals of the NIH. Fischer 344 male rats weighing 90–110 g (CLEA Japan) were used in our experiments. Rats were allocated to eight groups according to a CE-2 diet or a diet containing 4% Qing-Dai (Fujian Province) (600 mg/kg body weight, corresponding to the 10-fold amount of therapeutic dose for patients with UC), single subcutaneous injection of 20 mg/kg Sugen 5416 (SU5416) (Abcam), and gavage of 8 mg/kg/d AhR antagonist CH223191 (Selleck). Rats were housed in a normoxic environment for 8 weeks. A gavage of CH223191 was performed every day for the final 2 weeks. Real-time quantitative PCR was performed to evaluate the relative expression of cytochrome P450 1A1 (CYP1A1), which is activated by AhR signaling (5). The primers and PCR protocol were described previously (6). The expression of CYP1A1 and CD31 were assessed by lung immunohistochemistry. Rabbit anti-rat CYP1A1 polyclonal antibody (1:200; Abcam) and mouse anti-rat CD31 monoclonal antibody (1:20; Elabscience) were used as the primary antibodies. Comparisons between two groups were performed by Mann-Whitney U test, and comparisons among multiple groups by Kruskal-Wallis test followed by Holm’s method (post hoc analysis). A value of P < 0.05 was considered statistically significant.

Right ventricular systolic pressure was significantly higher in rats with the Qing-Dai diet with SU5416 compared with the normal diet group, which was ameliorated by the addition of CH223191 gavage (Figure 1A). Furthermore, the ratio of right ventricular weight to left ventricle plus septum weight as a parameter for right ventricular hypertrophy was highest in the Qing-Dai diet with SU5416 group and was significantly improved by CH223191 gavage (Figure 1B). The medial wall thickness was also increased in the Qing-Dai diet, SU5416, and Qing-Dai diet with SU5416 groups and was ameliorated by CH223191 gavage (Figures 1C and 1D). Quantitative PCR analysis revealed that the relative lung levels of CYP1A1 mRNA were significantly elevated in the Qing-Dai diet, SU5416, and Qing-Dai diet with SU5416 groups, and these elevated levels were significantly reduced by the addition of CH223191 gavage (Figure 1E). Immunostaining of lung specimens demonstrated that CYP1A1 was expressed in CD31-positive pulmonary arterial endothelial cells in rats fed with a Qing-Dai diet. Notably, rats in the Qing-Dai diet with SU5416 injection group showed higher expression of CYP1A1 compared with the other groups (Figure 1F).

The results in this study demonstrated that the combination of subcutaneous injection of SU5416 followed by Qing-Dai intake had synergistic or additive effects on the development of PAH in rats, and that these effects were suppressed by AhR signal inhibition. In addition, the expression of CYP1A1 in rat lungs demonstrated that these effects were mediated by activation of AhR signaling in pulmonary arterial endothelial cells. It has been reported that CYP1A1 was highly induced in the lungs of SU5416-treated and hypoxia-induced PAH rats (7). These findings suggest that...