A Phase 1 Drug Interaction Study Evaluating the Effects of Itraconazole on the Pharmacokinetics, Safety, and Tolerability of Etrasimod in Healthy Volunteers

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BACKGROUND

- Etrasimod, a once-daily (QD), oral, selective sphingosine 1-phosphate receptor modulator in clinical development for immune-mediated inflammatory disorders, is a substrate of cytochrome P450s (CYP450s) including CYP2C8, CYP2C9, CYP3A4, and, to a minor extent, CYP2C19 and CYP2J2[1]
- Drug-drug interactions (DDIs) can cause significant changes in the exposure of a drug and/or its major circulating metabolites, potentially leading to altered therapeutic efficacy and/or enhanced toxicity
- Etrasimod (the parent drug) is the most prevalent drug-related component in the systemic circulation and has no major circulating metabolites
- Etrasimod has the potential for DDIs with strong to moderate inhibitors or inducers of CYP2C8, CYP2C9, or CYP3A4
- Etrasimod was previously evaluated in the presence and absence of fluconazole (moderate CYP2C9 and CYP3A4 inhibitor; strong CYP2C19 inhibitor)[2]; etrasimod total plasma exposure measures increased moderately, up to 84% in the presence vs absence of fluconazole, most likely due to inhibition of both CYP2C9 and CYP3A4
  - When coadministered with rifampin (strong CYP2C19 and CYP3A4 inducer; moderate CYP2C8 and CYP2C9 inducer), etrasimod plasma exposure was previously shown to be reduced by approximately 50%[2]
  - It is therefore of interest to determine the relative effect of CYP3A4 inhibition only on etrasimod exposure measures
- This open-label, phase 1 study evaluated the pharmacokinetics (PK) and safety of etrasimod in the presence and absence of itraconazole, a strong CYP3A4 inhibitor[3]

CONCLUSIONS

- The results of this study further demonstrate that CYP3A4 is just one of several CYP isoforms, along with CYP2C8 and CYP2C9, primarily involved in the disposition of etrasimod
- The mild increases in etrasimod exposure seen with coadministration of etrasimod and itraconazole were not considered clinically relevant
- The involvement of multiple CYP isoforms reduces the likelihood of etrasimod having a clinically relevant DDI, particularly in cases where only a single CYP isoform is strongly or moderately inhibited/induced by a coadministered drug
- No serious adverse events or deaths were reported in this study

Disclosures

All authors are employees of Arena Pharmaceuticals, a wholly-owned subsidiary of Pfizer Inc, New York, NY, USA.

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References

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METHODS

Patient Population and Trial Design

- This single-center, phase 1, open-label, 2-period, fixed-sequence, crossover study planned to enroll 18 healthy male and female volunteers
- Individuals were enrolled if they met the following criteria:
  - 18 to 55 years of age
  - Body mass index of 18.0 to 30.0 kg/m^2
  - In good general health, including free from clinically significant medical or psychiatric illness or disease
  - Nonpregnant
- The study consisted of a screening period including from days −28 to −1, admission to the clinical unit on day −1, and a treatment period from day 1 until discharge on day 23 (**Figure 1**)
- Subjects were enrolled in a treatment group that included 2 dosing periods
  - Period 1: Etrasimod (1-mg tablet formulation) was administered alone as a single dose on day 1 followed by a washout period between days 2-9
  - Period 2: Starting on day 10, participants received an itraconazole solution (10 mg/mL) at a dose of 200 mg QD for 13 days. Etrasimod was given as a single dose in the presence of itraconazole 200 mg QD on day 14
- Subjects received etrasimod in the morning (on days 1 and 14) after an overnight fast of ≥8 hours; fasting restrictions continued (no food or drink other than water) for ≥2 hours post etrasimod dose
- Blood samples for the plasma PK analysis of etrasimod were collected on days 1 and 14 at predose (within 15 minutes before dosing with etrasimod) and through 216 hours post etrasimod dose

Figure 1. Overview of Study Design

Screening period		Treatment period (days) Confinement period (in-house stay)																	Follow-up phone call
Screening	Admission	Dosing period 1 Etrasimod 1 mg[a]		Dosing period 2 Itraconazole 200 mg (10 mg/mL) + etrasimod 1 mg[a]														Discharge	
Days −28 to −2	Day −1	1	2 to 9 Washout	10	11	12	13	14	15	16	17	18	19	20	21	22	23		Day 30 ± 3 days
		↑ Etrasimod 1 mg						↑ Etrasimod 1 mg											

[a] Overnight fast of ≥8 hours before etrasimod dose in dosing periods 1 and 2. Itraconazole solution (10 mg/mL) was administered at a dose of 200 mg once-daily for 13 days.

PK Endpoints

- Primary PK endpoints for etrasimod were maximum plasma concentration (C_{max}), area under the plasma–concentration curve (AUC) from time zero to the time of the last quantifiable concentration, and AUC from time zero to infinity and were determined in the presence and absence of itraconazole
- Secondary PK endpoints included (but were not limited to) AUC from 0 to 168 hours, time for compound to reach C_{max} (t_{max}), apparent terminal elimination half-life ($t_{1/2}$), total body clearance after oral administration (CL/F), and apparent volume of distribution after oral administration based on the terminal phase (Vz/F)

Safety and Tolerability Endpoints

- Subjects were continuously evaluated for safety during the screening period, in-house treatment period, and follow-up call
- Safety endpoints of the study included the following:
  - Treatment-emergent adverse events (TEAEs)
  - Clinical laboratory test results (hematologic tests, clinical chemistry analyses, urinalysis)
  - Vital signs (blood pressure, heart rate, temperature, respiratory rate)
  - Standard 12-lead electrocardiogram

Data Analysis

- PK parameters were calculated by the noncompartmental analysis method from concentration-time data using Phoenix WinNonlin, version 8.2 (Pharsight)
- Log-transformed primary PK parameters were compared using an analysis of variance with treatment as the fixed effect and subject as the random effect
- The geometric least-squares mean ratio (presence/absence of itraconazole) and 90% CIs were calculated by group for each primary PK parameter

RESULTS

Patient Demographics

- This study enrolled a total of 19 subjects consisting of 13 men (68.4%) and 6 women (31.6%); overall, mean (SD) age was 32.0 (8.1) years (**Table 1**)
  - One subject withdrew from the study before completion, resulting in a total of 18 subjects (94.7%) who completed the study and contributed to the evaluable PK data set

Table 1. Summary of Study Subject Demographic and Anthropometric Characteristics[a]

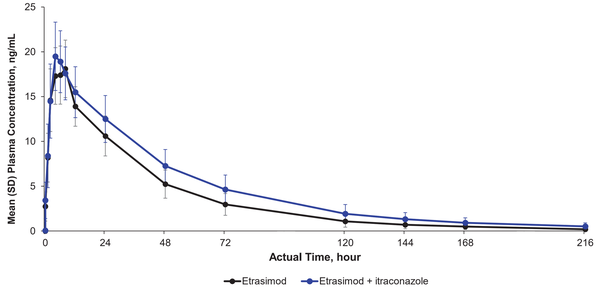
Characteristic, n (%)	Overall (N=19)
Age, mean (SD), years	32.0 (8.1)
Sex, n (%)	
Male	13 (68.4)
Female	6 (31.6)
Race, n (%)	
White	8 (42.1)
Black or African American	6 (31.6)
Asian	2 (10.5)
Asian, Korean	1 (5.3)
Other	2 (10.5)
Ethnicity, n (%)	
Hispanic or Latino	5 (26.3)
Not Hispanic or Latino	14 (73.7)
Height, mean (SD), cm	171.9 (8.6)
Weight, mean (SD), kg	75.7 (11.4)
BMI, mean (SD), kg/m^2	25.6 (2.9)

BMI, body mass index.
[a] Data are derived from the safety analysis set and include all subjects who received ≥1 dose of study treatment.

Etrasimod Plasma Concentration–Time Profiles

- Etrasimod absorption was rapid, with quantifiable etrasimod plasma concentrations observed at the first postdose time point (0.5 hours) in both dosing periods (**Figure 2**)
- Across evaluated time points, mildly higher mean plasma concentrations of etrasimod were typically seen in the presence (dosing period 2) vs absence of itraconazole (dosing period 1)

Figure 2. Mean Plasma Concentration–Time Profiles for Etrasimod in the Absence (Dosing Period 1) and Presence (Dosing Period 2) of Itraconazole



Etrasimod Plasma PK Parameters

- Itraconazole had little or no impact on the single-dose C_{max} of etrasimod but mildly increased AUC by ≤32% (**Tables 2** and **3**)
- Mean $t_{1/2}$ of etrasimod increased from 38.7 to 44.7 hours in the presence of itraconazole (**Table 2**)

Table 2. Etrasimod PK Parameters in the Absence and Presence of Itraconazole

Etrasimod PK parameter, mean (SD)	Etrasimod 1 mg (n=18)	Etrasimod 1 mg + itraconazole (n=18)
C_{max}, ng/mL	18.8 (3.3)	19.9 (3.5)
t_{max}, h[a]	6.0 (2.0-8.1)	4.0 (4.0-8.0)
$AUC_{0\text{-}168h}$, ng•h/mL	729 (181)	943 (236)
AUC_{last}, ng•h/mL	741 (195)	976 (258)
$AUC_{0\text{-}\infty}$, ng•h/mL	763 (207)	1020 (281)
$t_{1/2}$, h	38.7 (10.6)	44.7 (8.6)
CL/F, L/h	1.39 (0.306)	1.05 (0.265)
Vz/F, L	74.7 (19.2)	66.1 (14.9)

$AUC_{0\text{-}\infty}$, area under the plasma concentration–time curve from time zero to infinity; $AUC_{0\text{-}168h}$, area under the plasma concentration–time curve from 0 to 168 hours; AUC_{last}, area under the plasma concentration–time curve from time zero to the time of the last quantifiable concentration; CL/F, total body clearance after oral administration; C_{max}, maximum plasma concentration; PK, pharmacokinetic; $t_{1/2}$, apparent terminal elimination half-life; t_{max}, time to maximum concentration determined directly from the concentration–time profile; Vz/F, apparent volume of distribution after oral administration.
[a] Median (range) shown for t_{max}.

Table 3. Statistical Comparison of Etrasimod Primary PK Exposure Parameters in the Absence and Presence of Itraconazole

Analyte	C_{max}, GLSMR (90% CI)	AUC_{last}, GLSMR (90% CI)	$AUC_{0\text{-}\infty}$, GLSMR (90% CI)
	(Etrasimod + Itraconazole)/(Etrasimod)		
Etrasimod	1.06 (1.02-1.11)	1.31 (1.26-1.37)	1.32 (1.27-1.38)

$AUC_{0\text{-}\infty}$, area under the plasma concentration–time curve from time zero to infinity; AUC_{last}, area under the plasma concentration–time curve from time zero to the time of the last quantifiable concentration; C_{max}, maximum plasma concentration; GLSMR, geometric least-squares mean ratio; PK, pharmacokinetic.

Etrasimod Safety and Tolerability

- A total of 19 subjects were included in the Safety Set
- Overall, a total of 21 TEAEs were reported in 47.4% (9/19) of subjects; all TEAEs were grade 1 (mild)
  - In dosing period 1, all TEAEs were singular events; in dosing period 2, the most frequently reported TEAEs were nausea (3 subjects [15.8%]) and diarrhea (2 subjects [10.5%]), and all other TEAEs were singular events
- No clinically relevant abnormalities were observed in the findings from physical examination, laboratory parameters, vital signs, or 12-lead electrocardiograms
- No deaths or serious AEs occurred in this study