Safety and Immune Modulatory Properties of Etrasimod (APD334), a Next-Generation Oral, Selective Sphingosine 1-Phosphate Receptor Modulator, in Healthy Volunteers

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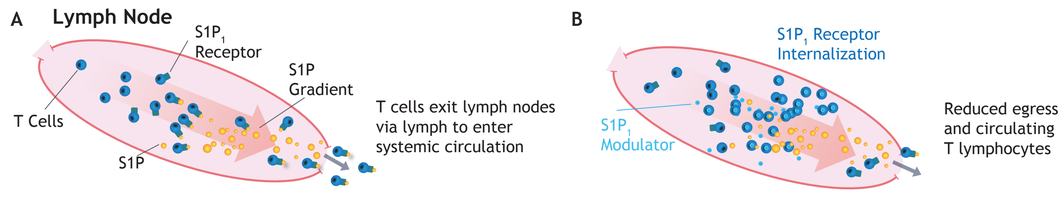
Background

- Sphingosine 1-phosphate (S1P), a membrane-derived lysophospholipid signalling molecule, influences many physiological processes through 5 different receptor subtypes: $S1P_1$, $S1P_2$, $S1P_3$, $S1P_4$, and $S1P_5$[1,2]
- In the immune system, the $S1P_1$ receptor regulates the migration of T and B cells out of lymphoid organs into blood (**Figure 1A**)[1–3]
- $S1P_1$ receptor modulators induce internalization and degradation of the $S1P_1$ receptor, selectively reducing migration of naïve and central memory T lymphocytes and B cells, thereby reducing the release of inflammatory cytokines while maintaining immune surveillance (**Figure 1B**)
- Etrasimod (APD334) is a potent, oral S1P receptor modulator that selectively targets $S1P_1$, $S1P_4$, and $S1P_5$, while avoiding the $S1P_2$ and $S1P_3$ receptor subtypes that have been associated with potentially serious adverse events (AEs)[4]
- Etrasimod is currently in development for the treatment of immune-mediated inflammatory disorders (IMIDs), including inflammatory bowel disease

Figure 1 $S1P_1$ Receptor Modulation Reduces Migration of T Lymphocytes From Lymph Nodes[a]

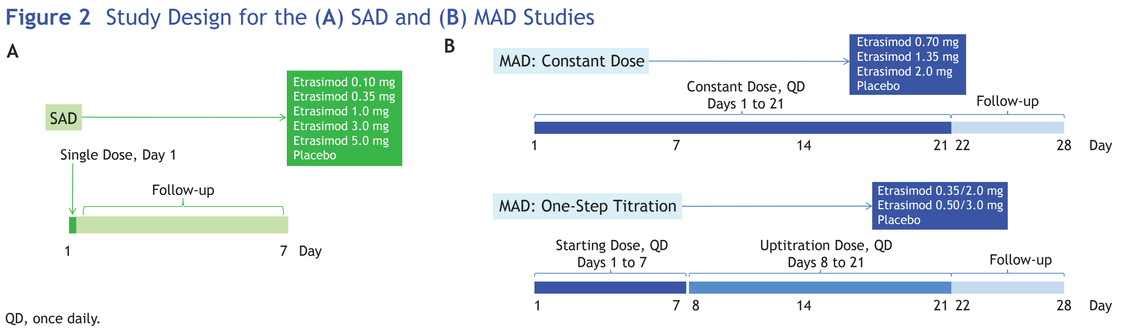


[a]Etrasimod had a similar effect on B cells.

Methods

- Two randomised, double-blind, placebo-controlled, phase 1 studies were conducted in healthy adults (aged 18–45 years; weight of 50–100 kg) to evaluate the safety, tolerability, and pharmacokinetics of etrasimod
  - In the single ascending dose (SAD) study, 5 cohorts of 8 subjects each were randomised 1:3 to receive a single dose of placebo or etrasimod 0.10 mg, 0.35 mg, 1.0 mg, 3.0 mg, or 5.0 mg. Subjects were observed for 7 days after study drug administration (**Figure 2A**)
  - In the multiple ascending dose (MAD) study, 5 cohorts of 12 subjects each were randomised 1:5 to receive either placebo or etrasimod, either constant or titrated (**Figure 2B**)
- Peripheral blood was collected predose and over the course of treatment for complete blood cell count and lymphocyte immunophenotyping
- Safety was assessed by AE reporting, electrocardiogram, continuous telemetry, physical examination with ophthalmoscopy, and pulmonary function testing

Figure 2 Study Design for the (**A**) SAD and (**B**) MAD Studies



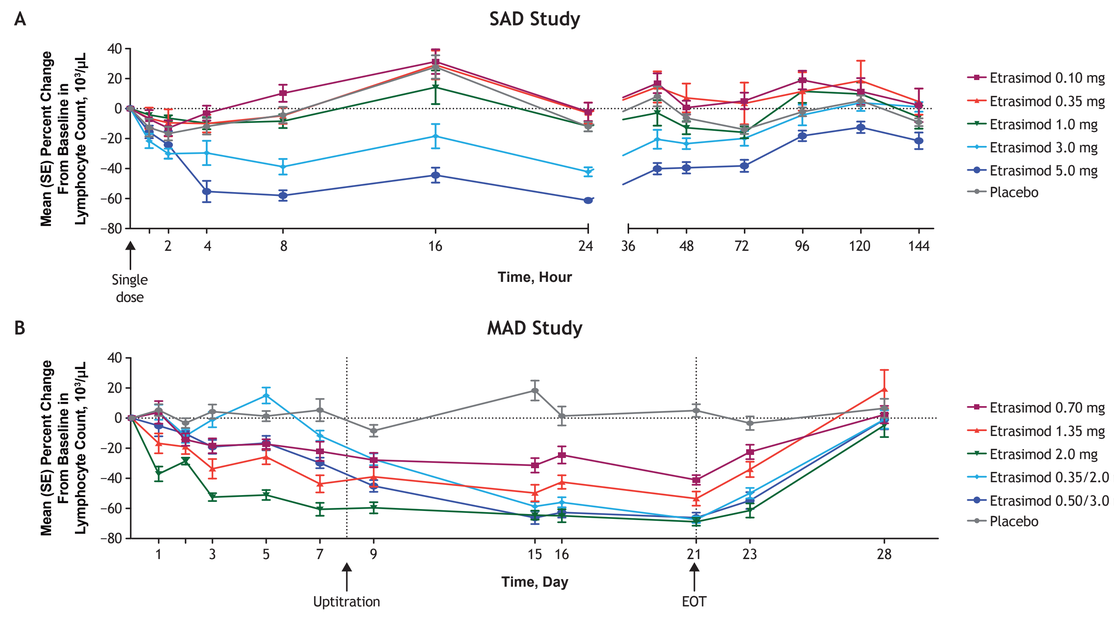
QD, once daily.

Results

Lymphocyte Reduction

- In both the SAD and MAD studies:
  - A dose-dependent reduction in total peripheral lymphocyte count occurred with etrasimod treatment (**Figure 3**)
  - Upon study medication discontinuation, lymphocyte levels increased towards baseline for the etrasimod 5.0 mg group and returned to baseline for all other etrasimod dose groups

Figure 3 Percent Change From Baseline in Total Peripheral Blood Lymphocyte Count Over Time by Treatment Group in the (**A**) SAD Study (Baseline to Day 7/Exit) and (**B**) MAD Study (Baseline to Day 28/Follow-up)



EOT, end of treatment; SE, standard error.

Immunophenotyping

- In the SAD study:
  - Etrasimod at doses ≤1.0 mg had little or no effect on T-cell subsets compared with the placebo group
  - Single etrasimod doses of 3.0 mg and 5.0 mg reduced total T-cell counts
- In the MAD study, the etrasimod 2.0-mg dose reduced total T- and B-cell counts (**Table 1**)
  - Etrasimod 2.0 mg decreased CD4 and CD8 T cells, particularly the T-naïve and T-central memory subsets (**Table 1**)
    - T-helper, T-cytotoxic, T-naïve, and T-central memory subsets were substantially decreased compared with placebo
    - T-effector memory cells were modestly reduced
    - There was no effect on natural killer cells

Table 1 Mean Percent Change From Baseline to Day 21 in Immune Cell Levels in the MAD Study

Cell Type	Percent Total (SE)	
	Etrasimod 2.0 mg QD[a] (n = 10)	Placebo (n = 2)
T-helper cell ($CD3^+/CD4^+$)	−81.2 (1.85)	−20.5 (12.85)
T-cytotoxic cell ($CD3^+/CD8^+$)	−43.3 (6.50)	−24.9 (14.01)
T-naïve cell ($CCR7^+/CD45RA^+/CD3^+$)	−80.3 (2.72)	−35.6 (6.86)
T-effector memory cell ($CCR7^-/CD45RA^-/CD3^+$)	−12.6 (9.34)	+9.4 (9.37)
T-central memory cell ($CCR7^+/CD45RA^-/CD3^+$)	−61.8 (3.68)	−10.8 (17.01)
B cell ($CD19^+$)	−73.7 (4.43)	−63.1 (0.57)
Natural killer cell ($CD3^-/CD56^+$)	51.8 (12.79)	67.5 (57.50)

[a]Constant dose. QD, once daily; SE, standard error.

Adverse Events

- Treatment-emergent AEs (TEAEs) are summarized in **Table 2**
- In the SAD study, a total of 38 TEAEs were reported by 20 subjects (50%)
  - AEs were reported by 17 subjects (57%) in the combined etrasimod groups and 3 subjects (30%) in the placebo group
- In the MAD study, a total of 155 TEAEs were reported by 50 subjects (83%)
  - AEs were reported by 40 subjects (80%) in the combined etrasimod groups and 10 subjects (100%) in the placebo group
- Most AEs were reported as mild in severity. None of the events resulted in study termination
- No deaths or serious AEs occurred in either study
- No clinically significant changes from baseline in physical examination, pulmonary function, clinical laboratory tests, visual acuity, or ophthalmoscopy findings were observed in either study

Table 2 Summary of TEAEs Reported by >1 Subject and More Frequently by Etrasimod-Treated Subjects in the SAD and MAD Studies

AE, n (%)	SAD Study						MAD Study					
	Placebo (n = 10)	Etrasimod 0.10 mg (n = 6)	Etrasimod 0.35 mg (n = 6)	Etrasimod 1.0 mg (n = 6)	Etrasimod 3.0 mg (n = 6)	Etrasimod 5.0 mg (n = 6)	Placebo (n = 10)	Etrasimod 0.70 mg (n = 10)	Etrasimod 1.35 mg (n = 10)	Etrasimod 2.0 mg (n = 10)	Etrasimod 0.35/2.0 mg (n = 10)	Etrasimod 0.50/3.0 mg (n = 10)
Cardiovascular												
1st or 2nd-degree AV block	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (50)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Gastrointestinal												
Constipation	1 (10)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (20)	3 (30)	3 (30)	2 (20)	0 (0)
Diarrhoea	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	1 (10)	3 (30)	2 (20)	0 (0)	2 (20)	0 (0)
Nausea	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	2 (20)	1 (10)	3 (30)	1 (10)	0 (0)	0 (0)
Abdominal pain	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (20)	0 (0)	0 (0)	1 (10)	3 (30)	0 (0)
Vomiting	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (20)	0 (0)	0 (0)
Dermatological												
Dermatitis contact	2 (20)	0 (0)	1 (17)	2 (33)	1 (17)	0 (0)	6 (60)	1 (10)	7 (70)	5 (50)	5 (50)	2 (20)
Pruritus	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (10)	0 (0)	1 (10)	0 (0)	0 (0)
Other												
Leucopenia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (40)
Neutropenia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (20)
Fatigue	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	1 (17)	0 (0)	0 (0)	0 (0)	0 (0)	1 (10)	0 (0)
Back pain	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	2 (20)	2 (20)	0 (0)	0 (0)	1 (10)
Headache	2 (20)	1 (17)	1 (17)	0 (0)	1 (17)	3 (50)	4 (40)	2 (20)	1 (10)	1 (10)	1 (10)	3 (30)
Dizziness	1 (10)	0 (0)	0 (0)	0 (0)	2 (33)	1 (17)	0 (0)	0 (0)	1 (10)	0 (0)	0 (0)	0 (0)
Menstrual disorder	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (20)
Ear discomfort	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (10)	0 (0)	0 (0)	1 (10)
Nasal congestion	1 (10)	1 (17)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (10)

AV, atrioventricular.

Table 3 Maximum Change From Baseline in HR During 24 Hours Postdose in the SAD Study (Day 1)

Treatment Group[a]	LSM Difference vs Placebo in HR, bpm	95% Confidence Interval	*P* Value
Etrasimod 0.10 mg	+0.18	−5.44 to +5.80	0.9482
Etrasimod 0.35 mg	−3.78	−9.41 to +1.85	0.1807
Etrasimod 1.0 mg	−3.12	−8.65 to +2.43	0.2622
Etrasimod 3.0 mg	−10.06	−15.65 to −4.48	0.0009
Etrasimod 5.0 mg	−13.06	−18.59 to −7.54	<0.0001

[a]n = 6 for each etrasimod dose.
bpm, beats per minute; HR, heart rate; LSM, least-squares mean.

Table 4 Maximum Change From Baseline in HR During the First 24 Hours Postdose in the MAD Study (Day 1)

Treatment Group[a]	LSM Difference vs Placebo in HR, bpm	95% Confidence Interval	*P* Value
Etrasimod 0.35 mg[b]	−1.24	−5.54 to +3.06	0.570
Etrasimod 0.50 mg[c]	−4.10	−8.40 to +0.20	0.060
Etrasimod 0.70 mg	−6.10	−10.30 to −1.70	0.007
Etrasimod 1.35 mg	−6.36	−10.66 to −2.06	0.005
Etrasimod 2.0 mg	−3.16	−7.48 to +1.15	0.150

[a]n = 10 for each etrasimod dose.
[b]Etrasimod 0.35 mg on day 1 with uptitration to etrasimod 2.0 mg on day 8.
[c]Etrasimod 0.50 mg on day 1 with uptitration to etrasimod 3.0 mg on day 8.
bpm, beats per minute; HR, heart rate; LSM, least-squares mean.

Cardiac AEs

- In the SAD study, 3 subjects treated with etrasimod 5.0 mg experienced atrioventricular (AV) block: first-degree AV block (n = 2) and 1 patient with second-degree AV block (Mobitz type I)
- In the MAD study, 3 subjects developed first-degree AV block after the initial dose, 1 each in the placebo, etrasimod 2.0-mg, and etrasimod 0.50/3.0-mg titration groups. All events were transient and resolved spontaneously
  - No second-degree or higher AV block or symptomatic bradycardia occurred

Heart Rate

- In both studies, there was a modest, transient, asymptomatic decline in heart rate (HR) which started about 1 hour postdose and reached a nadir approximately 4-8 hours postdose, attenuating thereafter
- In the SAD study, the maximum change from baseline in HR over 24 hours was significantly greater with the highest etrasimod doses (3.0 and 5.0 mg only) than with placebo (**Table 3**)
- In the MAD study, there was a modest decrease in HR over 24 hours following the first dose in all treatment groups (**Table 4**). Subsequent daily dosing did not lead to further reductions in heart rate
- Etrasimod dose titration from 0.35 to 2.0 mg or from 0.50 to 3.0 mg did not alter HR effects relative to constant doses of 2.0 or 3.0 mg over 21 days

Blood Pressure

- No clinically significant decreases in systolic and diastolic blood pressure were observed with etrasimod treatment in either study

Summary and Conclusions

- Etrasimod rapidly decreased circulating lymphocytes in healthy subjects with a fast recovery after treatment discontinuation
- The primary effect was on T-helper and T-naïve cells (T helper, T naïve > T central memory > T cytotoxic >> T effector memory), suggesting that etrasimod may selectively target T-cell subtypes involved in IMIDs
- Etrasimod appeared to be well tolerated in healthy subjects when administered up to the targeted therapeutic dose of 2.0 mg once daily
- At etrasimod doses up to 2.0 mg, modest asymptomatic declines in HR occurred on the first day of dosing which were not exacerbated by continuous dosing
- Titration of etrasimod did not alter cardiovascular effects
- Etrasimod may play an important role in treating a broad range of IMIDs by preferentially reducing the levels of T and B cells involved in autoimmunity, while preserving the levels of cells responsible for immune surveillance

References

1. Peyrin-Biroulet L, et al. *Autoimmun Rev*. 2017;16(5):495–503.
2. Nielsen OH, et al. *Trends Mol Med*. 2017;23(4):362–374.
3. Neurath MF. *Nat Rev Gastroenterol Hepatol*. 2017;14(5):269–278.
4. Christopher R, et al. Advances in Inflammatory Bowel Diseases (AIBD) Annual Meeting; December 8–10, 2016; Orlando, FL; Poster P-261.

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