Pharmacokinetics and Circulating Total Lymphocyte Count Pharmacodynamic Response From Single and Multiple Oral Doses of Etrasimod in Japanese and Caucasian Healthy Male Subjects

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Introduction

- Etrasimod (APD334) is an oral, synthetic, selective sphingosine 1-phosphate (S1P) receptor modulator in development for chronic immune-mediated inflammatory disorders
  - Etrasimod selectively targets S1P receptors 1, 4, and 5 ($S1P_{1,4,5}$)[1]
  - $S1P_1$ regulates lymphocyte egress from lymphoid organs[2]
- Etrasimod demonstrated efficacy in patients with moderately to severely active ulcerative colitis (UC) in the phase 2 OASIS study (NCT02447302) which reported significantly greater improvement in the modified Mayo Clinic score compared with placebo at Week 12[3]
- Prior characterisation of etrasimod pharmacokinetics (PK) in healthy subjects of Caucasian descent demonstrated that etrasimod is primarily cleared hepatically via oxidation, dehydrogenation, glucuronidation, and sulfation[4]
- In the present phase 1 study, we evaluated etrasimod PK and pharmacodynamics (PD) in healthy male subjects of Japanese or Caucasian descent

Methods

- This single-blind (subject only), placebo-controlled, phase 1 study included 49 healthy male subjects in 4 treatment groups randomised to receive etrasimod or placebo (10 etrasimod and 2 placebo per group)
  - Treatment groups were: Japanese, etrasimod 1 mg; Japanese, etrasimod 2 mg; Caucasian, etrasimod 1 mg; and Caucasian, etrasimod 2 mg
- Subjects met one of the following ethnicity criteria:
  - Japanese: both of the subject's biological parents and all four grandparents had to be Japanese
  - Caucasian: had to be of North American, South American, European, or Middle Eastern descent (subjects of Asian/Pacific Islander and African American descent were excluded)
- Subjects received etrasimod or matching placebo once daily (QD) from Days 1 to 7, followed by a 7-day washout and a single dose on Day 15 (**Figure 1**)
- Blood was sampled multiple times on Days 1 and 7 for plasma single- and multiple-dose PK assessment and each morning from Day 1 through Day 15 to assess lymphocyte counts and calculate lymphocyte PD parameters, including the minimum and maximum observed response values after dosing (R_{min} and R_{max}, respectively) and net area under the effect curve ($AUEC_{net}$)
  - $AUEC_{net}$ is equal to the area that is both above baseline and below the curve minus the area that is both below baseline and above the curve

Figure 1. Study Design

Screening	Treatment Period									Final Follow-up
	Admission	Confinement Period (In-house Stay)							Discharge	
Days −28 to −2	Day −1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Days 8 to 14 (7 days)	Day 15	Day 22 ± 3 days
Informed Consent		Dosing	Dosing	Dosing	Dosing	Dosing	Dosing	Dosing	Treatment-free Period (Washout)	Dosing	Subject's study completion

Results

Subjects

- Mean total body weight (TBW) of subjects receiving etrasimod was lower in subjects of Japanese descent compared with subjects of Caucasian descent (**Table 1**)

Table 1. Subject Demographic and Baseline Characteristics

	Etrasimod 1 mg		Etrasimod 2 mg		Pooled Placebo		Overall	
	Japanese (n = 10)	Caucasian (n = 10)	Japanese (n = 10)	Caucasian (n = 10)	Japanese (n = 4)	Caucasian (n = 5)	Japanese (n = 24)	Caucasian (n = 25)
Age, years, mean (SD)	35.9 (5.00)	35.0 (6.09)	34.9 (5.28)	33.2 (5.75)	33.8 (3.59)	37.8 (7.53)	35.1 (4.79)	34.8 (6.22)
TBW, kg, mean (SD)	64.0 (6.89)	72.8 (10.2)	64.1 (7.45)	82.8 (10.8)	76.1 (16.6)	87.9 (13.9)	66.0 (9.87)	79.8 (12.3)
BMI, kg/m², mean (SD)	22.3 (1.55)	23.7 (3.01)	21.6 (1.86)	26.0 (3.55)	25.4 (4.13)	27.4 (2.12)	22.5 (2.52)	25.3 (3.32)

SD, Standard Deviation; BMI, Body-Mass Index

Pharmacokinetics

- Etrasimod peak concentration (C_{max}) and total plasma exposure ($AUC_{0-\tau}$) values in both ethnic groups were dose-proportional following either a single dose or multiple doses (**Table 2**)
- Etrasimod mean C_{max} and $AUC_{0-\tau}$ were slightly to moderately higher in Japanese subjects compared with Caucasian subjects following either a single dose or multiple doses (**Table 2**)
  - There was low to moderate inter-subject variability

Table 2. Summary of Etrasimod Single Dose and Multiple Dose Plasma PK Parameters in Japanese and Caucasian Male Subjects

Dosing, Day	Parameter	Japanese		Caucasian	
		Etrasimod 1 mg (n = 10)	Etrasimod 2 mg (n = 10)	Etrasimod 1 mg (n = 10)	Etrasimod 2 mg (n = 10)
Single, 1	C_{max}, ng/mL	23.4 (4.80)	45.0 (6.30)	18.3 (2.52)	29.5 (3.64)
	$AUC_{0-\tau}$, ng*h/mL	379 (60.6)	687 (117)	312 (50.9)	481 (62.8)
Multiple, 7	C_{max}, ng/mL	48.9 (8.39)	91.4 (21.1)	38.7 (9.33)	73.8 (13.6)
	$AUC_{0-\tau}$, ng*h/mL	826 (156)	1570 (317)	660 (183)	1210 (194)
	$t_{1/2}$,hr	40.1 (6.39)	36.4 (6.78)	39.4 (5.09)	41.7 (9.14)

Data are presented as mean (SD)
$t_{1/2}$, elimination half-life

Results (cont'd)

- Geometric mean ratio (GMR) point estimates for etrasimod plasma exposure measures between Japanese and Caucasian subjects ranged from 120–146% (**Table 3**)
- After dose-body weight normalisation of etrasimod C_{max} and $AUC_{0-\tau}$, the GMR point estimates between Japanese and Caucasian subjects were near 100% (**Table 3**), which indicates that the etrasimod plasma exposure difference between the two ethnic groups appears mainly attributable TBW rather than ethnicity

Table 3. Summary of Japanese/Caucasian GMR of C_{max} and $AUC_{0-\tau}$ After Single and Multiple Doses

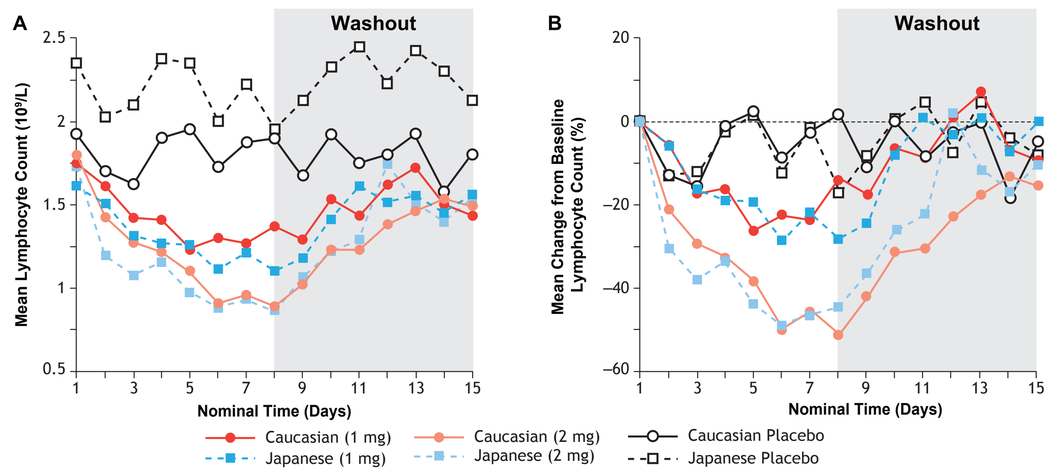
	Single Dose, Day 1			Multiple Doses, Day 7		
	Etrasimod 1 mg	Etrasimod 2 mg	Combined	Etrasimod 1 mg	Etrasimod 2 mg	Combined
C_{max}						
GMR J/C	124 (110, 140)	146 (127, 169)	135 (121, 149)	127 (108, 150)	121 (99, 147)	124 (108, 143)
GMR J/C, DWN	111 (97, 128)	118 (103, 135)	115 (104, 126)	113 (95, 134)	95 (80, 114)	104 (92, 117)
$AUC_{0-\tau}$						
GMR J/C	120 (105, 137)	137 (118, 160)	128 (115, 143)	124 (105, 147)	124 (102, 151)	124 (108, 143)
GMR J/C, DWN	107 (93, 124)	110 (96, 127)	109 (98, 120)	112 (95, 133)	101 (85, 119)	106 (94, 120)

Data are presented as % (90% confidence interval)
GMR (J/C), geometric mean ratio of Japanese (J) to Caucasian (C) subjects; DWN, Dose-Body Weight Normalised

Lymphocyte Pharmacodynamics

- Dose-dependent, progressive decreases in mean absolute and percent change from baseline lymphocyte count were observed across all four treatment groups from Day 2 to Day 8, followed by a subsequent increase to near baseline levels during the 7-day washout period (**Figure 2**) consistent with etrasimod half-life (**Table 2**)

Figure 2. Mean (A) Lymphocyte Count and (B) Change from Baseline Lymphocyte Count (%) Over Time



On Day 1, the lymphocyte count was measured prior to dosing

- Absolute and change from baseline nadir lymphocyte counts were dose-dependent and comparable across ethnic groups (**Table 4**)
  - Time to nadir (T_{min}) was similar between the etrasimod treatment groups

Table 4. Summary of Baseline and Nadir Lymphocyte Counts and Time to Nadir

PD Parameter	Etrasimod 1 mg		Etrasimod 2 mg		Pooled placebo	
	Japanese (n = 10)	Caucasian (n = 10)	Japanese (n = 10)	Caucasian (n = 10)	Japanese (n = 4)	Caucasian (n = 4)
Baseline Lymphocyte Count, 10^9/L	1.61 (0.482)	1.75 (0.682)	1.73 (0.295)	1.80 (0.316)	2.35 (1.22)	1.93 (0.479)
Nadir Lymphocyte Count, 10^9/L	0.99 (0.213)	1.16 (0.353)	0.80 (0.189)	0.82 (0.155)	1.80 (1.03)	1.47 (0.427)
Nadir CFB Lymphocyte Count, %	−36.1 (11.8)	−30.77 (17.6)	−53.6 (8.73)	−54.1 (7.46)	−24.1 (9.78)	−23.7 (4.94)
T_{min}, days	5.0 (1.0, 8.0)	4.0 (2.0, 7.0)	5.0 (2.0, 7.0)	5.5 (5.0, 7.0)	3.5 (1.0, 6.0)	6.5 (2.0, 13)

Data are presented as mean (SD), except for T_{min} shown as median (min, max)
CFB, change from baseline; T_{min}, time to nadir

- No statistically significant differences were seen between Japanese and Caucasian subjects for lymphocyte R_{min}, R_{max}, or $AUEC_{net}$ based on least square (LS) mean values (**Table 5**)

Table 5. Summary of Lymphocyte PD Parameters in Subjects Treated With Etrasimod (Day 1 to Day 15)

PD Parameter	Etrasimod 1 mg			Etrasimod 2 mg		
	Japanese (n = 10)	Caucasian (n = 10)	Difference	Japanese (n = 10)	Caucasian (n = 10)	Difference
R_{min}, 10^9/L	0.99 (0.87, 1.11)	1.14 (1.02, 1.26)	−0.15 (−0.33, +0.03)	0.78 (0.66, 0.90)	0.82 (0.70, 0.94)	−0.04 (−0.22, +0.14)
R_{max}, 10^9/L	1.84 (1.61, 2.07)	1.96 (1.73, 2.19)	−0.12 (−0.45, +0.21)	1.91 (1.68, 2.14)	1.86 (1.63, 2.09)	0.05 (−0.28, +0.38)
$AUEC_{net}$, day*10^9/L	−3.49 (−5.50, −1.47)	−3.95 (−5.96, −1.94)	0.47 (−2.38, +3.31)	−7.21 (−9.22, −5.20)	−7.92 (−9.93, −5.91)	0.71 (−2.13, +3.55)

Data are presented as LS mean (90% confidence interval)

Conclusions

- **Single and multiple dose etrasimod mean peak (C_{max}) and total plasma exposure (AUC) measures were slightly to moderately higher in subjects of Japanese descent compared with Caucasian descent, but were similar after dose-body weight normalisation**
- **No statistically significant differences were observed between subjects of Japanese and Caucasian descent in lymphocyte PD parameters of R_{min}, R_{max}, or $AUEC_{net}$ upon administration of multiple doses of etrasimod**
- **These results demonstrate a lack of clinically meaningful PK or PD (lymphocyte response) ethnic differences between healthy male subjects of Japanese and Caucasian descent**
- **This study supports the potential inclusion of Japanese patients with moderately to severely active UC in global phase 3 clinical trials evaluating an etrasimod 2 mg QD dosing regimen**

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.
3. Sandborn WJ et al. *Gastroenterology*. 2019 Nov 9. pii: S0016-5085(19)41247-X. doi: 10.1053/j.gastro.2019.08.027. [Epub ahead of print].
4. Lee CA et al. AAPS 2019; San Antonio, TX. Abstract 688619.

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Disclosures

CAL, **LA**, **DAO**, **PB**, **KG**, **KK**, **SM**, **TNC**, **YT**, **JZ**, and **JG** are employees of Arena Pharmaceuticals, Inc. **DH**, **SJ**, and **KS** are employees of PAREXEL International.

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