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ARTICLE

Pharmacokinetic and Drug–Drug Interaction Profiles of the Combination of Tezacaftor/Ivacaftor

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Drug–drug interaction (DDI) studies are described for tezacaftor/ivacaftor, a new cystic fibrosis transmembrane conductance regulator modulator therapy for the treatment of cystic fibrosis. Three phase I DDI studies were conducted in healthy subjects to characterize the DDI profile of tezacaftor/ivacaftor with cytochrome P450 (CYP)3A substrates, CYP3A inhibitors, and a permeability glycoprotein (P-gp) substrate. The effects of steady-state tezacaftor/ivacaftor on the pharmacokinetics (PKs) of digoxin (a P-gp substrate), midazolam, and ethinyl estradiol/norethindrone (CYP3A substrates) were evaluated. Effects of strong (itraconazole) and moderate (ciprofloxacin) CYP3A inhibitors on tezacaftor/ivacaftor PKs were also determined. Tezacaftor/ivacaftor increased digoxin area under the curve (AUC) by 30% but did not affect midazolam, ethinyl estradiol, or norethindrone exposures. Itraconazole increased the AUC of tezacaftor 4-fold and ivacaftor 15.6-fold. Ciprofloxacin had no significant effect on tezacaftor or ivacaftor exposure. Coadministration of tezacaftor/ivacaftor may increase exposure of sensitive P-gp substrates. Tezacaftor/ivacaftor is unlikely to impact exposure of drugs metabolized by CYP3A, including hormonal contraceptives. Strong CYP3A inhibitors significantly increase the exposures of tezacaftor and ivacaftor.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Disposition and pharmacokinetics of tezacaftor and its drug–drug interaction (DDI) profile in combination with ivacaftor on permeability glycoprotein (P-gp) substrates, cytochrome P450 (CYP) 3A substrates (including combined hormonal contraceptives), and CYP3A inhibitors (strong and moderate) have not been published.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ The DDI profile of tezacaftor/ivacaftor coadministered with digoxin (P-gp substrate), midazolam, ethinyl estradiol, and norethindrone (CYP3A substrates), itraconazole, and ciprofloxacin (CYP3A inhibitors) is reported.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ Results indicate that tezacaftor/ivacaftor does not affect exposure of CYP3A substrates, including hormonal contraceptives. Dose reductions of tezacaftor/ivacaftor are recommended with concomitant use of strong and moderate CYP3A inhibitors. Ciprofloxacin is unlikely to be an inhibitor of CYP3A4 *in vivo*, contrary to previous reports. Concomitant use of tezacaftor/ivacaftor may increase exposure of sensitive P-gp substrates, so caution and appropriate monitoring should be used.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ Results show that tezacaftor/ivacaftor can be used with commonly used drugs in patients with cystic fibrosis (CF), including hormonal contraceptives, and inform appropriate dose adjustments during coadministration with CYP3A inhibitors.

Cystic fibrosis (CF) is a life-shortening, genetic disease that is characterized by progressive respiratory decline and other systemic issues. Currently, there is no cure for CF, and the median predicted age of survival for individuals born today with CF is ~ 40 years of age.[1,2] CF transmembrane conductance regulator (CFTR) correctors, and potentiators are small molecules that target specific defects caused by mutations in the *CFTR* gene, which are the underlying cause of CF. Tezacaftor is a small-molecule CFTR corrector that facilitates the cellular processing and trafficking of CFTR, resulting in an increased amount of CFTR protein delivered to the cell surface. Ivacaftor is a CFTR potentiator that increases the channel-open probability (or gating) of CFTR at the cell surface to enhance total

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ion (chloride) transport. The combination of tezacaftor/ivacaftor significantly increases the quantity and function of CFTR at the cell surface, resulting in increases in chloride transport.[3] Tezacaftor/ivacaftor demonstrated a clinically meaningful and statistically significant effect across multiple end points in phase III studies of patients with CF homozygous for the *F508del-CFTR* mutation or heterozygous for the *F508del* and a second mutation that results in residual CFTR function.[4,5]

In vitro metabolism studies in human hepatocytes and recombinant human cytochrome P450 (CYP) show that tezacaftor and ivacaftor are both primarily metabolized via CYP3A-mediated oxidation. Unlike ivacaftor, tezacaftor also undergoes direct glucuronidation as a minor metabolic pathway. Thus, tezacaftor can be expected to be a less sensitive CYP3A substrate than ivacaftor. In clinical studies, tezacaftor and ivacaftor are metabolized extensively. The three major circulating metabolites of tezacaftor in humans are M1-TEZ, M2-TEZ, and M5-TEZ. M1-TEZ has similar potency to that of tezacaftor and is considered pharmacologically active. M2-TEZ is much less pharmacologically active than tezacaftor or M1-TEZ, and M5-TEZ is not considered pharmacologically active.[3] The two major metabolites of ivacaftor in humans are M1-IVA and M6-IVA.[3,6] M1-IVA has approximately one sixth the potency of ivacaftor and is considered pharmacologically active. M6-IVA is not considered pharmacologically active. Following oral administration, both tezacaftor and ivacaftor are excreted mainly in the feces (unchanged or as metabolites) with a small percentage of dose excreted in urine.[3] Following oral administration of ^{14}C-tezacaftor, the majority of the dose (72%) was excreted in the feces (unchanged or as the M2 metabolite) and about 14% was recovered in urine (mostly as the M2 metabolite), resulting in a mean overall recovery of 86% up to 21 days after the dose.[3] Less than 1% of the administered dose was excreted in urine as unchanged tezacaftor, showing that renal excretion is not the major pathway of tezacaftor elimination in humans.[3] Following oral administration of ivacaftor, the majority of ivacaftor (87.8%) is eliminated in the feces after metabolic conversion.[3] There was minimal elimination of ivacaftor and its metabolites in urine (only 6.6% of total radioactivity was recovered in the urine), and there was negligible urinary excretion of ivacaftor as unchanged drug.[3]

The pharmacokinetics (PKs) of tezacaftor and ivacaftor were similar between healthy adult subjects and patients with CF.[3] No clinically meaningful change in exposure has been identified for tezacaftor or ivacaftor when coadministered compared with administration of each component alone (unpublished data). Exposures of tezacaftor increase in an approximately dose-proportional manner with increasing doses ranging from 10–300 mg.[3] Although no food effect was observed with administration of tezacaftor alone, exposures of ivacaftor increased threefold (in comparison to administration in the fasted state) when administered with fat-containing food. Therefore, the regimen of tezacaftor/ivacaftor should be administered with fat-containing food.[3,6] Following once-daily dosing of tezacaftor and twice-daily dosing of ivacaftor in patients with CF, plasma concentrations reach steady state within 8 days for tezacaftor and within 3 to 5 days for ivacaftor, and the mean (SD) terminal half-lives were ~ 156 (52.7) hours for tezacaftor and 9.3 (1.7) hours for ivacaftor (unpublished data).

As CF is a systemic and chronic illness, patients are expected to use many medications concomitantly with tezacaftor/ivacaftor. Therefore, the drug–drug interaction (DDI) profile of tezacaftor/ivacaftor is an important consideration. *In vitro* studies showed that tezacaftor, ivacaftor, and their metabolites had low potential for causing DDIs via CYP3A inhibition or induction.[3] Clinical data also showed that ivacaftor is a weak inhibitor of CYP3A.[6] In addition, *in vitro* studies suggest that tezacaftor is not an inhibitor of the permeability glycoprotein (P-gp) efflux transporter,[3] whereas ivacaftor was shown to be a P-gp inhibitor *in vitro* and a mild P-gp inhibitor in a clinical study using digoxin as a model P-gp substrate.[6] Many drugs commonly used in patients with CF are metabolized by CYP3A (e.g., steroids, hormonal contraceptives, and antibiotics), inhibit CYP3A (e.g., itraconazole and ciprofloxacin), or are sensitive P-gp substrates (e.g., cyclosporine and tacrolimus). Therefore, the potential for tezacaftor/ivacaftor to have a DDI with CYP3A inhibitors, inducers, and substrates, as well as with P-gp substrates, was evaluated in several clinical studies. This paper presents key data about the DDI profile of tezacaftor/ivacaftor with CYP3A substrates (midazolam, ethinyl estradiol, and norethindrone), CYP3A inhibitors (itraconazole and ciprofloxacin), and the P-gp substrate digoxin.

METHODS

Study designs

Study VX14-661-006 (study 006) was a phase I, open-label, two-cohort, two-period, fixed-sequence crossover design study to evaluate the effect of itraconazole, a strong CYP3A inhibitor, on tezacaftor and ivacaftor PK (cohort 1) and to evaluate the effect of tezacaftor/ivacaftor on the exposure of midazolam, a sensitive CYP3A substrate, and digoxin, a P-gp substrate (cohort 2). Itraconazole, midazolam, and digoxin were selected for inclusion in study 006 because they are widely accepted strong index CYP3A inhibitors (itraconazole) or probe substrates for CYP3A (midazolam) and P-gp (digoxin).[7,8] Male and female subjects in cohort 1 (N = 18) were administered tezacaftor 25 mg q.d. and ivacaftor 50 mg q.d. as separate tablets in the absence of itraconazole in dosing period 1 (day 1 through day 14) and in the presence of itraconazole 200 mg q.d. during dosing period 2 (day 15 through day 28). An additional dose of itraconazole 200 mg was administered on the first day of dosing in dosing period 2 (day 15) ~ 12 hours after administration of the morning dose of itraconazole to help achieve steady state of itraconazole faster. Male and female subjects in cohort 2 (N = 16) were administered single doses of midazolam (2 mg) and digoxin (0.5 mg) on day 1 of dosing period 1 (day 1 through day 5), and tezacaftor 100 mg q.d./ivacaftor 150 mg q12 h during dosing period 2 (day 6 through day 19) with single doses of midazolam and digoxin on day 15. All subjects were confined to the clinic from day-1 through completion of all assessments (day 29 for cohort 1 and day 20 for cohort 2). Blood samples were

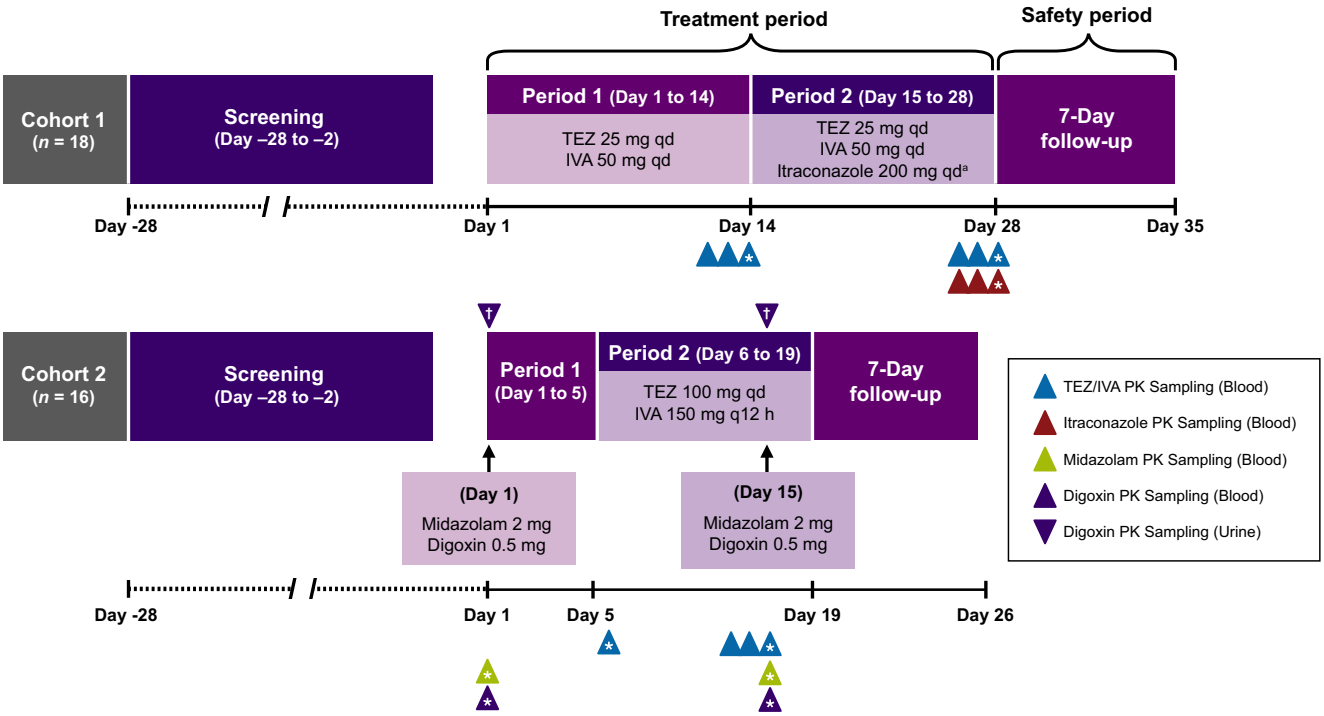

Figure 1 VX14-661-006 study design. Coadministration of TEZ/IVA With itraconazole, midazolam, and digoxin. TEZ/IVA was administered within 30 minutes of starting a breakfast (morning dose). Itraconazole was administered in the fasting state. Digoxin was administered 1 hour after midazolam dosing. Samples were collected before the morning dose unless otherwise noted. [a]An additional dose of itraconazole 200 mg was administered on day 15. *Denotes the day of intensive PK sampling; PK samples were drawn after TEZ/IVA administration at 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours; after itraconazole administration at 2 hours; after midazolam administration at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours; and after digoxin administration at 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 10, 12, 24, 48, 72, 96, and 120 hours. †Time increments for urine collection were 0–6, 6–12, 12–24, 24–48, 48–72, 72–96, and 96–120 hours. IVA, ivacaftor; PK, pharmacokinetic; TEZ, tezacaftor.

collected predose and postdose for the measurement of plasma concentrations of tezacaftor, M1-TEZ, M2-TEZ, ivacaftor, M1-IVA, M6-IVA, midazolam, 1-hydroxymidazolam, itraconazole, 2-hydroxyitraconazole, and digoxin. Urine samples were collected predose and postdose for the measurement of digoxin. Additional details of the study design and sampling times are provided in **Figure 1**.

Study VX15-661-008 (study 008) was a phase I, open-label, crossover study to evaluate the effect of tezacaftor/ivacaftor on the exposure of an oral contraceptive in 25 female subjects of childbearing potential. The study included a single, fixed-sequence crossover in which each subject acted as her own control. Ethinyl estradiol and norethindrone, which are both metabolized by CYP3A, were selected for inclusion in study 008 because they are common components of combined oral contraceptives (COCs). All subjects were taking a COC regimen that contained 35 μg of ethinyl estradiol and 1,000 μg of norethindrone for at least 28 days before cycle 1, day 1. During cycle 1, subjects took a regimen containing 35 μg of ethinyl estradiol and 1,000 μg of norethindrone (Ortho-Novum 1/35; Janssen Pharmaceuticals, Titusville, NJ) for 28 days. During cycle 2, subjects continued with the ethinyl estradiol/norethindrone regimen while receiving tezacaftor 100 mg q.d./ivacaftor 150 mg q12 h. Consistent with the Ortho-Novum 1/35 product labeling, subjects took inert tablets on the last 7 days of each cycle. Blood samples were collected predose and postdose during both cycles for the measurement of ethinyl estradiol/norethindrone. During cycle 2, blood samples were collected predose and postdose for the measurement of tezacaftor and ivacaftor. Additional details of the study design and sampling times are provided in **Figure 2**.

Study VX13-770-017 (study 770-017, NCT02015507) was a phase I, open-label, nonrandomized, two-period study that evaluated the effects of ciprofloxacin on the PK of tezacaftor/ivacaftor in 17 healthy adult male and female subjects. Ciprofloxacin, a moderate CYP3A inhibitor, was evaluated in study 770-017 because it is a commonly prescribed antibiotic for patients with CF. In period 1 (days 1–10), subjects received tezacaftor/ivacaftor only (50 mg q12 h/150 mg q12 h). In period 2 (days 11–20), subjects received tezacaftor/ivacaftor at the same dose as period 1 and ciprofloxacin (750 mg q12 h). Intensive PK samples for the measurement of ciprofloxacin, tezacaftor, M1-TEZ, M2-TEZ, ivacaftor, M1-IVA, and M6-IVA were collected on days 10 and 20. Additional details of the study design and sampling times are provided in **Figure 3**.

All study protocols, informed consent forms, and necessary study documents were reviewed and approved by an independent ethics committee or institutional review board before initiation of any study-related procedures. All studies were conducted in accordance with good clinical

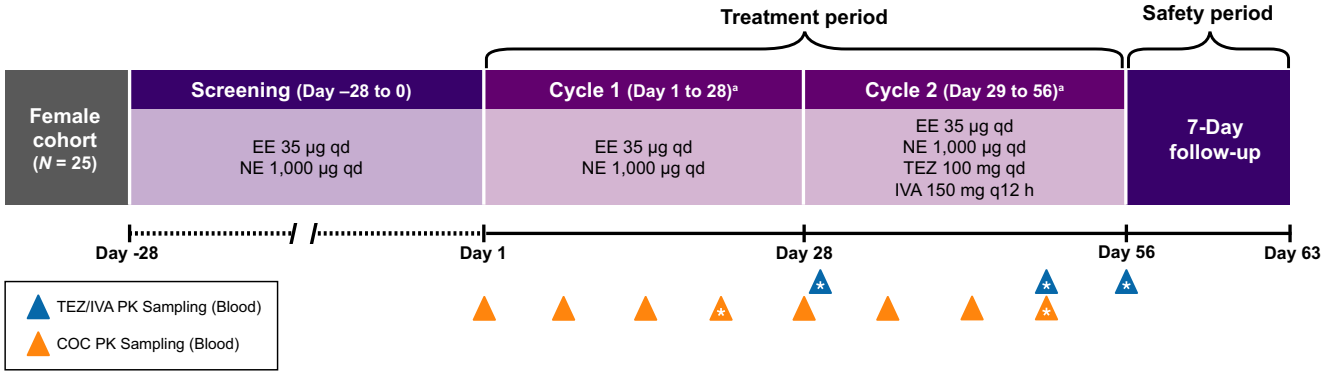

Figure 2 VX15-661-008 study design. Coadministration of TEZ/IVA with ethinyl estradiol/norethindrone. Samples were collected before the morning dose unless otherwise noted. [a]COC was administered for the first 21 days of the cycle, and an inert tablet was administered for the subsequent 7 days, consistent with prescribing information. *Denotes the day of intensive PK sampling; PK samples were drawn after TEZ/IVA administration at 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours and after COC administration at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hours. On days of intensive PK sampling, subjects abstained from all food and drink (except water) for at least 8 hours before the start of the morning meal (except as permitted for dosing). TEZ/IVA was administered as a fixed-dose combination tablet containing TEZ 100 mg/IVA 150 mg in the morning and an IVA 150 mg tablet in the evening. Study drugs (EE/NE, TEZ, and IVA) were administered within 30 minutes after starting a standard meal except on days of intensive PK sampling. On days of intensive PK sampling (days 21, 29, 49, and 56), subjects abstained from all food and drink (except water) for at least 8 hours before the start of the morning meal (to be consumed within 30 minutes). COC, combined oral contraceptive; EE, ethinyl estradiol; IVA, ivacaftor; NE, norethindrone; PK, pharmacokinetics; TEZ, tezacaftor.

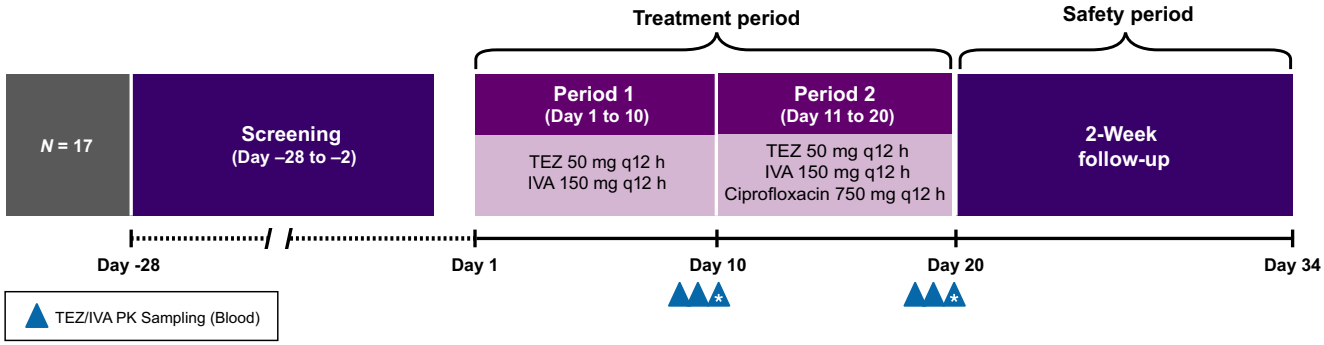

Figure 3 VX12-770-017 study design. Coadministration of TEZ/IVA with ciprofloxacin. Study drug was administered within 30 minutes after a standard meal. Samples were collected before the morning dose unless otherwise noted. *Denotes the day of intensive PK sampling; PK samples were drawn after TEZ/IVA administration at 0.5, 1, 2, 3, 4, 5, 6, 8, and 12 hours. IVA, ivacaftor; PK, pharmacokinetics; TEZ, tezacaftor.

practice as described in the International Conference on Harmonisation Guideline E6, Good Clinical Practice, Consolidated Guidance, and were consistent with the World Medical Assembly Declaration of Helsinki. All subjects provided written informed consent and were given an opportunity to ask questions on all aspects of the study.

Bioanalytical methods

PK samples were collected from human plasma at the time points indicated in the study design figures in the **Supplementary Material**. Tezacaftor, M1-TEZ, M2-TEZ, ivacaftor, M1-IVA, and M6-IVA were quantitated using liquid-liquid extraction of plasma and a validated liquid chromatography-mass spectrometry method. Calibration curves for tezacaftor, M1-TEZ, and M2-TEZ ranged from 2.00–2,000 ng/mL for studies 006, 008, and 770-107. Calibration curves for ivacaftor, M1-IVA, and M6-IVA ranged from 2.00–2,000 ng/mL for studies 006 and 008. Additional calibration curves ranges were as follows: ethinyl estradiol (2.00–500 pg/mL), norethindrone (50.0–25,000 pg/mL), midazolam and 1-hydroxymidazolam (0.100–100 ng/mL), and digoxin (plasma: 0.0100–10 ng/mL; urine: 0.200–200 ng/mL). The results from calibration and quality control samples demonstrated acceptable performance of the bioanalytical methods based upon standard, prespecified criteria for all analytes.

PK and statistical analysis

Standard noncompartmental analysis methods were used to determine PK parameters for each analyte. PK analyses were done using Phoenix WinNonlin software versions 5.3 or later. Area under the curve (AUC) was computed using the linear-log trapezoidal rule. Area under the curve from 0 to infinity ($AUC_{0-\infty}$) and parameters dependent on $AUC_{0-\infty}$ were not computed or reported if the extrapolated component of AUC was > 20% of $AUC_{0-\infty}$.

Table 1 Demographics and baseline characteristics in the TEZ/IVA studies of pharmacokinetics and drug–drug interactions

Parameter	TEZ/IVA + COC (*N* = 25)	TEZ/IVA + digoxin or midazolam (*N* = 16)	TEZ/IVA + itraconazole (*N* = 18)	TEZ/IVA + ciprofloxacin (*N* = 34)
Age, mean (SD), years	27.1 (5.5)	36.6 (9.5)	32.6 (8.8)	34.4 (10.2)
Weight, mean (SD), kg	64.7 (11.1)	77.6 (11.9)	74.8 (15.2)	74.1 (10.8)
BMI, mean (SD), kg/m^2	23.7 (3.1)	25.6 (3.3)	25.7 (3.6)	25.1 (3.4)
Sex, *n* (%)				
Male	0	6 (37.5)	11 (61.1)	17 (50.0)
Female	25 (100.0)	10 (62.5)	7 (38.9)	17 (50.0)
Race, *n* (%)				
White	15 (60.0)	9 (56.3)	3 (16.7)	13 (38.2)
Black	9 (36.0)	6 (37.5)	9 (50.0)	21 (61.8)
Asian	0	0	1 (5.6)	0
Native American/ Alaskan	0	0	2 (11.1)	0
Other	1 (4.0)	1 (6.3)	3 (16.7)	0

BMI, body mass index; COC, combined oral contraceptives; IVA, ivacaftor; TEZ, tezacaftor.

Clinical significance of DDIs was determined by the geometric least squares mean (GLSM) ratio and their 90% confidence interval (CI) of the victim drug in the presence and absence of the coadministered perpetrator. Based on the US Food and Drug Administration's guidance for DDIs, the default "no clinically significant effect" limits for the 90% CI for GLSM ratios were set as 0.80–1.25.[7] If the 90% CI fell outside this range, clinical significance was adjudicated based on the therapeutic window of the victim drug. The sample size for each study was based on the intrasubject variability determined from previous studies and the number of subjects (accounting for two dropouts in each cohort) was chosen to provide at least 90% confidence that the mean ratios for AUC of the victim drug in the presence/absence of the perpetrator will be within 25% of the true population ratio (90% CI: 0.75–1.33), assuming the true mean ratio is 1.00.

RESULTS

Demographics

Studies 006, 008, and 770-017 enrolled subjects with a mean age ranging from 27.1–36.6 years (range: 18–54 years). The number of subjects enrolled was 25 (oral contraceptives), 16 (midazolam/digoxin), 18 (itraconazole), and 34 (ciprofloxacin). All DDI studies enrolled male and female subjects, with the exception of the oral contraceptives study (study 008), which only enrolled female subjects of childbearing potential. Mean body mass index ranged from 23.7–25.7 kg/m^2 (**Table 1**).

DDIs in healthy subjects

Effects of tezacaftor/ivacaftor on CYP3A substrates. Coadministration of tezacaftor/ivacaftor did not have a clinically significant effect on the peak plasma concentration (C_{max}) and AUC of the model CYP3A substrate midazolam (**Table 2**); the 90% CI for the GLSM ratio of C_{max} and AUC for midazolam were within the default "no-effect" range of 0.80–1.25.

Coadministration of tezacaftor/ivacaftor with the COC did not have a clinically significant effect on the steady-state PK parameters of the COC components ethinyl estradiol and norethindrone (**Table 2**). The 90% CI for the GLSM ratio of the AUC and C_{max} of norethindrone and the AUC of ethinyl estradiol were within the default "no-effect" criteria range of 0.80–1.25, whereas the C_{max} for ethinyl estradiol was marginally outside this range (0.99–1.33). The PK of tezacaftor and ivacaftor and their metabolites when coadministered with ethinyl estradiol/norethindrone were consistent with historical data.[3]

Plasma concentration-vs.-time profiles for midazolam, 1-hydroxymidazolam, ethinyl estradiol, and norethindrone have been provided in the supplementary materials (**Figures S1 and S2**).

Table 2 Effect of TEZ/IVA on PKs of digoxin, midazolam, EE, and NE

Drug coadministered with TEZ/IVA	Effect of TEZ/IVA on PK	GLSM ratio (90% CI) with/without TEZ/IVA[a]	
		AUC	C_{max}
Digoxin	↑	1.30 (1.17–1.45)	1.32 (1.07–1.64)
Midazolam	↔	1.12 (1.01–1.25)	1.13 (1.01–1.25)
EE	↔	1.12 (1.03–1.22)	1.15 (0.99–1.33)
NE	↔	1.05 (0.98–1.12)	1.01 (0.87–1.19)

AUC, area under the curve; CI, confidence interval; C_{max}, peak plasma concentration; EE, ethinyl estradiol; GLSM, geometric least squares mean; IVA, ivacaftor; NE, norethindrone; PKs, pharmacokinetics; TEZ, tezacaftor.
[a]No effect ratio = 1.0. No clinical significance boundaries for 90% CI, 0.80–1.25; if the 90% CI is outside this range, clinical significance is determined by therapeutic index. TEZ/IVA was administered as morning fixed-dose combination tablet (TEZ 100 mg/IVA 150 mg) and evening tablet (IVA 150 mg). All study drugs were administered orally in the fed state (digoxin 0.5 mg single dose, midazolam 2.0 mg single dose, EE 35 μg/NE 1,000 μg q.d.).

Effects of CYP3A inhibitors on tezacaftor/ivacaftor. **Figure 4** shows the plasma concentration-vs.-time profiles of tezacaftor, ivacaftor, and their major circulating metabolites

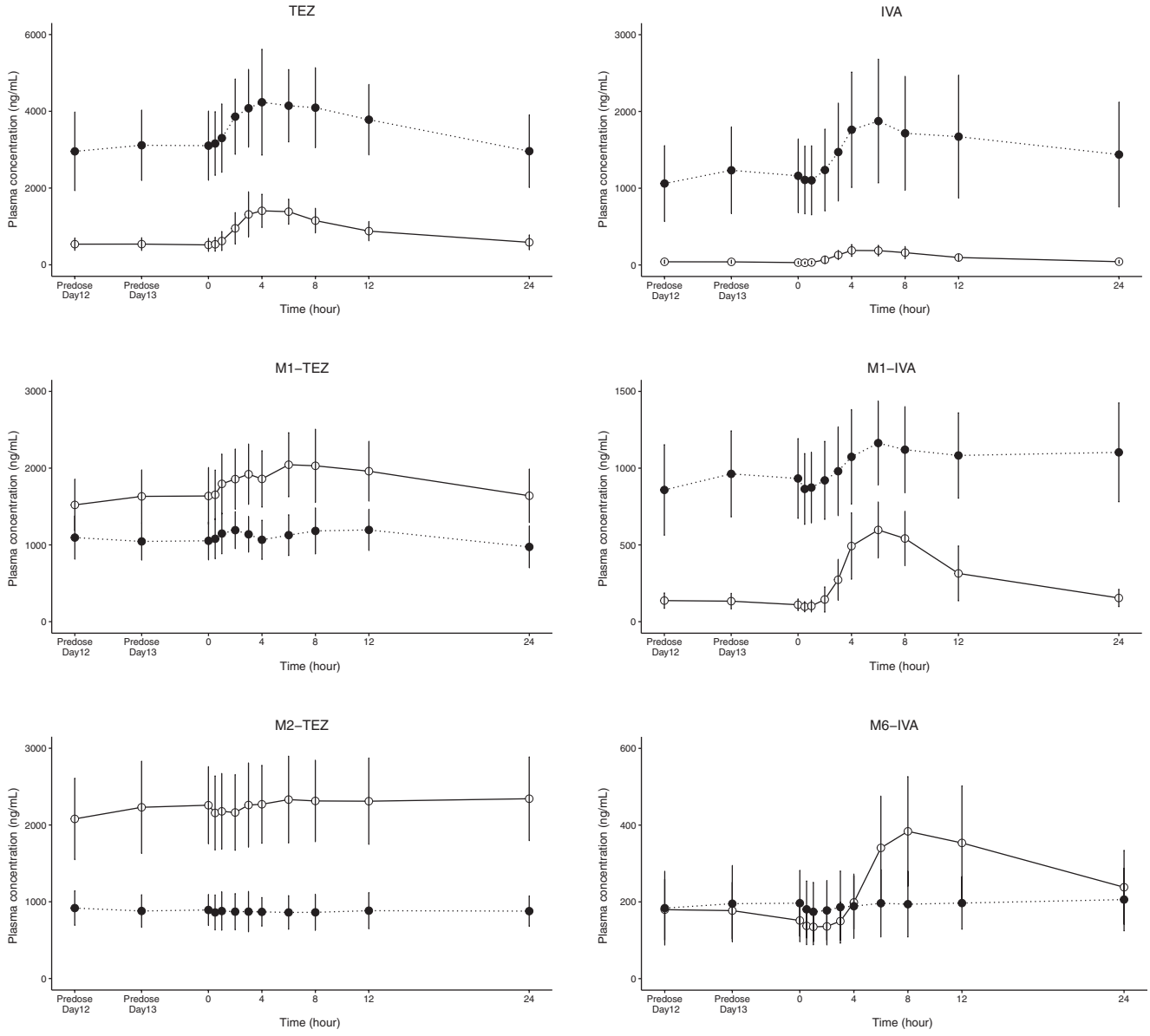

Figure 4 Mean (SD) plasma concentration-vs.-time profiles of tezacaftor, ivacaftor, and their metabolites at steady-state dosing in the absence or presence of itraconazole. Representative data are from study 006 cohort 1. PK profiles are presented for administration of TEZ 25 mg q.d./IVA 50 mg q.d. in the absence (open circles) or presence (closed circles) of itraconazole. For the closed circles, days 12–14 correspond to period 2, days 26–28 (coadministration of itraconazole). IVA, ivacaftor; PK, pharmacokinetic; TEZ, tezacaftor.

after 14 days of administration to healthy subjects in the fed state in the absence or presence of itraconazole co-administration. Predose levels on days 12–14 show that steady state for tezacaftor, ivacaftor, and their metabolites were achieved. When tezacaftor/ivacaftor was administered in combination with the strong CYP inhibitor itraconazole, the AUC of tezacaftor increased by 4-fold (GLSM ratio: 4.02; 90% CI: 3.71–4.63) and the AUC of ivacaftor increased by 15.6-fold (GLSM ratio: 15.60; 90% CI: 13.40–18.10; **Table 3**). Predose levels of itraconazole and its metabolite, hydroxyitraconazole (which contributes to CYP3A inhibitory activity), show that steady state was achieved (**Figure S4**). There was also an increase in the GLSM ratio of C_{max} for tezacaftor (2.8-fold) and ivacaftor (8.6-fold). Although M1-IVA AUC increased 3.6-fold and C_{max} increased 1.8-fold, the AUC of M6-IVA decreased by 30%, and C_{max} decreased by 46%. The AUC and C_{max} of M1-TEZ decreased by ~ 40%, and M2-TEZ AUC and C_{max} decreased by ~ 60%. Collectively, these data demonstrate that strong CYP3A inhibitors may increase exposure of tezacaftor, ivacaftor, and M1-IVA. Ivacaftor results are consistent with those previously seen with ivacaftor coadministered with ketoconazole.[6]

Ciprofloxacin (750 mg q12 h), which is a moderate CYP3A inhibitor commonly used by patients with CF, did not have a significant effect on the AUC or C_{max} of tezacaftor or ivacaftor when administered with tezacaftor 50 mg q12 h and

Table 3 Effects of itraconazole and ciprofloxacin on the PKs of TEZ, IVA, and their metabolites

Drug coadministered with TEZ/IVA	Effect	GLSM ratio (90% CI) with/without itraconazole or ciprofloxacin[a]	
		AUC	C_{max}
Effect of itraconazole and ciprofloxacin on the PK of TEZ and IVA			
	Effect on TEZ		
Itraconazole[b]	↑	4.02 (3.71–4.63)	2.83 (2.62–3.07)
Ciprofloxacin[c]	↔	1.08 (1.03–1.13)	1.05 (0.99–1.11)
	Effect on IVA		
Itraconazole[b]	↑	15.60 (13.40–18.10)	8.60 (7.41–9.98)
Ciprofloxacin[c]	↔	1.17 (1.06–1.30)	1.18 (1.06–1.31)
Effect of itraconazole and ciprofloxacin on the PK of M1-IVA and M6-IVA			
	Effect on M1-IVA		
Itraconazole[b]	↑	3.56 (3.32–3.82)	1.80 (1.66–1.95)
Ciprofloxacin[c]	↔	1.09 (1.00–1.18)	1.10 (1.03–1.18)
	Effect on M6-IVA		
Itraconazole[b]	↓	0.71 (0.62–0.80)	0.53 (0.46–0.62)
Ciprofloxacin[c]	↔	0.97 (0.90–1.06)	0.96 (0.86–1.06)
Effect of itraconazole and ciprofloxacin on the PK of M1-TEZ and M2-TEZ			
	Effect on M1-TEZ		
Itraconazole[b]	↓	0.60 (0.55–0.66)	0.60 (0.54–0.66)
Ciprofloxacin[c]	↔	1.19 (1.14–1.24)	1.17 (1.12–1.23)
	Effect on M2-TEZ		
Itraconazole[b]	↓	0.39 (0.36–0.42)	0.39 (0.36–0.42)
Ciprofloxacin[c]	↔	1.25 (1.20–1.31)	1.24 (1.18–1.29)

AUC, area under the curve; CI, confidence interval; C_{max}, peak plasma concentration; GLSM, geometric least squares mean; IVA, ivacaftor; PKs, pharmacokinetics; TEZ, tezacaftor.
[a]No effect ratio = 1.0. No clinical significance boundaries for 90% CI, 0.80–1.25; if the 90% CI is outside this range, clinical significance is determined by therapeutic index.
[b]TEZ 25 mg and IVA 50 mg were administered orally in the fed state. Itraconazole 200-mg solution was administered orally after an overnight fast, 1 hour before administration of TEZ/IVA.
[c]Ciprofloxacin 50 mg q12 h was administered orally in the fed state. TEZ/IVA was administered orally in the fed state as separate tablets (TEZ 50 mg q12 h, IVA 150 mg q12 h).

ivacaftor 150 mg q12 h (**Table 3**). For AUC, GLSM ratios were 1.08 (90% CI: 1.03–1.13) for tezacaftor and 1.17 (90% CI: 1.06–1.30) for ivacaftor. In addition, ciprofloxacin did not have an effect on AUC or C_{max} of the metabolites M1-IVA or M6-IVA, with GLSM ratios ranging from 0.96–1.10. Although the GLSM ratio range for AUC and C_{max} of the metabolites M1-TEZ or M2-TEZ was slightly higher (1.17–1.25), they fell within the default no-effect boundaries of 0.80–1.25.

Effects of tezacaftor/ivacaftor on P-gp substrate. Administration of tezacaftor 100 mg q.d./ivacaftor 150 mg q12 h increased exposure of digoxin compared with digoxin alone (**Table 2**). Digoxin AUC and C_{max} increased by 30% and 32%, respectively. The mean (SD) renal clearance of digoxin decreased only slightly, from 7.71 (1.29) L/h to 7.26 (1.62) L/h. Plasma and urine concentration-vs.-time profiles for digoxin have been provided in the supplementary materials (**Figure S3**).

DISCUSSION

Tezacaftor/ivacaftor treats the underlying cause of CF, defective function and quantity of CFTR at the cell membrane. It is intended to be taken concomitantly with other medications that manage CF symptoms. Therefore, the DDI profile of tezacaftor/ivacaftor is an important consideration. Consistent with the *in vitro* findings that both tezacaftor and ivacaftor are substrates of CYP3A, coadministration of itraconazole was associated with significant increases in the exposures of tezacaftor and ivacaftor. Ivacaftor is a sensitive CYP3A substrate[6]; results of the current study with itraconazole confirmed this and also showed that tezacaftor is not as sensitive a substrate of CYP3A as ivacaftor. This is consistent with *in vitro* metabolism data that show that tezacaftor can undergo additional phase II glucuronidation, whereas ivacaftor is almost exclusively cleared via CYP3A-mediated metabolism. Because ivacaftor is a sensitive CYP3A substrate, itraconazole can be expected to also decrease the first-pass metabolism and increase its oral bioavailability to a greater extent than tezacaftor. This may explain the larger increase in exposure of ivacaftor (15.6-fold) when coadministered with itraconazole compared with the increase in tezacaftor (4-fold).

Based on its effects on digoxin, ivacaftor has been previously shown to be a weak inhibitor of P-gp.[6] In the current study, tezacaftor/ivacaftor was also found to be a weak inhibitor of P-gp, with the same magnitude of effect on digoxin. Therefore, coadministration of tezacaftor/ivacaftor may increase systemic exposure of medicinal

products that are sensitive substrates of P-gp, which may increase or prolong their therapeutic effects and may result in adverse reactions. Caution and appropriate monitoring are recommended when tezacaftor/ivacaftor is administered with digoxin or other P-gp substrates with a narrow therapeutic index, such as cyclosporine, everolimus, sirolimus, and tacrolimus.[3] Given that the effect of tezacaftor/ivacaftor on digoxin renal clearance was less than its effect on systemic digoxin exposure, inhibition of gastrointestinal P-gp is likely more impactful than the effect on renal P-gp.

Unlike ivacaftor alone,[6] which increased midazolam exposure by 50%, tezacaftor/ivacaftor did not increase midazolam to a clinically significant level. Based on *in vitro* data, tezacaftor is unlikely to be an inhibitor or inducer of CYP3A and, in clinical studies, ivacaftor PK is not significantly altered in the presence of tezacaftor (and conversely, ivacaftor did not affect tezacaftor PK). Thus, it is not clear why the combination of tezacaftor and ivacaftor had less of an effect on midazolam than ivacaftor alone. Other than this difference in midazolam, the DDI profile of tezacaftor/ivacaftor as a perpetrator is comparable to the profile of ivacaftor alone. Consistent with the effects of ivacaftor alone, tezacaftor/ivacaftor had no significant effect on the PK of ethinyl estradiol and norethindrone, common components of COCs. The DDI profile of tezacaftor/ivacaftor is noteworthy when compared with that of the CFTR modulator lumacaftor, which is a strong inducer of CYP3A. Ivacaftor is a sensitive CYP3A substrate, and administration of lumacaftor with ivacaftor resulted in ~ 80% decrease in ivacaftor exposure.[9] Furthermore, administration of lumacaftor/ivacaftor may decrease systemic exposure of medicinal products that are substrates of CYP3A, thereby decreasing their therapeutic effect.[9] Administration of lumacaftor/ivacaftor is not recommended with sensitive CYP3A substrates, so tezacaftor/ivacaftor is an important treatment alternative to lumacaftor/ivacaftor for patients who could benefit from medications that are metabolized by CYP3A, including hormonal contraceptives and certain immunosuppressants.

The marketed regimen of tezacaftor/ivacaftor is administered as two tablets: a tezacaftor 100 mg/ivacaftor 150 mg fixed-dose combination (FDC) tablet in the morning and an ivacaftor 150 mg tablet in the evening. Based on the results of the study with itraconazole, when administered with strong inhibitors of CYP3A, the tezacaftor/ivacaftor dose should be reduced to 1 FDC tablet twice weekly, taken ~ 3–4 days apart, with no evening dose of ivacaftor, which results in a 3.5-fold and 7-fold reduction in tezacaftor and ivacaftor doses, respectively. When tezacaftor/ivacaftor is administered with moderate CYP3A inhibitors, one FDC tablet should be administered every other day (e.g., days 1, 3, and 5) and one ivacaftor tablet should be administered on the alternate days (e.g., days 2, 4, and 6), providing a 50% reduction in the dose of tezacaftor and ivacaftor. The recommended dose reductions for tezacaftor and ivacaftor in the setting of strong or moderate CYP3A inhibition were selected to provide similar overall exposure (i.e., daily or weekly AUC), relative to full-dose tezacaftor/ivacaftor. The dose reductions for ivacaftor are also consistent with those recommended for ivacaftor monotherapy.[6]

Ciprofloxacin, a commonly used antibiotic for treatment of CF-related lung infections, has previously been characterized as a moderate inhibitor of CYP3A.[8] In this study, ciprofloxacin had no meaningful effect on tezacaftor or ivacaftor exposures, and no dose adjustment is needed when tezacaftor/ivacaftor is administered with ciprofloxacin, consistent with previous data showing no effect on ivacaftor exposure when ivacaftor is administered as monotherapy.[6] The lack of effect of ciprofloxacin on ivacaftor, a sensitive CYP3A substrate, suggests that ciprofloxacin is not an inhibitor of CYP3A when administered at a dose of 750 mg q12 h.

CONCLUSIONS

In clinical studies with healthy subjects, the combination of tezacaftor and ivacaftor did not inhibit or induce CYP3A enzymes but was shown to be a weak inhibitor of P-gp. Therefore, tezacaftor/ivacaftor can be used with other classes of commonly used drugs, including CYP3A substrates, such as hormonal contraceptives. Tezacaftor/ivacaftor may increase systemic exposure of sensitive P-gp substrates, which may increase or prolong their therapeutic effect and may increase adverse reactions. Coadministration with itraconazole increased the systemic exposures of tezacaftor and ivacaftor; tezacaftor/ivacaftor dosing should be reduced when strong or moderate CYP3A inhibitors are coadministered. However, no dose adjustment is necessary during coadministration with ciprofloxacin (currently classified as a moderate CYP3A inhibitor), which had no clinically relevant effect on the exposure of tezacaftor or ivacaftor.

Supporting Information. Supplementary information accompanies this paper on the *Clinical and Translational Science* website (www.cts-journal.com).

Figure S1. Mean (SD) plasma concentration-vs.-time profiles of midazolam and 1-hydroxymidazolam after oral administration of midazolam with and without TEZ/IVA.
Figure S2. Mean (SD) plasma concentration-vs.-time profiles of ethinyl estradiol and norethindrone after administration of oral contraceptive with and without TEZ/IVA.
Figure S3. Mean (SD) digoxin plasma and urine concentration-vs.-time profiles after oral administration of digoxin with and without TEZ/IVA.
Figure S4. Mean (SD) predose plasma concentrations of itraconazole and hydroxyitraconazole during coadministration of itraconazole with tezacaftor/ivacaftor.

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