Pharmacokinetics, Safety, and Tolerability of Etrasimod: Results From a Phase 1 Drug-Drug Interaction Study in Healthy Volunteers

E0361

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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 P450 (CYP)2C8, CYP2C9, CYP3A4, and, to a minor extent, CYP2C19 and CYP2J2[1]
- Maximum plasma concentration (C_{max}) determined directly from concentration-time profile and area under the concentration-time curve (AUC) values of etrasimod are dose proportional following a single dose of 0.1 to 5 mg
- Drug-drug interactions (DDIs) can cause significant changes in the exposure of a drug, leading to either reduced therapeutic efficacy or enhanced toxicity
- Etrasimod has the potential for DDIs with strong to moderate inhibitors or inducers of CYP2C8, CYP2C9, and CYP3A4
- This open-label phase 1 study evaluated the pharmacokinetics (PK) and safety of etrasimod in the presence and absence of fluconazole (moderate CYP2C9 and CYP3A4 inhibitor; strong CYP2C19 inhibitor), gemfibrozil (strong CYP2C8 inhibitor), or rifampin (moderate CYP2C8 and CYP2C9 inducer; strong CYP3A4 and CYP219 inducer)[2]

CONCLUSIONS

- The results of this study are consistent with CYP2C8, CYP2C9, and CYP3A4 being involved in etrasimod metabolism, with no single enzyme appearing to dominate its elimination
- The involvement of multiple CYP isoforms reduces the likelihood of etrasimod having a clinically relevant DDI when only a single CYP isoform is strongly or moderately inhibited/induced by a coadministered drug
  - However, given the multiple CYP isoform inhibition or induction with fluconazole and rifampin, respectively, coadministration of etrasimod with these drugs is not recommended

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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2. US Food and Drug Administration. https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers. Accessed May 16, 2022

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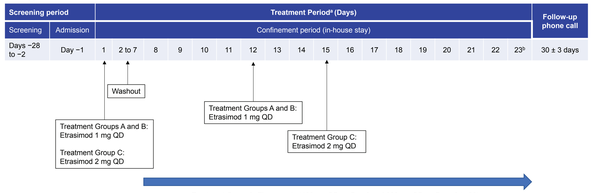
METHODS

Patient Population and Trial Design

- In this single-center, phase 1, open-label, parallel-group, 2-period, fixed-sequence study, 56 healthy male and female volunteers were enrolled
- Individuals were enrolled if they met the following criteria:
  - Aged 18 to 55 years
  - 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
- Subjects were enrolled in 1 of 3 treatment groups (A, B, or C, as depicted in **Figure 1**), each of which included 2 periods:
  - Period 1: Etrasimod (1-mg strength immediate-release [IR] tablet formulation for groups A and B; 2-mg strength IR tablet formulation for group C) was administered alone followed by a 7-day washout prior to starting any perpetrator drug
  - Period 2: Etrasimod was given as a single dose in the presence of a perpetrator drug
- Perpetrator drugs were fluconazole (group A: 400-mg loading dose followed by 200 mg QD), gemfibrozil (group B: 600 mg twice daily), and rifampin (group C: 600 mg QD)
- On applicable study days in all 3 groups, subjects received etrasimod in the morning after an overnight fast of ≥10 hours; fasting restrictions continued (no food or drink other than water) for ≥2 hours post etrasimod dose
- The study consisted of a screening period 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**)
- 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



BID, twice daily; QD, once daily.
[a] Dosing period 1, day 1; dosing period 2, days 8 to 22.
[b] Subjects were discharged from the clinical unit on day 23.

Primary PK Endpoints

- Primary PK endpoints were C_{max}, AUC from 0 to 168 hours, and AUC from time zero to infinity of etrasimod in the presence and absence of fluconazole, gemfibrozil, or rifampin
- Secondary PK endpoints included time for compound to reach C_{max} (t_{max}), terminal elimination half-life ($t_{½}$), 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 (hematology, clinical chemistry, urinalysis)
  - Vital signs (blood pressure, heart rate, temperature, respiratory rate)
  - Standard 12-lead electrocardiogram

Data Analysis

- PK parameters were calculated by the noncompartmental analysis from concentration-time data using Phoenix WinNonlin (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 perpetrator) and 90% CIs were calculated by group for each primary PK parameter

RESULTS

Patient Demographics

- The study population consisted of 36 male subjects (64.3%) and 20 female (35.7%) subjects; overall, mean (SD) age was 37.0 (10.1) years (**Table 1**)
- A total of 19 subjects were assigned to group A, 19 to group B, and 18 to group C

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

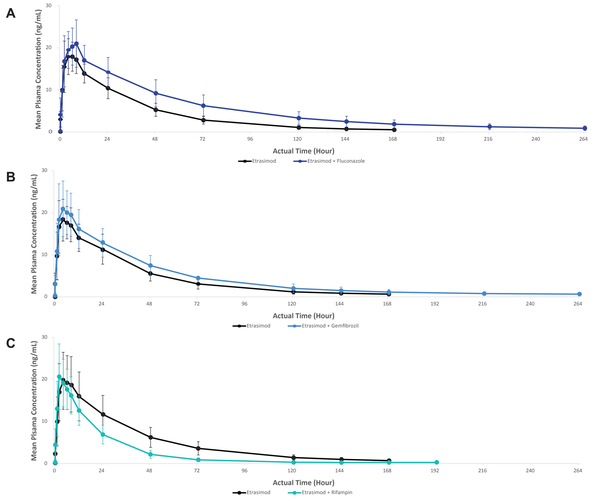
Characteristic, n (%)	Overall (N=56)	Group A (n=19)	Group B (n=19)	Group C (n=18)
Age, mean (SD), years	37.0 (10.1)	35.3 (10.4)	36.4 (10.6)	39.4 (9.1)
Male, n (%)	36 (64.3)	14 (73.7)	7 (36.8)	15 (83.3)
Race, n (%)				
White	14 (25.0)	4 (21.1)	3 (15.8)	7 (38.9)
Asian	2 (3.6)	2 (10.5)	0	0
Black or African American	40 (71.4)	13 (68.4)	16 (84.2)	11 (61.1)
Ethnicity, n (%)				
Hispanic or Latino	11 (19.6)	2 (10.5)	4 (21.1)	5 (27.8)
Non-Hispanic or Latino	45 (80.4)	17 (89.5)	15 (78.9)	13 (72.2)
Height, mean (SD), cm	170.5 (10.9)	169.5 (10.2)	170.4 (14.1)	171.7 (7.6)
Weight, mean (SD), kg	77.0 (13.9)	73.5 (14.2)	77.1 (16.5)	80.6 (9.5)
BMI, mean (SD), kg/m^2	26.3 (2.6)	25.4 (2.9)	26.3 (2.4)	27.3 (2.3)

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 relatively rapid, with plasma concentrations observed at the first post-dose time point (0.5 hours) (**Figure 2**)
- Moderate and mild increases in systemic exposure of etrasimod occurred in the presence of fluconazole and gemfibrozil, respectively
- A moderate decrease in systemic exposure of etrasimod was observed in the presence of rifampin

Figure 2. Plasma Concentration-Time Profiles for Etrasimod in the Absence and Presence of (A) Fluconazole, (B) Gemfibrozil, or (C) Rifampin



Etrasimod Plasma PK Parameters

- In group A, fluconazole had little or no impact on the single-dose C_{max} of etrasimod but increased AUC by ≤84% (**Tables 2** and **3**), consistent with fluconazole being a moderate inhibitor of CYP2C9 and CYP3A4 and strong inhibitor of CYP2C19
- In group B, gemfibrozil had little or no impact on the single-dose C_{max} of etrasimod but increased AUC by ≤36% (**Tables 2** and **3**), consistent with gemfibrozil being a strong inhibitor of CYP2C8
- In group C, rifampin appeared to slightly increase the single-dose C_{max} of etrasimod but moderately decreased AUC by ≤50% (**Tables 2** and **3**), with the latter consistent with rifampin being a moderate inducer of CYP2C8 and CYP2C9 and strong inducer of CYP3A4 and CYP2C19
- Mean $t_{½}$ of etrasimod increased from 43 to 88 hours in the presence of fluconazole and from 46 to 73 hours in the presence of gemfibrozil and decreased by approximately half in the presence of rifampin (**Table 2**)
  - The longer post-dose sampling times in period 2 (compared with period 1) for groups A and B may also have contributed, at least in part, to the observed $t_{½}$ increases in period 2

Table 2. Etrasimod PK Parameters in the Absence and Presence of Fluconazole, Gemfibrozil, and Rifampin

PK parameter, mean (SD)	Group A: Etrasimod 1 mg (day 1) (n=18)	Group A: Etrasimod 1 mg + fluconazole (day 12) (n=18)	Group B: Etrasimod 1 mg (day 1) (n=18)	Group B: Etrasimod 1 mg + gemfibrozil (day 12) (n=18)	Group C: Etrasimod 2 mg (day 1) (n=18)	Group C: Etrasimod 2 mg + rifampin (day 15) (n=18)
C_{max}, ng/mL	19.0 (4.4)	21.4 (5.4)	19.5 (5.0)	22.0 (6.6)	34.2 (11.1)	36.0 (11.8)
t_{max}, h[a]	5.0 (2.0-8.0)	7.0 (4.0-8.1)	4.0 (2.0-24.1)	4.0 (2.0-8.0)	4.0 (2.0-8.0)	2.0 (2.0-6.0)
$AUC_{0\text{-}168h}$, ng•h/mL	726 (178)	1200 (381)	763 (213)	976 (304)	1450 (460)	765 (237)
$AUC_{0\text{-}\infty}$, ng•h/mL	759 (196)	1440 (514)	802 (232)	1100 (381)	1510 (488)	770 (243)
$t_{½}$, h	42.5 (7.6)	88.2 (16.7)	45.6 (7.2)	72.6 (18.9)	41.1 (8.1)	20.9 (6.7)
CL/F, L/h	1.39 (0.287)	0.78 (0.255)	1.35 (0.384)	1.01 (0.351)	1.43 (0.378)	2.80 (0.834)
Vz/F, L	83.6 (17.4)	97.0 (32.3)	86.7 (22.0)	99.0 (23.0)	84.2 (23.6)	79.1 (18.7)

[a] Median (range) shown for t_{max}.
$AUC_{0\text{-}\infty}$, area under the plasma concentration–time curve from time 0 to infinity; $AUC_{0\text{-}168h}$, area under the plasma concentration–time curve from 0 to 168 hours; CL/F, total body clearance after oral administration; C_{max}, maximum plasma concentration; PK, pharmacokinetic; $t_{½}$, terminal elimination half-life; t_{max}, time of maximum concentration determined directly from the concentration-time profile; Vz/F, apparent volume of distribution after oral administration.

Table 3. Statistical Comparison of Etrasimod Primary PK Exposure Parameters in the Presence and Absence of Fluconazole, Gemfibrozil, or Rifampin

Analyte	C_{max}, GLSMR (90% CI), ng/mL	$AUC_{0\text{-}168h}$, GLSMR (90% CI), ng•h/mL	$AUC_{0\text{-}\infty}$, GLSMR (90% CI), ng•h/mL
	Group A (n=18): (Etrasimod + Fluconazole)/(Etrasimod)		
Etrasimod	1.12 (1.09-1.16)	1.62 (1.52-1.72)	1.84 (1.71-1.99)
	Group B (n=18): (Etrasimod + Gemfibrozil)/(Etrasimod)		
Etrasimod	1.12 (1.06-1.19)	1.27 (1.20-1.35)	1.36 (1.26-1.46)
	Group C (n=18): (Etrasimod + Rifampin)/(Etrasimod)		
Etrasimod	1.24 (0.82-1.88)	0.53 (0.49-0.56)	0.51 (0.47-0.54)

$AUC_{0\text{-}\infty}$, area under the plasma concentration–time curve from time 0 to infinity; $AUC_{0\text{-}168h}$, area under the plasma concentration–time curve from 0 to 168 hours; C_{max}, maximum plasma concentration; GLSMR, geometric least-squares mean ratio; PK, pharmacokinetic.

Etrasimod Safety and Tolerability

- All TEAEs were mild or moderate
  - One subject discontinued the study due to AEs
  - No clinically relevant abnormalities were found in laboratory parameters, vital signs, or 12-lead electrocardiograms
- No grade ≥3 TEAEs occurred, and reported TEAEs were predominantly mild
  - No deaths or serious AEs occurred in this study