P291

Pharmacokinetics, Safety, and Tolerability of Etrasimod (APD334) in Participants With Mild, Moderate, or Severe Hepatic Impairment: A Single-Dose, Open-Label, Parallel-Group Study

Caroline A. Lee, Yong Tang, Cassandra Schroeder, Jinkun Zhang, Thai Nguyen-Cleary, Michael Ma, Naomi Lyon, John S. Grundy

Arena Pharmaceuticals, Inc., San Diego, CA, USA.

BACKGROUND

- Etrasimod (APD334), a once-daily, oral, selective sphingosine 1-phosphate (S1P) receptor modulator designed to target $S1P_1$, $S1P_4$, and $S1P_5$, is in clinical development for the treatment of immune-mediated inflammatory disorders, including ulcerative colitis, Crohn's disease, eosinophilic esophagitis, and atopic dermatitis
- Etrasimod impedes the recruitment of peripheral lymphocytes to sites of inflammation[1,2]
- Liver disease can alter drug disposition and pharmacokinetics (PK), reducing hepatic or biliary clearance; plasma protein binding may also be affected, which could influence the efficacy and safety of a drug

OBJECTIVE

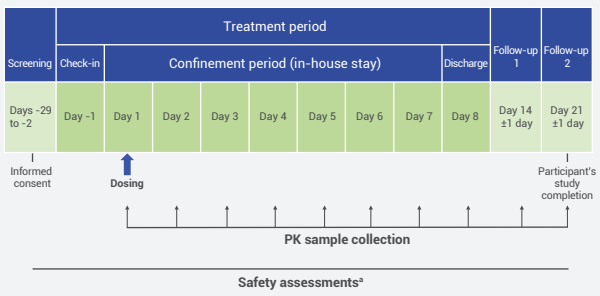
- To evaluate the effect of hepatic impairment on the PK, safety, and tolerability of etrasimod

METHODS

STUDY DESIGN

- This open-label, parallel-group, phase 1 study enrolled participants aged 18 to 80 years with a body mass index (BMI) ≥18
- Participants with mild, moderate, or severe hepatic impairment (based on Child-Pugh [CP] score at baseline) were enrolled and demographically matched (by age, sex, and BMI) with healthy control participants who had normal hepatic function
  - Mild hepatic impairment (CP score, 5-6; n=8)
  - Moderate hepatic impairment (CP score, 7-9; n=8)
  - Severe hepatic impairment (CP score, 10-14; n=6)
  - Normal hepatic function (n=14)
- The first participant with severe hepatic impairment was enrolled after ≥2 participants with mild and ≥2 participants with moderate hepatic impairment were enrolled and monitored for ≥48 hours after dosing to ensure no observed significant safety signals
- On day 1, participants received a single oral dose of etrasimod 2 mg after a ≥10-hour fast (**Figure 1**)
- Etrasimod concentrations were monitored via PK blood sampling for 21 days
- Safety was assessed by adverse event (AE) monitoring, vital signs, physical and neurological examinations, 12-lead electrocardiogram (ECG), and clinical laboratory evaluations

Figure 1. Study Design



[a]Safety was assessed from Informed consent to Follow-up 2.
For abbreviations, see below.

ANALYTIC METHODOLOGY

- Plasma concentrations of etrasimod were determined via liquid chromatography-tandem mass spectrometry (LC-MS/MS) from matrix-matched calibration curves between 0.25 to 100.0 ng/mL and 0.1 to 120.4 ng/mL for total etrasimod (bound + unbound) and unbound etrasimod, respectively
- Analyte LC-MS/MS quantitation reagents included an ACE C18 column, a 20-mM ammonium acetate/acetonitrile mobile phase, a Shimadzu LC pump and autosampler, and a Sciex API6500+ MS with an electrospray probe in negative multiple reaction monitoring

UNBOUND SAMPLE PREPARATION AND BIOANALYSIS

- Plasma protein-free supernatant was collected via ultracentrifugation at 223,000*g* for 4 hours
- Unbound etrasimod concentrations were only measured 4 hours post dose and results assumed to apply to other PK collection times
- For protein precipitation, acetonitrile was applied to a 1:1 mixed matrix of plasma:supernatant
- The positive control was warfarin

PK STATISTICAL METHODOLOGY

- Plasma concentrations and PK parameters C_{max}, t_{max}, AUC_{0-t}, AUC_{0-24}, $AUC_{0-\infty}$, $t_{1/2}$, CL/F, and V_z/F were summarized by hepatic function using descriptive statistics
  - Unbound etrasimod PK parameters were based on total etrasimod PK parameters adjusted by percent unbound
  - Mean plasma concentration-time profiles were presented graphically
  - Phoenix WinNonlin™ (Certara USA, Inc., Version 6.4 or higher) was used for PK analysis
- Based on a 1:1 matching, the calculated primary PK exposure parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ and the unbound PK exposure parameters $C_{max,u}$, $AUC_{0-t,u}$, and $AUC_{0-\infty,u}$ were analyzed using an analysis of covariance model for each comparison (eg, mild vs normal, moderate vs normal, and severe hepatic impairment group vs normal)
  - Age, sex, BMI, and body weight were evaluated as potential covariates
  - The participant was treated as random
- For each comparison, only matched participants were included in the analysis
- ESTIMATE and/or LSMEANS statements were used to calculate least squares (LS) means and 90% CIs for each hepatic group

RESULTS

PARTICIPANTS

- Thirty-six participants were enrolled and received etrasimod; 35 completed the study (1 participant in the severe hepatic impairment group was lost to follow-up)
  - The percentage of males and females was matched in each hepatic impairment and respective normal control group (**Table 1**)
  - Mean age and BMI were similar in the hepatic impairment and normal control groups (**Table 1**)

Table 1. Screening Demographic Data

	Mild hepatic impairment (n=8)	Matched controls (n=8)	Moderate hepatic impairment (n=8)	Matched controls (n=8)	Severe hepatic impairment (n=6)	Matched controls (n=6)
Age, mean (SD), years	57 (6.3)	53 (5.7)	58 (6.2)	55 (6.3)	55 (5.8)	55 (5.6)
Sex, n (%)						
Male	5 (62.5)	5 (62.5)	3 (37.5)	3 (37.5)	2 (33.3)	2 (33.3)
Female	3 (37.5)	3 (37.5)	5 (62.5)	5 (62.5)	4 (66.7)	4 (66.7)
Race, n (%)						
White	8 (100)	7 (87.5)	8 (100)	8 (100)	6 (100)	5 (83.3)
Black	0	1 (12.5)	0	0	0	1 (16.7)
Ethnicity, n (%)						
Hispanic or Latino	7 (87.5)	6 (75.0)	4 (50.0)	6 (75.0)	6 (100)	5 (83.3)
Not Hispanic or Latino	1 (12.5)	2 (25.0)	4 (50.0)	2 (25.0)	0	1 (16.7)
Weight, mean (SD), kg	97.5 (18.74)	86.6 (14.35)	93.0 (18.70)	89.0 (15.03)	76.5 (18.53)	75.9 (16.60)
Height, mean (SD), cm	164.1 (9.79)	167.1 (10.48)	162.9 (8.97)	165.6 (12.79)	158.9 (11.36)	162.0 (10.83)
BMI, mean (SD)	36.0 (4.46)	31.0 (4.48)	35.1 (7.14)	32.5 (5.15)	30.2 (5.99)	28.8 (5.85)

For abbreviations, see below.

ETRASIMOD PLASMA PK PARAMETERS

- Etrasimod mean plasma concentration-time profiles overlapped between the normal hepatic function and mild hepatic impairment groups and were slightly higher in the moderate and severe hepatic impairment groups (**Figure 2**; **Table 2**)
- Across all groups, etrasimod was absorbed with a median t_{max} ranging from 4 to 8 hours (**Table 2**)
- Etrasimod terminal $t_{1/2}$ only moderately increased as hepatic function decreased, with mean values ranging from 43.9 to 59.5 hours in the demographically matched normal control group and mean values of 55.7, 69.7, and 76.5 hours in the mild, moderate, and severe hepatic impairment groups, respectively (**Table 2**)

Figure 2. Arithmetic Mean Plasma Concentration-Time Profiles of Total Etrasimod

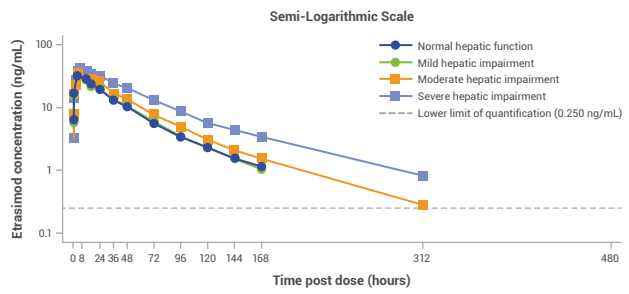


Table 2. Summary of Total Etrasimod Plasma PK Parameters

	Mild hepatic impairment (n=8)	Matched controls (n=8)	Moderate hepatic impairment (n=8)	Matched controls (n=8)	Severe hepatic impairment (n=6)	Matched controls (n=6)
C_{max}, ng/mL	31.6 (28.7)	33.4 (15.2)	31.5 (30.5)	35.3 (26.3)	42.0 (22.5)	40.5 (29.5)
t_{max}, h[a]	5.00 (2.00-12.00)	5.00 (1.98-8.08)	8.00 (4.00-12.00)	4.00 (1.98-8.00)	7.00 (4.00-12.00)	5.00 (1.98-8.00)
AUC_{0-t}, h•ng/mL	1350 (33.7)	1320 (20.5)	1710 (30.9)	1370 (21.3)	2570 (26.9)[a]	1710 (23.5)[b]
AUC_{0-24}, h•ng/mL	561 (30.0)	576 (15.9)	614 (29.9)	611 (20.1)	809 (20.7)	703 (22.2)
$AUC_{0-\infty}$, h•ng/mL	1390 (34.1)	1370 (20.1)	1760 (31.1)	1410 (20.3)	2730 (26.4)	1740 (20.6)
$t_{1/2}$, h	55.7 (33.8)	43.9 (14.9)	69.7 (39.2)	49.0 (16.6)	76.5 (15.0)	59.5 (14.8)
CL/F, L/h	1.44 (34.1)	1.46 (20.1)	1.13 (31.1)	1.42 (20.3)	0.732 (26.4)	1.15 (20.6)
V_z/F, L	102 (30.8)	88.4 (19.8)	102 (28.6)	95.4 (24.7)	79.3 (35.8)	95.9 (11.7)

Results are presented as geometric mean (geometric CV%) unless otherwise indicated. Median (min-max) is presented for t_{max}. Arithmetic mean (SD) is presented for $t_{1/2}$.
[a]n=5. [b]n=13.
For abbreviations, see below.

- When compared with their respective demographically matched normal control group, single-dose etrasimod peak exposure (C_{max}) was comparable for all hepatic impairment groups (**Table 3**)
- Etrasimod total exposure (AUC) measures were progressively higher (from 12.9 to 57.3%) in the mild, moderate, and severe hepatic impairment groups compared with their respective demographically matched normal control group (**Table 3**)

Table 3. Statistical Parametric Analysis of the Effect of Hepatic Impairment on Total Etrasimod Plasma Exposure PK Parameters

	Comparison, test vs ref	Test n	Test Geo LS mean (90% CI)[a]	Ref n	Ref Geo LS mean (90% CI)[a]	Geo LS mean ratio, test:ref,[b] %	90% CI,[c] %
C_{max}, ng/mL	Mild vs normal	8	33.5 (30.5, 36.9)	8	33.0 (29.9, 36.5)	101.6	88.4, 116.9
	Moderate vs normal	8	31.3 (28.2, 34.8)	8	34.0 (30.6, 37.6)	92.3	80.0, 106.6
	Severe vs normal	6	41.7 (35.6, 48.9)	6	40.0 (34.2, 46.8)	104.3	84.4, 128.9
AUC_{0-t}, h•ng/mL	Mild vs normal	8	1440 (1260, 1660)	8	1270 (1100, 1470)	113.3	94.9, 135.3
	Moderate vs normal	8	1720 (1520, 1950)	8	1330 (1180, 1510)	129.1	108.6, 153.3
	Severe vs normal[d]	4	2310 (1500, 3580)	4	1600 (1040, 2470)	144.7	91.8, 228.1
$AUC_{0-\infty}$, h•ng/mL	Mild vs normal	8	1490 (1300, 1710)	8	1320 (1140, 1530)	112.9	94.1, 135.5
	Moderate vs normal	8	1770 (1570, 2010)	8	1380 (1220, 1550)	128.9	108.6, 153.0
	Severe vs normal	6	2710 (2160, 3410)	6	1730 (1380, 2160)	157.3	122.0, 202.8

[a]LS means for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ calculated by transforming the natural log means back to the linear scale. [b]Ratio of LS means for natural log–transformed parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, natural log–transformed back to the linear scale. [c]90% CI for ratio of LS means of natural log–transformed parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ (expressed as a percent), natural log transformed back to the linear scale. [d]Due to potential underestimation of AUC_{0-t}, 2 participants with severe hepatic impairment (and their demographically matched normal controls) were excluded from the statistical comparison of severe hepatic impairment vs normal hepatic function for AUC_{0-t}.
For abbreviations, see below.

UNBOUND ETRASIMOD PLASMA EXPOSURE PK PARAMETERS

- Unbound etrasimod C_{max} values were reduced to 90.4%, 69.5%, and 58.0% in the mild, moderate, and severe hepatic impairment groups when compared with their respective demographically matched normal control group (**Table 4**)
- Unbound etrasimod AUC values were typically comparable for all hepatic impairment groups when compared with their respective demographically matched normal control group (**Table 4**)

Table 4. Statistical Parametric Analysis of the Effect of Hepatic Impairment on Unbound[a] Etrasimod Plasma Exposure PK Parameters

	Comparison, test vs ref	Test n	Test Geo LS mean (90% CI)[b]	Ref n	Ref Geo LS mean (90% CI)[b]	Geo LS mean ratio, test:ref,[c] %	90% CI,[d] %
$C_{max,u}$, ng/mL	Mild vs normal	8	1.45 (1.13, 1.87)	8	1.61 (1.24, 2.09)	90.4	62.7, 130.5
	Moderate vs normal	8	1.23 (1.05, 1.44)	8	1.77 (1.52, 2.07)	69.5	56.0, 86.2
	Severe vs normal	6	1.15 (0.849, 1.57)	6	1.99 (1.47, 2.70)	58.0	38.5, 87.3
$AUC_{0-t,u}$, h•ng/mL	Mild vs normal	8	62.5 (47.3, 82.5)	8	62.3 (46.5, 83.3)	100.3	66.4, 151.5
	Moderate vs normal	8	67.7 (57.3, 79.9)	8	69.7 (59.1, 82.1)	97.1	77.2, 122.2
	Severe vs normal[e]	4	50.9 (30.6, 84.8)	4	74.0 (44.5, 123)	68.8	35.9, 131.5
$AUC_{0-\infty,u}$, h•ng/mL	Mild vs normal	8	64.5 (49.0, 84.8)	8	64.5 (48.4, 86.0)	100.0	66.4, 150.5
	Moderate vs normal	8	69.6 (59.0, 82.2)	8	71.8 (61.0, 84.5)	97.0	77.2, 121.9
	Severe vs normal	6	75.2 (49.8, 113)	6	86.0 (57.4, 129)	87.4	49.6, 154.2

[a]Geometric mean (geometric CV%) f_u was 4.35% (37.0%) in the mild hepatic impairment group and 5.02 (27.1) in the demographically matched normal control group; 3.84 (26.6) in the moderate hepatic impairment group and 5.11 (31.5) in the demographically matched normal control group; and 2.59 (45.7) in the severe hepatic impairment group and 4.67 (27.2) in the demographically matched normal control group. [b]LS means for $C_{max,u}$, $AUC_{0-t,u}$, and $AUC_{0-\infty,u}$ calculated by transforming the natural log means back to the linear scale. [c]Ratio of LS means for natural log–transformed parameters $C_{max,u}$, $AUC_{0-t,u}$, and $AUC_{0-\infty,u}$, natural log–transformed back to the linear scale. [d]90% CI for ratio of LS means of natural log–transformed parameters $C_{max,u}$, $AUC_{0-t,u}$, and $AUC_{0-\infty,u}$ (expressed as a percent), natural log transformed back to the linear scale. [e]Due to potential underestimation of $AUC_{0-t,u}$, 2 participants with severe hepatic impairment (and their demographically matched normal controls) were excluded from the statistical comparison of severe hepatic impairment vs normal hepatic function for $AUC_{0-t,u}$.
For abbreviations, see below.

SAFETY

- A single oral dose of etrasimod 2 mg was well tolerated in all participants
- There were no AEs, serious AEs, or clinically significant findings related to vital signs, 12-lead ECGs, or clinical laboratory test results

CONCLUSIONS

- A single oral dose of etrasimod 2 mg was well tolerated, with relatively small-to-modest changes in etrasimod exposure observed in participants with mild, moderate, or severe hepatic impairment
- There was modest change in total geometric mean $AUC_{0-\infty}$ in participants with severe hepatic impairment compared with those with normal hepatic function and little change for unbound $AUC_{0-\infty,u}$ across all hepatic impairment groups compared with their respective normal hepatic function groups
- These results suggest that etrasimod dose adjustment may not be warranted in patients with hepatic impairment

Presented at European Crohn's and Colitis Organisation (ECCO)
July 2-3 & 8-10, 2021 • Virtual

ABBREVIATIONS: AUC, area under the concentration-time curve; AUC_{0-t}, AUC from time zero to the last measurable concentration; $AUC_{0-t,u}$, unbound AUC from time zero to the last measurable concentration; AUC_{0-24}, AUC from time zero to 24 hours post dose; $AUC_{0-\infty}$, AUC from time zero to infinity; $AUC_{0-\infty,u}$, unbound AUC from time zero to infinity; BMI, body mass index; CL/F, apparent total plasma clearance after oral administration; C_{max}, maximum observed plasma concentration; $C_{max,u}$, unbound maximum observed plasma concentration; CV, coefficient of variation; f_u, arithmetic mean value of duplicate binding determinations; geo LS mean, geometric least squares mean; PK, pharmacokinetic; ref, reference group (demographically matched normal control group); $t_{1/2}$, apparent terminal elimination half-life; t_{max}, time to maximum observed plasma concentration; V_z/F, apparent volume of distribution during the terminal phase.

REFERENCES: **1.** Al-Shamma H et al. *J Pharmacol Exp Ther.* 2019;369:311-317. **2.** Matloubian M et al. *Nature.* 2004;427:355-360.

ACKNOWLEDGEMENTS AND DISCLOSURES: This study was funded by Arena Pharmaceuticals, Inc. Support for medical writing, furnished by Health Interactions, Inc., was provided by Arena Pharmaceuticals, Inc. All authors are employees of Arena Pharmaceuticals, Inc.

An electronic version of this poster may be obtained by scanning this QR code with your smartphone app.