Tezacaftor/Ivacaftor in Subjects with Cystic Fibrosis and *F508del/F508del-CFTR* or *F508del/G551D-CFTR*

Scott H. Donaldson¹, Joseph M. Pilewski², Matthias Griesse³, Jon Cooke^{4*}, Lakshmi Viswanathan⁵, Elizabeth Tullis⁶, Jane C. Davies⁷, Julie A. Lekstrom-Himes⁴, and Linda T. Wang⁵; on behalf of the VX11-661-101 Study Group

¹University of North Carolina School of Medicine, Chapel Hill, North Carolina; ²University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; ³Department of Pediatric Pneumology, Dr. von Hauner Children's Hospital, Ludwig-Maximilians-University, Munich, Germany; ⁴Vertex Pharmaceuticals (Europe) Limited, London, United Kingdom; ⁵Vertex Pharmaceuticals Incorporated, Boston, Massachusetts; ⁶St. Michael's Hospital and Keenan Research Centre, Li Ka Shing Knowledge Institute, University of Toronto, Toronto, Ontario, Canada; and ⁷Paediatric Respiratory Medicine, Imperial College and Royal Brompton and Harefield Foundation Trust, London, United Kingdom

Abstract

Rationale: Tezacaftor (formerly VX-661) is an investigational small molecule that improves processing and trafficking of the cystic fibrosis transmembrane conductance regulator (CFTR) *in vitro*, and improves CFTR function alone and in combination with ivacaftor.

Objectives: To evaluate the safety and efficacy of tezacaftor monotherapy and of tezacaftor/ivacaftor combination therapy in subjects with cystic fibrosis homozygous for *F508del* or compound heterozygous for *F508del* and *G551D*.

Methods: This was a randomized, placebo-controlled, double-blind, multicenter, phase 2 study (NCT01531673). Subjects homozygous for *F508del* received tezacaftor (10 to 150 mg) every day alone or in combination with ivacaftor (150 mg every 12 h) in a dose escalation phase, as well as in a dosage regimen testing phase. Subjects compound heterozygous for *F508del* and *G551D*, taking physician-prescribed ivacaftor, received tezacaftor (100 mg every day).

Measurements and Main Results: Primary endpoints were safety through Day 56 and change in sweat chloride from baseline through Day 28. Secondary endpoints included change in percent predicted FEV₁ (ppFEV₁) from baseline through Day 28 and pharmacokinetics. The incidence of adverse events was similar across treatment arms. Tezacaftor (100 mg every day)/ivacaftor (150 mg every 12 h) resulted in a 6.04 mmol/L decrease in sweat chloride and 3.75 percentage point increase in ppFEV₁ in subjects homozygous for *F508del*, and a 7.02 mmol/L decrease in sweat chloride and 4.60 percentage point increase in ppFEV₁ in subjects compound heterozygous for *F508del* and *G551D* from baseline through Day 28 ($P < 0.05$ for all).

Conclusions: These results support continued clinical development of tezacaftor (100 mg every day) in combination with ivacaftor (150 mg every 12 h) in subjects with cystic fibrosis.

Clinical trial registered with www.clinicaltrials.gov (NCT01531673).

Keywords: cystic fibrosis transmembrane conductance regulator corrector; CFTR modulator; forced expiratory volume; sweat chloride

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*Present address: Biostatistics Limited, Sandhurst, United Kingdom.

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Correspondence and requests for reprints should be addressed to Linda T. Wang, M.D., Vertex Pharmaceuticals Incorporated, 50 Northern Avenue, Boston, MA 02210. E-mail: linda_wang@vrtx.com.

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At a Glance Commentary

Scientific Knowledge on the

Subject: The most common mutation in the cystic fibrosis transmembrane conductance regulator gene (*CFTR*) is *F508del*, which causes independent defects in processing and trafficking that reduce the amount of protein on the cell membrane while also disrupting channel gating. In contrast, the *G551D* mutant protein trafficks but does not gate normally. Ivacaftor is a *CFTR* potentiator that increases chloride transport and improves lung function in patients with *CFTR* gating mutations. Tezacaftor (formerly VX-661) is a novel corrector that increases processing and trafficking of *CFTR* to the cell membrane. In combination, tezacaftor and ivacaftor have been shown to enhance *CFTR* activity in human bronchial epithelial cells homozygous for *F508del* and compound heterozygous for *F508del* and *G551D*.

What This Study Adds to the

Field: We show that in the first clinical trial evaluating tezacaftor combined with ivacaftor, the combination has an acceptable safety profile, reduces sweat chloride, and improves lung function in subjects homozygous for *F508del* or compound heterozygous for *F508del* and *G551D*.

Cystic fibrosis (CF) affects an estimated 70,000 children and adults worldwide and is the most common fatal genetic disease in persons of European descent (1). CF is caused by mutations in the *CF* transmembrane conductance regulator gene (*CFTR*) that lead to a deficiency in the amount and/or function of *CFTR* protein at the epithelial cell surface (2–4). Two complementary approaches using *CFTR* modulators to increase *CFTR*-mediated chloride secretion in epithelia have been studied (5). *CFTR* correctors modify the cellular processing and trafficking of the *CFTR* protein to increase the amount of functional *CFTR* at the cell surface. *CFTR* potentiators increase the channel gating activity of protein kinase A-activated *CFTR* at the cell surface to enhance ion transport.

Depending on the amount of residual *CFTR* channel activity in the membrane and its functionality (reflecting the *CFTR* genotype of the patient and other factors), both approaches may be required to effectively treat the clinical manifestations resulting from defective *CFTR*-mediated chloride transport.

The most common *CFTR* mutation, *F508del*, is present on at least one allele in approximately 87% of patients with CF who were entered into the United States–based CF Foundation Patient Registry and is on both alleles in approximately 46% (6). The *F508del* mutation causes a processing and trafficking defect that reduces the amount of protein on the epithelial membrane while also disrupting gating of the few channels that reach the surface; these combined effects result in minimal *CFTR*-mediated chloride transport (7–10). Improving chloride transport in patients homozygous for *F508del* requires combination therapy with both a *CFTR* corrector, such as lumacaftor, and a *CFTR* potentiator (11–13).

Ivacaftor is an approved *CFTR* modulator for the treatment of patients with CF and at least one of 33 CF-causing mutations (14), accounting for approximately 10% of all patients with CF in the United States. It was first approved for patients with *G551D* (approximately 4% of all patients with CF) or similar gating mutations (15–18). Most patients with *G551D* carry *F508del* on their second allele. Both *in vitro* and clinical data indicate that the beneficial impact of ivacaftor in those with a gating mutation is attributable to its effects on the gating allele (11). Tezacaftor is a broad-acting *CFTR* corrector similar to lumacaftor that facilitates the cellular processing and trafficking of normal *CFTR* and multiple mutant *CFTR* forms, including *F508del*, thereby increasing the amount of *CFTR* protein at the cell surface, resulting in increased chloride transport. The addition of a *CFTR* corrector to potentiator therapy provides clinical benefit to those who carry processing and trafficking mutations such as *F508del*, the most common CF-causing *CFTR* mutation (6). In addition, *CFTR* corrector and potentiator combination therapy may provide benefit to patients who are compound heterozygous for *F508del* and an ivacaftor-responsive mutation.

Tezacaftor is a new *CFTR* corrector currently being studied in clinical trials.

Tezacaftor in combination with ivacaftor has the potential to fill an important unmet need for *CFTR* modulators, including improving the benefit-to-risk profile of *CFTR* modulation in patients homozygous for *F508del* and enhancing the benefit of *CFTR* modulation for patients with ivacaftor-responsive mutations. One of the important advantages of tezacaftor is that, unlike lumacaftor, it is not an inducer of CYP3A4 enzymes (our unpublished data) and does not interfere with the metabolism of ivacaftor or many other medications that are frequently used in CF, reducing drug–drug interactions and dosing complexities (19). This phase 2, placebo-controlled study evaluated the safety and efficacy of tezacaftor monotherapy and tezacaftor/ivacaftor combination therapy in subjects with CF who were homozygous for *F508del* or compound heterozygous for *F508del* and *G551D*.

Some of the results of these studies have been previously reported in the form of abstracts (20–22).

Methods

Study Design

This was a randomized, placebo-controlled, double-blind, multicenter phase 2 study (NCT01531673) using a multiple ascending dose and parallel-arm design that included a 28-day treatment period followed by a 28-day post-treatment observation (washout) period. There were 14 study arms as shown in the study schema (Figure 1). Because this was a proof-of-concept study, each dose of tezacaftor was tested for tolerability as monotherapy before testing in combination with ivacaftor during the dose escalation phase. Results across treatment arms were assessed to evaluate dose–response profiles and define dosing strategies in subjects homozygous for *F508del* and to characterize safety and tolerability in subjects homozygous for *F508del* or compound heterozygous for *F508del* and *G551D*.

Study Oversight

The protocol was reviewed and approved by the institutional review board or ethics committee at each participating center before the study began. Written informed consent and participant assent were obtained from each subject or caregiver as appropriate. An independent data-monitoring

Figure 1. Study design. ^aStudy arm analyzed in both the dose escalation and dosage regimen testing phases. ^bFive subjects counted in both pooled placebo groups. q12h = every 12 hours; qday = every day.

committee conducted safety reviews throughout the course of the trial.

Study Subjects

All eligible subjects were required to have received a confirmed diagnosis of CF (23), defined as a sweat chloride value greater than 60 mmol/L by quantitative pilocarpine iontophoresis or two CF-causing mutations, and chronic sinopulmonary disease or gastrointestinal/nutritional abnormalities; an FEV₁ of 40–90% of the predicted value for persons of their age, sex, race, and height (24); and a body weight of at least 40 kg and body mass index of at least 18.5 kg/m².

Eligible subjects in the dose escalation and alternative dosage regimen testing phases were at least 18 years of age and homozygous for *F508del*. Eligible heterozygous subjects were at least 12 years of age, were compound heterozygous for *F508del* and *G551D*, and must have been taking physician-prescribed ivacaftor for at least 28 days at the time of screening. Confirmation of genotype results was required before enrollment.

All subjects were randomly assigned at a 4:1 ratio to receive active drug or matched placebo for 28 days, with an additional 28-day follow-up. Subjects who prematurely discontinued treatment were required to complete the safety follow-up visit

approximately 28 days after administration of the last dose of study drug. During the course of the study, subjects were required to continue their routine, stable medication regimen. In the dose escalation phase, subjects received increasing doses by cohort. Subjects received tezacaftor (10, 30, 100, or 150 mg every day) alone or in combination with ivacaftor (150 mg every 12 h). In the alternative dosage regimen testing phase, subjects received tezacaftor (100 mg every day)/ivacaftor (50 mg every 12 h) or tezacaftor (50 mg every 12 h)/ivacaftor (150 mg every 12 h). Subjects who were compound heterozygous for *F508del* and *G551D* received tezacaftor (100 mg every day) in combination with physician-prescribed ivacaftor (150 mg every 12 h). Placebo subjects in this group continued to receive physician-prescribed ivacaftor throughout the study.

Endpoints

The primary endpoints were safety through Day 56, as determined by adverse events, clinical laboratory values, standard digital ECGs, and vital signs, and change in sweat chloride from baseline through Day 28. Secondary endpoints included absolute and relative changes in percent predicted FEV₁ (ppFEV₁) from baseline through Day 28, pharmacokinetic (PK) parameters, and change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score from baseline to each visit up to Day 28. Endpoints were assessed every 7 days during the treatment and washout periods.

Statistical Analyses

Because this was a proof-of-concept study, no formal sample size determination was conducted. Safety and efficacy were evaluated in all subjects who received at least one dose of study drug. Independent comparisons of efficacy (e.g., ppFEV₁) were done, and other clinical parameters were determined, in subjects homozygous for *F508del* and in those compound heterozygous for *F508del/G551D*. Comparisons were made both within and between treatment groups. Change in sweat chloride or ppFEV₁ from baseline through Day 28 was analyzed via a mixed model for repeated measures. The average treatment effect across all postbaseline visits obtained from the mixed model for repeated measures was used as the effect estimate for within- and between-group comparisons.

No α -level adjustment for multiple comparisons was performed. Statistical significance was defined as a P value less than 0.05 and is reported only for the combination treatment of the two higher

doses of tezacaftor (100 and 150 mg every day).

Placebo subjects were pooled for between-group comparisons in the dose escalation and alternative dosage regimen

testing phases. Subjects who received tezacaftor (100 mg every day)/ivacaftor (150 mg every 12 h) in the dose escalation phase were included in the analyses with the alternative dosage regimens.

A

B

C

Figure 2. Subject disposition. (A and B) Disposition of subjects homozygous for *F508del*-pooled groups in (A) the dose escalation phase and (B) the alternative dosage regimen testing phase; and (C) disposition of subjects compound heterozygous for *F508del* and *G551D*. Figure E1 (see the online supplement) provides more detail on each study arm. ^aFive subjects were counted in both pooled placebo groups. ^bSeventeen subjects who received tezacaftor (100 mg every day)/ivacaftor (150 mg every 12 h) were counted in both the dose escalation and dosage regimen testing phases.

Table 1. Baseline Characteristics

	Subjects Homozygous for <i>F508del</i>			Subjects Compound Heterozygous for <i>F508del</i> and <i>G551D</i>	
	Pooled Tezacaftor Monotherapy (n = 33)	Pooled Tezacaftor Combination (n = 106)	Pooled Placebo (n = 33)	Active Combination Drug (n = 14)	Placebo (Ivacaftor Monotherapy) (n = 4)
Tezacaftor dose	10–150 mg every day	10–150 mg every day or 50 mg every 12 h	NA	100 mg every day	100 mg every day
Ivacaftor dose	NA	150 mg every day or 50 mg every 12 h	NA	150 mg every 12 h	NA
Female, n (%)	14 (42.4)	47 (44.3)	13 (39.4)	6 (42.9)	3 (75.0)
Age, mean (SD), yr	30.8 (7.9)	29.5 (8.0)	30.7 (8.4)	26.6 (7.0)	34.5 (7.6)
BMI, mean (SD), kg/m ²	22.4 (3.1)	22.5 (2.8)	21.8 (3.0)	24.6 (3.9)	22.9 (1.0)
Sweat chloride, mean (SD), mmol/L	101.8 (9.2)	99.0 (12.6)	98.4 (13.7)	52.9 (19.6)	56.7 (22.1)
ppFEV ₁					
Mean (SD)	61.1 (14.0)	61.5 (13.8)	58.0 (14.5)	59.1 (16.6)	62.6 (12.7)
Range	35.6–89.0	34.2–90.7	35.2–89.9	31.1–79.4	52.6–80.9

Definition of abbreviations: BMI = body mass index; NA = not applicable; ppFEV₁ = percent predicted FEV₁.

Results

Results for baseline demographics, subject disposition, and safety were pooled into monotherapy and combination therapy groups. Detailed results for each study arm are presented in the online supplement.

Study Population

The study was conducted from February 2012 through March 2014 at 37 CF centers in the United States, Canada, Germany, and the United Kingdom. The screening, randomization, and follow-up of subjects are shown in Figure 2 and in Figure E1 in the online supplement. Overall, 185 of 190 subjects (97.4%) completed the study and follow-up; 94.2% of subjects completed the full dosage regimen, with a mean compliance (calculated as the number of tablets consumed relative to the number of tablets administered) of 97.9%.

Baseline characteristics were well balanced among all study arms in subjects homozygous for *F508del* (Table 1 and Table E1). Overall, the mean age was 30 years (SD, 8.0), 44% were female, the mean sweat chloride concentration was 95 mmol/L (SD, 18.7), and the mean ppFEV₁ was 61 (SD, 14.1). Baseline mean sweat chloride for subjects compound heterozygous for *F508del/G551D* was 52.9 mmol/L (SD, 19.6) in the active drug arm and 56.7 mmol/L

(SD, 22.1) in the placebo arm, consistent with the effects of ivacaftor (15, 18).

Safety

The incidence of adverse events through Day 56 was similar across study arms. Five subjects homozygous for *F508del* discontinued the study (one because of an adverse event, one because of noncompliance, one was lost to follow-up, and two for other reasons, which were unspecified). Four discontinuations occurred during the dose escalation phase: two subjects receiving monotherapy (tezacaftor, 10 mg every day; and tezacaftor, 100 mg every day) and two subjects receiving combination therapy (one receiving tezacaftor, 10 mg every day; and one receiving tezacaftor, 30 mg every day). One discontinuation occurred during the dosage regimen

testing phase: one subject receiving tezacaftor (100 mg every day)/ivacaftor (50 mg every 12 h). No subjects in the *F508del/G551D* genotype cohort discontinued the study.

Table 2 and Table E2 summarize the overall adverse events, serious adverse events, and discontinuations that occurred through Day 56. A total of 152 of 172 subjects homozygous for *F508del* (88.4%) had at least one adverse event, with an incidence of 30 subjects (90.9%) in the tezacaftor monotherapy arm, 92 subjects (86.8%) in the tezacaftor/ivacaftor arm, and 30 subjects (90.9%) in the placebo arm. The majority (81.4%) of adverse events were mild to moderate in nature. The most common adverse events by subject ($\geq 15\%$ in any treatment group) were infective pulmonary exacerbation of CF, cough, increased sputum, nausea, diarrhea,

Table 2. Adverse Events in Subjects Homozygous for *F508del*

	Pooled Tezacaftor Monotherapy (n = 33)	Pooled Tezacaftor Combination (n = 106)	Pooled Placebo (n = 33)
Any AE	30 (90.9)	92 (86.8)	30 (90.9)
Any serious AE	2 (6.1)	8 (7.5)	5 (15.2)
Serious pulmonary exacerbation	2 (6.1)	7 (6.6)	5 (15.2)
Discontinuation due to AE	1 (3.0)	4 (3.8)	0

Definition of abbreviation: AE = adverse event. Data are n (%).

Table 3. Adverse Events in Subjects Homozygous for *F508del* Occurring in At Least 15% of Subjects in Any Active Drug Arm

Adverse Event	Pooled Tezacaftor Monotherapy (n = 33)	Pooled Tezacaftor Combination (n = 106)	Pooled Placebo (n = 33)
Infective pulmonary exacerbation of CF	4 (12.1)	24 (22.6)	9 (27.3)
Cough	10 (30.3)	17 (16.0)	6 (18.2)
Headache	4 (12.1)	16 (15.1)	8 (24.2)
Increased sputum	7 (21.2)	11 (10.4)	2 (6.1)
Fatigue	7 (21.2)	7 (6.6)	3 (9.1)
Nausea	8 (24.2)	11 (10.4)	1 (3.0)
Diarrhea	5 (15.2)	6 (5.7)	2 (6.1)

Definition of abbreviation: CF = cystic fibrosis.
Data are n (%).

headache, and fatigue. Adverse events occurring in at least 15% of subjects in any active drug arm are shown in Table 3 and Table E3. Four adverse events, including cough, nausea, fatigue, and increased sputum, were more common in the tezacaftor monotherapy arm compared with combination therapy (Table 3). However, the number of patients in the pooled monotherapy arms was low ($n = 30$), and examination of adverse events by cohort does not suggest a dose relationship or dose-related increased intolerability. Serious adverse events were reported in 15 subjects homozygous for *F508del*; 10 of 139 subjects (7%) were in an active drug arm, and 5 of 33 subjects (15%) were in a placebo arm. Fourteen of the 15 serious adverse events were pulmonary exacerbations. One subject compound heterozygous for *F508del*/*G551D* and who received tezacaftor reported a serious adverse event of arthritis that was considered not related to the study drug by the investigator. No deaths occurred during the study.

Adverse events that occurred during the 28-day washout period were collected and are reported separately in Tables E4 and E5. During the washout period, a total of 120 of 172 subjects homozygous for *F508del* (69.8%) had at least one adverse event, with an incidence of 20 subjects (60.6%) in the tezacaftor monotherapy arm, 76 subjects (71.7%) in the tezacaftor/ivacaftor arm, and 24 subjects (72.7%) in the placebo arm. The most common adverse events by subject ($\geq 15\%$ in any treatment group) were infective pulmonary exacerbation of CF, cough, headache, and nausea.

There were no clinically significant trends for laboratory tests, ECG parameters, vital signs, weight, and body mass index.

Pharmacokinetics

Table E6 summarizes the PK of tezacaftor in all subjects. In subjects homozygous for *F508del*, tezacaftor was rapidly absorbed after oral administration and reached steady state by approximately 2 weeks. In the monotherapy arms, exposures of tezacaftor increased in an approximately dose-proportional manner. Exposures of tezacaftor and its metabolites, M1 and M2, were similar after tezacaftor monotherapy and tezacaftor/ivacaftor combination therapy. In the dosage regimen testing phase, steady state area under the curve (AUC) estimates of tezacaftor were similar when dosed at 50 mg every 12 hours or 100 mg every day. The geometric least-squares mean ratios interval for tezacaftor exposures with combination therapy (tezacaftor [100 mg every day]/ivacaftor [150 mg every 12 h]) relative to tezacaftor (100 mg every day) monotherapy were 0.998 (90% confidence interval [CI], 0.768–1.30) for AUC and 1.07 (90% CI, 0.844–1.36) for C_{max} . The mean accumulation ratios of tezacaftor based on $AUC_{0-24\text{ h}}$ (Day 28/Day 1) were also similar after daily dosing of tezacaftor monotherapy and tezacaftor (100 mg every day)/ivacaftor (150 mg every 12 h).

Table E7 summarizes the PK of ivacaftor in all subjects treated in the combination therapy groups. Exposures of ivacaftor and its metabolites, M1 and M6, were also unaffected by the

coadministration with increasing doses of tezacaftor and were consistent with previously observed exposures (25).

Tezacaftor (100 mg every day)/ivacaftor (150 mg every 12 h) in subjects compound heterozygous for *F508del*/*G551D* yielded steady state exposures of tezacaftor and ivacaftor that were similar to subjects homozygous for *F508del* (Tables E6 and E7).

Efficacy in the Dose Escalation Phase in Subjects Homozygous for *F508del*

In subjects homozygous for *F508del*, treatment resulted in mean within-group decreases in sweat chloride from baseline through Day 28 with the two higher doses of tezacaftor monotherapy (100 and 150 mg every day) and with tezacaftor doses of 10, 30, and 100 mg every day given in combination with ivacaftor at 150 mg every 12 hours ($P < 0.05$ for 100 mg every day; Figure 3). Sweat chloride changes with tezacaftor (100 mg every day)/ivacaftor (150 mg every 12 h) were also significant when compared with placebo through Day 28 ($P < 0.05$; Table E8). A clear dose-response pattern was not observed in monotherapy or combination therapy treatment arms. However, the size of the treatment arms, particularly in the monotherapy groups, was small. In all treatment arms, sweat chloride returned to near pretreatment levels 28 days after stopping treatment.

Treatment resulted in within-group improvements from baseline in ppFEV₁ (absolute) through Day 28 with tezacaftor (10 mg every day) monotherapy, whereas no treatment effect was observed at the three higher doses. With combination therapy, within-group improvements from baseline in ppFEV₁ (absolute) were observed with tezacaftor doses of 30, 100, and 150 mg every day in combination with ivacaftor at 150 mg every 12 hours ($P < 0.05$ for 100 and 150 mg every day; Figure 3), in a pattern that suggested a dose-response relationship. The absolute increase in ppFEV₁ observed at the two higher doses of tezacaftor/ivacaftor was also significant when compared with placebo through Day 28 ($P < 0.05$ for both; Table E8). The analyses of relative change in ppFEV₁ were consistent

Figure 3. Efficacy in subjects homozygous for *F508del* in the dose escalation phase. (A) Change in sweat chloride and (B) absolute change in ppFEV₁ from baseline through Day 28. Subjects in the combination therapy arms were treated with ivacaftor at 150 mg every 12 hours. * $P < 0.05$ versus baseline within group; † $P < 0.05$ versus placebo; P values only reported for tezacaftor (100 mg every day)/ivacaftor (150 mg every 12 h) and tezacaftor (150 mg every day)/ivacaftor (150 mg every 12 h). CI = confidence interval; LS = least squares; ppFEV₁ = percent predicted FEV₁; qday = every day.

with those of absolute change in ppFEV₁ (Table E8). In all treatment arms, ppFEV₁ returned to near pretreatment levels 28 days after stopping treatment (Figure 4).

The largest improvement in ppFEV₁ (absolute) was observed in the tezacaftor (100 mg every day)/ivacaftor (150 mg every 12 h) combination therapy arm (within-group increase from baseline of 3.75

percentage points [Figure 3]; treatment effect vs. placebo: 3.89 percentage points; 95% CI, 0.94–6.83; $P < 0.05$ [Table E8]). The proportion of subjects experiencing an increase in ppFEV₁ from baseline through

Figure 4. Efficacy of combination treatment in subjects homozygous for *F508del* during the dose escalation phase. (A) Mean absolute changes in ppFEV₁ for the treatment and washout periods for tezacaftor plus ivacaftor (150 mg every 12 h) in the dose escalation phase; and individual subject absolute changes in ppFEV₁ at Day 28 for the (B) tezacaftor (100 mg every day) plus ivacaftor (150 mg every 12 h) cohort and (C) placebo cohort. Analysis of change from baseline at all measurements up to Day 28 was based on a mixed-effect model for repeated measures. For the washout period, summary statistics are shown. LS = least squares; ppFEV₁ = percent predicted FEV₁; q12h = every 12 hours; qday = every day.

Day 28 in this treatment arm was larger than that observed in the placebo arm (Figure 4).

Combination therapy consisting of tezacaftor at 100 or 150 mg every day with ivacaftor at 150 mg every 12 hours resulted in within-group increases from baseline in CFQ-R respiratory domain score through

Day 28 of 5.15 points ($P = 0.093$) and 7.62 points ($P = 0.011$), respectively. No significant within-group changes in CFQ-R respiratory domain were observed in any other treatment groups. No significant changes were observed when compared with placebo for any monotherapy or combination therapy groups.

Efficacy in the Dosage Regimen Testing Phase in Subjects Homozygous for *F508del*

Tezacaftor (100 mg every day) in combination with ivacaftor (150 mg every 12 h) was selected during the dose escalation phase as the most effective dose. During the dosage regimen testing phase, alternative

regimens, including a twice-daily tezacaftor regimen (tezacaftor [50 mg every 12 h]/ivacaftor [150 mg every 12 h]) and a low-dose ivacaftor regimen (tezacaftor [100 mg every day]/ivacaftor [50 mg every 12 h]), were compared with responses to tezacaftor (100 mg every day) with ivacaftor (150 mg every 12 h) observed during the dose escalation phase. All three dosage regimens resulted in within-group decreases in sweat chloride from baseline through Day 28 (Figure 5). Tezacaftor (50 mg every 12 h)/ivacaftor (150 mg every 12 h) also resulted in a reduction in sweat chloride compared with placebo (Table E9). However, treatment with the twice-daily regimen or the low-dose ivacaftor regimen did not result in improvements (either within group or vs. placebo) in ppFEV₁ (Figure 5; Table E9). Similarly, no changes (either within group or vs. placebo) in CFQ-R respiratory domain

score were observed with either alternative regimen.

Efficacy in Subjects Compound Heterozygous for *F508del* and *G551D*

Subjects who were compound heterozygous for *F508del* and *G551D* received tezacaftor at 100 mg every day or matched placebo while continuing to receive physician-prescribed ivacaftor at 150 mg every 12 hours. Although the within-group decrease in sweat chloride from baseline through Day 28 was not significant (Figure 6), treatment resulted in a statistically significant mean absolute decrease compared with placebo (treatment effect, -17.20 ; $P < 0.05$; Table E10). Treatment also resulted in statistically significant mean absolute and relative within-group increases in ppFEV₁ from baseline through Day 28 (4.60 and 7.29 percentage points, respectively;

$P < 0.05$ for both; Figure 6 and data not shown). The treatment effect versus placebo, however, was not significant for either absolute or relative change in ppFEV₁ (Table E10). Concentrations of sweat chloride and ppFEV₁ values returned to near pretreatment levels 28 days after stopping treatment (Day 56) (Figure E2). Individual absolute changes in ppFEV₁ responses indicated that 12 of 14 subjects (86%) receiving tezacaftor in combination with ivacaftor experienced increases in ppFEV₁ from baseline through Day 28 (Figure E2).

The combination of tezacaftor (100 mg every day) with ivacaftor (150 mg every 12 h) showed a mean within-group increase in the CFQ-R respiratory domain score of 3.79 points ($P = 0.1679$) from baseline through Day 28. The treatment effect versus placebo was 6.81 points ($P = 0.2451$).

Discussion

This study is the first clinical trial of oral tezacaftor treatment in combination with ivacaftor in subjects with CF homozygous for *F508del* and compound heterozygous for *F508del*/*G551D*. Our results demonstrate that tezacaftor monotherapy and in combination with ivacaftor is well tolerated, with low rates of discontinuation and similar incidences of adverse events in the placebo, tezacaftor monotherapy, and tezacaftor/ivacaftor combination groups.

The most common adverse events were pulmonary or infectious in nature, which is consistent with common manifestations of CF. The majority of adverse events were mild to moderate in severity. The incidence of serious adverse events was lower in the tezacaftor monotherapy and tezacaftor/ivacaftor combination groups than in the placebo group, due largely to the numerically lower number of pulmonary exacerbations. No other clinically significant differences in safety profile were observed across any of the treatment groups.

In subjects homozygous for *F508del*, within-group and between-group decreases in sweat chloride from baseline through Day 28 were observed in the higher-dose tezacaftor monotherapy groups (100 and 150 mg every day) and in most tezacaftor/ivacaftor combination therapy groups. Changes in sweat chloride after tezacaftor monotherapy or tezacaftor/ivacaftor combination therapy were not clearly dose dependent, suggesting

Figure 5. Efficacy in subjects homozygous for *F508del* in the dosage regimen testing phase.

(A) Change in sweat chloride and (B) absolute change in ppFEV₁ from baseline through Day 28.

^aSubjects also analyzed in the dose escalation phase. ^bComparison versus placebo not calculated.

* $P < 0.05$ versus baseline within group; P values reported only for tezacaftor (100 mg every day)/ivacaftor (150 mg every 12 h). CI = confidence interval; LS = least squares; ppFEV₁ = percent predicted FEV₁; q12h = every 12 hours; qday = every day.

Figure 6. Efficacy in subjects compound heterozygous for *F508del* and *G551D* who received combination therapy. (A) Change in sweat chloride and (B) absolute change in ppFEV₁ from baseline through Day 28. * $P < 0.05$ versus baseline within group; † $P < 0.05$ versus placebo through Day 28. CI = confidence interval; LS = least squares; ppFEV₁ = percent predicted FEV₁; q12h = every 12 hours; qday = every day.

that there may be a threshold response among subjects homozygous for *F508del*. For absolute and relative change in ppFEV₁, within group or compared with placebo, statistically significant improvements were observed with tezacaftor/ivacaftor at the higher doses of tezacaftor (100 and 150 mg every day). The increases observed in the monotherapy groups were variable and not dose dependent. By contrast, the increases in ppFEV₁ in the combination therapy groups showed dose dependency. After discontinuation of treatment, sweat chloride and lung function values returned to near pretreatment levels (Day 28 to Day 56), providing further evidence that the effects observed during active dosing were treatment related.

The greatest improvements in both sweat chloride and lung function were observed in the tezacaftor (100 mg every day)/ivacaftor (150 mg every 12 h) group during the dose escalation phase. In the dosage regimen testing phase, lung function improvements were smaller when using a twice-daily dosage regimen of tezacaftor (50 mg every 12 h) with ivacaftor (150 mg every 12 h) or tezacaftor (100 mg every day) with a reduced dose of ivacaftor (50 mg every 12 h).

Improvements in lung function in patients homozygous for *F508del* were generally comparable to or numerically greater than those observed in patients treated with lumacaftor/ivacaftor in the phase 3, 24-week TRAFFIC/TRANSPORT studies (26). Treatment initiation with lumacaftor/ivacaftor is sometimes associated with respiratory events and acute lung

function decline (26–30), which can restrict the number of patients willing to start treatment. The improved benefit-to-risk profile makes tezacaftor/ivacaftor a potential treatment option for a greater proportion of patients homozygous for *F508del*.

In subjects compound heterozygous for *F508del* and *G551D*, a numerical mean within-group decrease in sweat chloride from baseline through Day 28 was observed in the group receiving tezacaftor at 100 mg every day. Statistically significant within-group improvements from baseline through Day 28 were also observed in the tezacaftor group for the absolute and relative change in ppFEV₁. It is important to note that these subjects had been receiving physician-prescribed ivacaftor for at least 28 days before initiation of tezacaftor treatment and continued taking ivacaftor through the treatment and follow-up period; likewise, placebo subjects were also taking ivacaftor during the study period. Therefore the treatment effects observed with the addition of tezacaftor in these heterozygous subjects are greater than the effect observed from ivacaftor alone, suggesting the potential to further enhance the benefit of ivacaftor monotherapy in those who are compound heterozygous for *F508del* and an ivacaftor-responsive mutation.

Lumacaftor/ivacaftor combination therapy is the only approved CFTR modulator treatment for patients with CF homozygous for the *F508del* mutation. The combination of a CFTR corrector and potentiator was a milestone treatment approach for CF (13) but is not approved for patients with the *F508del*

mutation who carry gating or other ivacaftor-responsive mutations on their second allele. Tezacaftor in combination with ivacaftor may provide an enhanced benefit-to-risk profile that could benefit a broader population of patients with CF than either ivacaftor or lumacaftor/ivacaftor combination therapy.

Overall, these clinical trial results support the continued development of tezacaftor (100 mg every day) in combination with ivacaftor (150 mg every 12 h) in patients with CF. On the basis of these results, this dosage regimen was chosen for phase 3 development. At the time this study was initiated, ivacaftor was approved only for patients with the *G551D* gating mutation, and therefore patients with other gating mutations were not enrolled. Phase 3 studies are currently underway to continue to evaluate tezacaftor/ivacaftor combination therapy in subjects heterozygous for *F508del* and a gating mutation that has been shown to be clinically responsive to ivacaftor (NCT02412111), in subjects homozygous for *F508del* (NCT02347657), and in subjects heterozygous for *F508del* and a second mutation resulting in residual function (NCT02392234). ■

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