P-180

Etrasimod (APD334), a Potent, Selective, Oral S1P Receptor Modulator With Preclinical Autoimmune Disease-modifying Activity Exhibits Favorable PK/PD Properties 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 is an oral, potent, next-generation S1P modulator in clinical development for the chronic treatment of ulcerative colitis. It was designed to selectively target S1P receptor subtypes 1, 4, and 5 in order to provide systemic and local immune cell modulation,[6] while reducing immunosuppressive side effects and avoiding cardiotoxicity (arrhythmia) associated with other S1P receptor activation, [3–5] as well as potentially improving adherence (with decreased dosing frequency)
- The objective of this study was to evaluate the safety, tolerability, pharmacokinetic (PK) properties, and pharmacodynamic (PD) responses of multiple ascending doses of etrasimod in healthy adult subjects

Methods

- This was a Phase 1, randomized, double-blind, placebo-controlled, multiple ascending-dose study in 5 subject cohorts
- Subjects included healthy adult men and women, 18–45 years, body weight of 50–100 kg, who were not taking any prescription medications
- Etrasimod was administered once daily for 21 days (**Table 1**)
  - Dosing began at 0.7 mg for 21 days in Cohort 1, followed by escalating dose levels of 1.35 mg and 2.0 mg for 21 days in Cohorts 2 and 3, respectively
  - Cohorts 4 and 5 included titration schemes:
    - Cohort 4: dosing was started at 0.35 mg (Days 1–7) followed by 2.0 mg for the remainder of the study duration (Days 8–21)
    - Cohort 5: dosing was started at 0.5 mg (Days 1–7), followed by 3.0 mg (Days 8–21)
    - A lower dose was originally planned for both titration cohorts but deemed unnecessary based on interim safety results from the single dose cohorts
- All subjects fasted overnight for at least 10 hours prior to dosing, and food was withheld for 1 hour after each dose
- Assessments included safety, PK properties, and PD responses

Results

- 60 subjects were enrolled and 59 completed the study: one patient in the 1.35 mg cohort withdrew consent due to personal reasons
- All subjects were included in the safety and PK analyses

Table 1. Dose escalation scheme

Cohort[a] Dosing duration	Placebo, once daily Days 1–21	Etrasimod once daily, mg		
Dose		0.7	1.35	2.0
1	2 subjects	10 subjects		
2	2 subjects		10 subjects	
3	2 subjects			10 subjects
Dosing duration	**Days 1–21**	**Days 1–7**	**Days 8–21**	
Dose		0.35	2.0	
4	2 subjects	10 subjects		
Dose		0.5	3.0	
5	2 subjects	10 subjects		

[a]Dosing with etrasimod progressed to the next cohort after the previous dose had been determined to be safe and tolerated

Safety and Tolerability

- Etrasimod was well tolerated at all doses tested in the study
- No serious adverse events (SAEs) occurred during the study
- Common adverse events (AEs) included contact dermatitis, constipation, headache, and diarrhea (**Table 2**)
  - Most AEs were mild, and not dose responsive (with the exception of leukopenia and neutropenia, which both occurred only with the highest dose, Cohort 5)
  - Similar AE profiles were reported with titration regimens as with single dose regimens
- No subjects discontinued due to an AE
- Safety findings of interest included small asymptomatic declines in blood pressure and heart rate
  - No symptomatic bradycardia, or second or third degree heart block was reported
  - Titration regimens did not lessen these heart rate effects
- No other clinically significant safety issues were shown with respect to vital signs, electrocardiograms, pulmonary function tests, ophthalmoscopy, or clinical laboratory signs

Table 2. Summary of treatment-emergent AEs reported by >1 subjects receiving etrasimod or placebo for 21 days

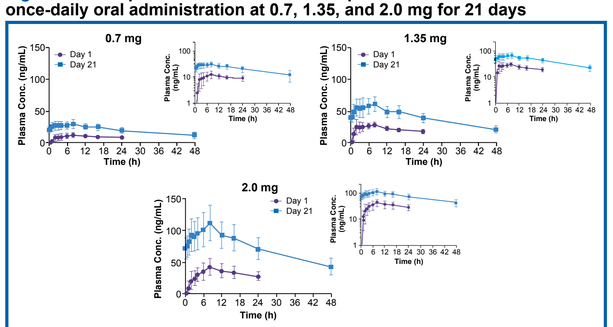
Cohort	Placebo, once daily	Etrasimod once daily, mg				
		1	2	3	4	5
Dose		0.7	1.35	2.0	0.35, 2.0	0.5, 3.0
Subject, n	**10**	**10**	**10**	**10**	**10**	**10**
AE, n (%)						
Dermatitis contact	6 (60)	1 (10)	7 (70)	5 (50)	5 (50)	2 (20)
Headache	4 (40)	2 (20)	1 (10)	1 (10)	1 (10)	3 (30)
Constipation	0	2 (20)	3 (30)	3 (30)	2 (20)	0
Diarrhea	1 (10)	3 (30)	2 (20)	0	2 (20)	0
Nausea	2 (20)	1 (10)	3 (30)	1 (10)	0	0
Abdominal pain	2 (20)	0	0	1 (10)	3 (30)	0
Back pain	0	2 (20)	2 (20)	0	0	1 (10)
Leukopenia	0	0	0	0	0	4 (40)
Neutropenia	0	0	0	0	0	2 (20)
Ear discomfort	0	0	1 (10)	0	0	1 (10)
Vomiting	0	0	0	2 (20)	0	0
Laceration	0	0	0	1 (10)	1 (10)	0
Menstrual disorder	0	0	0	0	0	2 (20)
Pruritus	0	1 (10)	0	1 (10)	0	0

AE = adverse event

Pharmacokinetic Properties

- Absorption of etrasimod was rapid with plasma concentrations observed at the first time point (0.5 hours) after single and multiple oral dosing in Cohorts 1–3 (**Figure 1**)
- Median maximum absorption occurred between 6–8 hours across all dose levels
- Mean elimination half-life of etrasimod in plasma was 26.2–32.5 hours
- Mean terminal half-life of etrasimod was consistent between dosing paradigms: 26.2–33.3 hours

Figure 1. Mean plasma concentration-time profiles of etrasimod after once-daily oral administration at 0.7, 1.35, and 2.0 mg for 21 days



Mean ± SD; Conc, concentration; SD, standard deviation

- Etrasimod plasma exposure accumulation after 21 days of once-daily oral administration was greater than 2-fold compared with a single dose administration (C_{max}: 2.12–2.72; $AUC_{0\text{-}24}$: 2.33–3.03) across all doses (**Table 3**)
- Median time to reach maximum plasma concentrations (t_{max}) was 6.0–8.0 hours, independent of dose and sequence
- With titration:
  - Cohort 4: increasing dose from 0.35 to 2.0 mg resulted in a dose proportional 6-fold increase in etrasimod plasma exposure (Day 8 vs. Day 1; **Table 4**)
  - Cohort 5: increasing dose from 0.5 to 3.0 mg resulted in an approximate 7-fold increase in exposure (Day 8 vs. Day 1; **Table 5**)

Table 3. Summary of mean plasma pharmacokinetic parameters* of etrasimod after once-daily oral administration at 0.7, 1.35, and 2.0 mg for 21 days (Cohorts 1–3)

Pharmacokinetic parameter		Etrasimod 0.7 mg (n = 9–10)	Etrasimod 1.35 mg (n = 9–10)	Etrasimod 2.0 mg (n = 9–10)
Day 1	λ_z (l/h)	0.026 (0.003)	0.0248 (0.0037)	0.0281 (0.0068)
	$T_{1/2Z}$ (h)	27.0 (3.14)	28.5 (4.25)	26.2 (7.3)
	T_{max} (h)	8.0 (3.0–12.0)	6.0 (2.0–8.0)	8.0 (2.0–12.0)
	C_{max} (ng/mL)	12.9 (2.84)	29.2 (8.37)	43.8 (12.9)
	AUC_{last} (ng·h/mL)	225 (51.5)	497 (101)	751 (197)
	$AUC_{0\text{-}inf}$ (ng·h/mL)	571 (139)	1216 (295)	1846 (472)
	V_z/F (mL)	49700 (9830)	47400 (10600)	42300 (12000)
	CL/F (mL/h)	1300 (346)	1180 (314)	1150 (298)
	MRT (h)	12.6 (1.11)	11.8 (0.65)	12.6 (1.0)
	$AUC_{0\text{-}24}$ (ng·h/mL)	225 (51.5)	497 (101)	751 (197)
Day 21	λ_z (l/h)	0.0233 (0.0060)	0.0252 (0.0031)	0.0224 (0.0049)
	$T_{1/2Z}$ (h)	32.2 (11.0)	27.9 (3.5)	32.5 (8.3)
	T_{max} (h)[a]	8.0 (1.0–8.0)	8.0 (2.0–8.0)	8.0 (2.0–8.0)
	C_{max} (ng/mL)	30.8 (6.61)	63.5 (11.8)	113 (27.5)
	AUC_{last} (ng·h/mL)	966 (236)	1895 (369)	3500 (820)
	$AUC_{0\text{-}inf}$ (ng·h/mL)	1590 (755)	2760 (650)	5602 (1766)
	V_z/F (mL)	21500 (3610)	20400 (3760)	17500 (4470)
	CL/F (mL/h)	509 (179)	515 (123)	394 (137)
	MRT (h)	20.3 (1.11)	20.0 (0.59)	20.4 (0.9)
	$AUC_{0\text{-}24}$ (ng·h/mL)	596 (122)	1197 (226)	2162 (488)
AI	C_{max} Day 21/Day 1	2.42 (0.42)	2.12 (0.28)	2.72 (0.93)
	$AUC_{0\text{-}24}$ Day 21/Day 1	2.71 (0.51)	2.33 (0.21)	3.03 (1.09)

Table 4. Summary of mean plasma pharmacokinetic parameters* of etrasimod after titration from 0.35 to 2.0 mg (Cohort 4)

Pharmacokinetic parameter	Etrasimod 0.35 mg (n = 10) Day 1	Etrasimod 2.0 mg (n = 10) Day 8	Etrasimod 2.0 mg (n = 10) Day 21
λ_z (l/h)	0.0239 (0.0051)	0.0245 (0.0085)	0.0260 (0.0073)
$T_{1/2Z}$ (h)	30.3 (6.52)	33.2 (17.3)	28.0 (5.34)
T_{max} (h)	8.0 (2.0–8.0)	6.0 (2.0–8.0)	8.0 (2.0–8.0)
C_{max} (ng/mL)	6.26 (1.29)	38.5 (7.9)	80.5 (17.4)
AUC_{last} (ng·h/mL)	109 (26)	682 (148)	2410 (599)
$AUC_{0\text{-}inf}$ (ng·h/mL)	274 (80)	1778 (686)	3559 (1066)
V_z/F (mL)	58500 (14800)	53400 (11200)	23700 (4790)
CL/F (mL/h)	1390 (430)	1270 (449)	618 (213)
MRT (h)	12.0 (0.8)	11.7 (0.7)	20.0 (0.9)
$AUC_{0\text{-}24}$ (ng·h/mL)	NA	NA	NA
C_{max} Day 21/Day 8	NA	NA	2.09 (0.20)
$AUC_{0\text{-}24}$ Day 21/Day 8	NA	NA	2.22 (0.27)

Table 5. Summary of mean plasma pharmacokinetic parameters* of etrasimod after titration from 0.5 to 3.0 mg (Cohort 5)

Pharmacokinetic parameter	Etrasimod 0.5 mg (n = 10) Day 1	Etrasimod 3.0 mg (n = 10) Day 8	Etrasimod 3.0 mg (n = 10) Day 21
λ_z (l/h)	0.0226 (0.0060)	0.0241 (0.0072)	0.0220 (0.0050)
$T_{1/2Z}$ (h)	32.4 (7.5)	31.1 (9.1)	33.3 (8.6)
T_{max} (h)	8.0 (3.0–8.0)	6.0 (2.0–12.0)	7.0 (2.0–12.0)
C_{max} (ng/mL)	10.1 (1.0)	73.7 (10.3)	151 (19)
AUC_{last} (ng·h/mL)	180 (22)	1304 (178)	4658 (779)
$AUC_{0\text{-}inf}$ (ng·h/mL)	469 (8.2)	3243 (978)	7586 (2346)
V_z/F (mL)	49700 (7320)	41800 (6230)	19400 (2270)
CL/F (mL/h)	1100 (219)	994 (266)	430 (136)
MRT (h)	12.1 (0.6)	11.6 (0.6)	20.4 (0.9)
$AUC_{0\text{-}24}$ (ng·h/mL)	NA	NA	NA
C_{max} Day 21/Day 8	NA	NA	2.06 (0.19)
$AUC_{0\text{-}24}$ Day 21/Day 8	NA	NA	2.20 (0.15)

*All data are mean (SD), except t_{max} = median (min-max). AI, accumulation index; $AUC_{0\text{-}24}$, area under the plasma concentration-time curve from time zero to 24 hours post-dosing; $AUC_{0\text{-}inf}$, area under the plasma concentration-time curve from time zero to infinity; $AUC_{0\text{-}last}$, area under the plasma concentration-time curve from time zero to last measured; CL/F, apparent clearance; C_{max}, maximum plasma concentration; MRT, mean residence time; NA, not applicable; 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

- Etrasimod exposure increased in a dose proportional manner after a single dose ($AUC_{0\text{-}24}$ and $AUC_{0\text{-}inf}$; **Table 6**)
- After 21 days of dosing, C_{max} and $AUC_{0\text{-}24}$ increased in more than a dose proportional manner (**Table 6**)

Table 6. Etrasimod dose proportionality

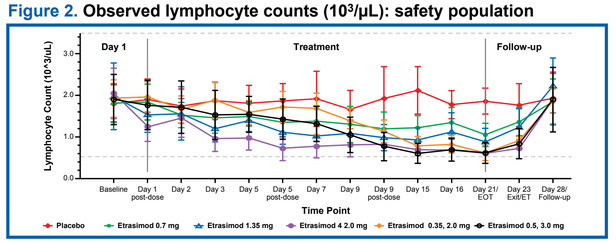
Pharmacokinetic parameter		Slope	90% CI Slope
Day 1	C_{max}	1.094	1.008 – 1.180
	$AUC_{0\text{-}24}$	1.145	0.972 – 1.318
	$AUC_{0\text{-}inf}$	1.067	0.969 – 1.164
Day 21	C_{max}	1.087	0.977 – 1.198
	$AUC_{0\text{-}24}$	1.205	1.050 – 1.361

$AUC_{0\text{-}24}$, area under the plasma concentration-time curve from time zero to 24 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

- A dose-dependent effect on lymphocyte lowering was observed, with the maximal effect plateauing at 2.0 mg once-daily (**Figure 2**)
- Mean lymphocyte counts returned to baseline levels within 7 days of dosing discontinuation (by Day 28/Exit; **Figure 2**)

Figure 2. Observed lymphocyte counts (10^3/µL): safety population



Note: Normal range [0.4–4.5 (10^3/µL)] of lymphocyte count is indicated by dotted lines

- Median reduction in lymphocyte counts of approximately 67% were shown for the higher doses of etrasimod (2.0 and 3.0 mg once-daily) after 21 days of dosing
- Primary effects were seen in the T-Helper and T-Naïve subpopulations and (to a lesser extent) in T-Central Memory cells; T-Suppressor and T-Effector memory populations were relatively spared
- No effects were seen on serum proteins (assessed by either serum protein electrophoresis or immunoelectrophoresis), except potentially for a small dose-responsive effect on serum IgG levels (ranging from -0.3% to -4.8%)

Conclusions

- Etrasimod was well tolerated at all doses tested in this study
- The pharmacokinetics were dose-proportional after single doses of 0.7 mg to 2.0 mg
- Treatment with etrasimod produced a dose-dependent and sustained decrease in lymphocyte count, with the maximal effects plateauing at the 2.0 mg dose
- These results support etrasimod clinical development at doses of 1.0 mg and 2.0 mg in ulcerative colitis, and potentially other autoimmune indications

References

1. Blaho VA & Hla T. *J Lipid Res* 2014;55(8):1596–608.
2. Spiegel S, et al. IUPHAR/BPS Guide to pharmacology. 2014.
3. Cohen JA, et al. *N Engl J Med.* 2010;362:402–15.
4. Kappos L, et al. *N Engl J Med.* 2010;362:387–401.
5. Calabresi P, et al. *Lancet Neurol.* 2014;13:545-56. Erratum in: *Lancet Neurol.* 2013;13:536.
6. Peyrin-Biroulet L, et al. Presented at: UEG Week, October 15–19, 2016; Vienna, Austria. LB20.

Disclosures

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