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Safety, Pharmacokinetics and Pharmacodynamics of Etrasimod (APD334), an Oral, Selective S1P Receptor Modulator, after Single Dose Escalation in Healthy Volunteers

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Background

- Sphingosine-1-phosphate (S1P), a membrane-derived lysophospholipid signaling molecule, is implicated in a vast array of physiological and pathophysiological processes, primarily via extracellular activation of S1P1–S1P5 receptors[1,2]
- Although targeting S1P modulators provides opportunities for managing inflammatory conditions, non-selective S1P modulators have been associated with potentially serious adverse events, including bradycardia[3–5]
- Etrasimod – an oral, potent, next-generation S1P modulator in clinical development for the chronic treatment of ulcerative colitis – was designed to selectively target S1P receptor subtypes 1, 4, and 5 in order to provide systemic and local immune cell modulation[6]
- The objective of this study was to evaluate the safety, tolerability, pharmacokinetic (PK) properties, and pharmacodynamics (PD) responses of ascending doses of etrasimod administered as a single oral dose to healthy adult subjects

Methods

- This was a Phase 1, randomized, double-blind, placebo-controlled, single dose-escalation study
- Subjects included healthy adult men and women, 18–45 years, body weight of 50–100 kg, who were non-smokers and not taking any prescription medications
- Following a screening period of up to 21 days, a single dose was administered on Day 1 with prior and subsequent inpatient observations and procedures undertaken until at least Day 7/Exit
  - Dosing began at 0.1 mg, with planned escalation up until 40 mg
  - For each dose, a separate cohort of up to 8 subjects were randomized: 6 to etrasimod and 2 to placebo
- Assessments included safety, tolerability, PK properties, and PD responses

Results

- Forty subjects in 5 cohorts (6 subjects in each etrasimod cohort; 2 subjects in each placebo cohort) were enrolled and completed the study with the following doses:
  - Cohort 1 – 0.1 mg
  - Cohort 2 – 0.35 mg
  - Cohort 3 – 1 mg
  - Cohort 4 – 3 mg
  - Cohort 5 – 5 mg

Safety and tolerability

- Etrasimod was well tolerated at doses ≤3 mg both male and female subjects
- The safety profile of etrasimod observed in this single-dose study of healthy subjects is consistent with that anticipated for an S1P receptor agonist
- Headache and contact dermatitis were the most commonly reported adverse events (AEs); % of subjects experiencing these events were similar or slightly higher in the placebo group:
  - Headache, n (%): 2 with placebo (20%); 6 with etrasimod (20%)
  - Contact dermatitis, n (%): 2 with placebo (20%); 4 with etrasimod (13%)
- In the 5 mg etrasimod cohort:
  - 1 subject: asymptomatic, first degree and second degree atrioventricular (AV) block with bradycardia
  - 2 subjects: asymptomatic, first degree AV block, 1 associated with bradycardia
  - Further dose escalation was discontinued
- Mild-to moderate, asymptomatic declines in heart rate and blood pressure were observed but only changes in heart rate at the 3 and 5 mg doses reached statistical significance
- No other clinically significant safety issues with respect to vital signs, electrocardiograms (ECG), pulmonary function tests (PFT), ophthalmoscopy, or clinical laboratory tests were found

Pharmacokinetic Properties

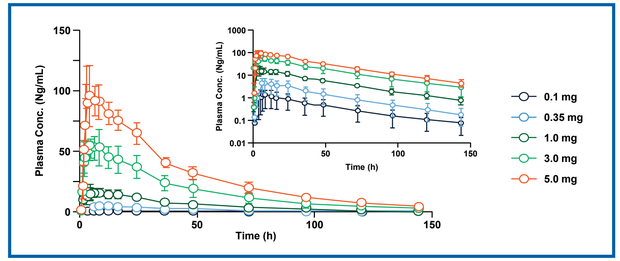
- Median time to reach maximum plasma concentrations (t_{max}) was longer for the lower-doses of etrasimod (6.0–7.0 hours) than with the 3 and 5 mg doses (3.5 and 4.0 hours, respectively; **Table 1; Figure 1**)
- Mean terminal half-life of etrasimod was consistent between dose groups, ranging from 30.7–37.4 hours
- Apparent oral clearance (CL/F) was dose independent and low compared with hepatic blood flow
- Apparent volume of distribution (V/F) was ~2-fold that of total body water and also dose independent
- Urine concentrations of etrasimod were below the lower limit of quantification at all time points

Table 1. Summary of plasma pharmacokinetic parameters* of etrasimod by treatment group

Pharmacokinetic parameter	Etrasimod, n = 6 per cohort				
	0.1 mg	0.35 mg	1.0 mg	3.0 mg	5.0 mg
C_{max} (μg/mL)	0.00173 (0.00061)	0.00628 (0.00036)	0.0172 (0.0055)	0.0605 (0.0117)	0.102 (0.019)
T_{max} (h)	6.00 (4.00–12.00)	7.00 (1.50–24.0)	6.00 (2.00–8.00)	3.50 (1.50–8.00)	4.00 (3.00–6.00)
λ_z (l/h)	0.0189 (0.0028)	0.0227 (0.0018)	0.0215 (0.0029)	0.0203 (0.0034)	0.0206 (0.0014)
$T_{1/2Z}$ (h)	37.4 (5.6)	30.7 (2.7)	32.8 (5.0)	35.0 (5.8)	33.8 (2.3)
$AUC_{0\text{-}144}$ (μg·h/mL)	0.0748 (0.0204)	0.257 (0.027)	0.753 (0.157)	2.44 (0.70)	4.17 (0.55)
$AUC_{0\text{-}inf}$ (μg·h/mL)	0.0798 (0.0213)	0.268 (0.031)	0.793 (0.168)	2.60 (0.84)	4.39 (0.61)
CL/F (L/h)	1.33 (0.37)	1.32 (0.15)	1.30 (0.25)	1.23 (0.29)	1.16 (0.15)
MRT (h)	40.8 (3.4)	37.6 (2.5)	39.5 (3.5)	39.1 (4.5)	39.4 (3.9)
V_z/F (L)	73.4 (29.2)	58.2 (3.5)	61.2 (11.9)	60.3 (9.5)	56.2 (6.7)

*All data are mean (SD), except t_{max} = median (min-max). $AUC_{0\text{-}144}$, area under the plasma concentration-time curve from time zero to 144 hours post-dosing; $AUC_{0\text{-}inf}$, area under the plasma concentration-time curve from time zero to infinity; CL/F, apparent clearance; C_{max}, maximum plasma concentration; MRT, mean residence time; SD, standard deviation; t_{max}, time of maximum plasma concentration; $t_{1/2z}$, elimination half-life; V_z/F, apparent volume of distribution; λ_z, terminal-phase rate constant

Figure 1. Plasma concentration-time profiles of orally administered etrasimod



Mean ± SD, n = 6 per treatment group

- Both $AUC_{0\text{-}144}$, and $AUC_{0\text{-}inf}$ were dose proportional following escalating administration of etrasimod doses between 0.1 mg and 5 mg (**Table 2**)

Table 2. Assessment of dose proportionality of etrasimod

Pharmacokinetic parameter	Estimate (90% CI)[a]
C_{max}	1.050 (1.001, 1.099)
$AUC_{0\text{-}144}$	1.033 (0.991, 1.075)
$AUC_{0\text{-}inf}$	1.032 (0.988, 1.075)

[a]Values are from a linear regression model of the log-transformed data. $AUC_{0\text{-}144}$, area under the plasma concentration-time curve from time zero to 144 hours post-dosing; $AUC_{0\text{-}inf}$, area under the plasma concentration-time curve from time zero to infinity; CI, confidence interval; C_{max}, maximum plasma concentration

Pharmacodynamic Responses

- Administration of etrasimod at 3 mg and 5 mg decreased total peripheral blood lymphocyte counts to 52.5% and 35.9% of baseline, respectively (**Table 3**)
- Time to nadir lymphocyte counts was ~15 hours and ~11 hours post-dose with 3 mg and 5 mg doses, respectively

Table 3. Summary of nadir lymphocyte counts and time to nadir

Parameter	Placebo n=10	Etrasimod, n = 6 per cohort				
		0.1 mg	0.35 mg	1.0 mg	3.0 mg	5.0 mg
Baseline lymphocyte count (x10³/μL)[a]						
Mean (SD)	2.16 (0.50)	2.08 (0.30)	2.01 (0.79)	1.94 (0.38)	1.86 (0.66)	2.05 (0.63)
Median	2.08	2.13	1.80	1.95	1.53	1.98
Min – max	1.65–3.25	1.70–2.40	1.20–3.15	1.45–2.45	1.35–2.75	1.40–3.20
Nadir lymphocyte counts (x10³/μL)						
Mean (SD)	1.61 (0.24)	1.68 (0.34)	1.57 (0.52)	1.52 (0.40)	0.98 (0.41)	0.75 (0.34)
Median	1.60	1.60	1.40	1.55	0.85	0.65
Min – max	1.20–2.00	1.30–2.30	1.10–2.40	1.00–2.00	0.60–1.70	0.40–1.40
% Nadir over baseline lymphocyte counts						
Mean (SE)	75.94 (3.26)	81.24 (4.67)	80.48 (5.24)	77.49 (3.81)	52.47 (2.80)	35.91 (3.17)
Median	76.70	79.93	76.03	80.82	52.59	37.97
Min – max	55.38–90.91	63.83–95.83	65.12–100.00	62.50–87.80	44.44–61.82	25.00–43.75
Time to nadir (h)						
Mean (SD)	6.40 (9.31)	25.17 (47.31)	9.00 (11.63)	28.00 (19.27)	15.33 (9.61)	11.33 (9.93)
Median	2.00	2.00	2.00	30.00	16.00	6.00
Min – max	1.00–24.00	1.00–120.00	1.00–24.00	4.00–48.00	4.00–24.00	4.00–24.00

[a]Baseline is the mean of Day -1 and Day 1 pre-dose measure. SD, standard deviation; SE, standard error of the mean

- Total lymphocyte counts were reduced from baseline by ≥30%, ≥40%, and ≥ 60% in a high proportion of subjects with etrasimod 3 mg and 5 mg (**Table 4**)

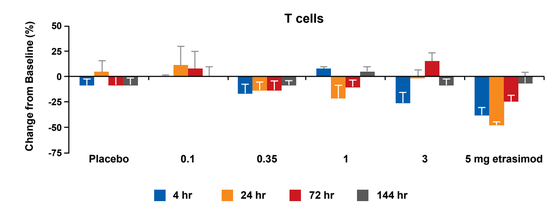
Table 4. Percent reduction from baseline in total lymphocyte counts at nadir

Reduction from baseline[a]	Placebo , n = 10	Etrasimod, n = 6 per cohort				
		0.1 mg	0.35 mg	1.0 mg	3.0 mg	5.0 mg
Numbers (%) of subjects with indicated reduction						
≥30%	3 (30.00)	1 (16.67)	1 (16.67)	1 (16.67)	6 (100.00)	6 (100.00)
≥45%	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	4 (66.67)	6 (100.00)
≥60%	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	4 (66.67)

[a]Baseline is the mean of Day -1 and Day 1 pre-dose measures

- Etrasimod at 0.1 mg, 0.35 mg, and 1 mg had little or no effect on numbers of total peripheral lymphocytes or T cells when compared with baseline or placebo at each dose (**Figure 2**)
- Etrasimod 3 mg showed reductions in T cells at 4 hours; this was not sustained
- At etrasimod 5 mg, T cells were markedly reduced at all time points through 72 hours
- Magnitude of effect with etrasimod 3 mg on T cell subsets at 4 hours was:
  - Naïve T cells (TN) > T suppressor (TS) > T helper (TH) > central memory T cells (TCM)
- Magnitude of effect with etrasimod 5 mg on T cell subsets was:
  - 4 hours: TN > TH > TS > TCM
  - 24 hours: TN > TH > TCM > TS
  - 72 hours: TH >TN >TCM >TS
  - 144 hours: TN > TH > TS > TCM

Figure 2. Change in T cells from baseline to Day7/Exit



Mean ± SE; n = 10 for placebo; n = 6 for etrasimod dose groups; baseline was the Day 1 pre-dose sample. SE, standard error of the mean

Conclusions

- Etrasimod was well tolerated when orally administered to healthy subjects at dose levels from 0.1 mg up to 3 mg
- Exposure of etrasimod was dose proportional from 0.1 mg to 5 mg, with a consistent mean terminal half-life, and no quantifiable levels in urine analysis
- Etrasimod established target dynamic validation (lymphocyte lowering) in this single dose study
- Etrasimod at doses between 1 mg to 3 mg provides the potential for therapeutic effect in the management of ulcerative colitis
- Etrasimod is currently in Phase 2 clinical development at doses of 1 mg and 2 mg, based on the single ascending dose and multiple ascending dose studies[7]

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Disclosures

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