Steady-State Trough Concentrations and Their Relationship to Selected Demographic and Clinical Response Measures in Etrasimod-Treated Patients with Moderately-to-Severely Active Ulcerative Colitis

D. Alexander Oh, PhD, Caroline A. Lee, PhD, Yong Tang, PhD, Christopher H. Cabell, MD, MHS, John S. Grundy, PhD

Arena Pharmaceuticals, Inc., San Diego, CA

Background

- Etrasimod (APD334) is a once-daily (QD), oral, sphingosine 1-phosphate (S1P) receptor modulator that selectively targets $S1P_1$, $S1P_4$, and $S1P_5$ receptors[1-3]
- S1P receptor modulators reduce lymphocyte egress from lymph nodes, thereby decreasing circulating lymphocytes and subsequent tissue inflammation and damage[1]

Phase 2 Study (OASIS)

- A phase 2, randomized, double-blind, placebo-controlled, parallel group, multicenter, multinational, proof-of-concept, dose-ranging study evaluated the efficacy and safety of etrasimod in adult patients with moderately-to-severely active ulcerative colitis (UC) (OASIS [ClinicalTrials.gov identifier: NCT02447302])[3]
  - A total of 156 patients were randomized to receive etrasimod 1 mg (n = 52), etrasimod 2 mg (n = 50), or placebo (n = 54) QD for 12 weeks
- Study results demonstrated a positive and clinically meaningful efficacy and safety profile for etrasimod 2 mg QD[3,4]

Objective

- To assess steady-state plasma trough concentrations ($C_{ss,trough}$) of etrasimod and their relationship to selected demographic characteristics (sex, age, total body weight) and clinical responses (modified Mayo Clinic Score [MCS] and lymphocyte counts) in adult patients with UC from the OASIS study

Methods

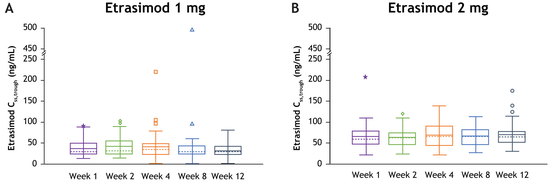
- Pre-dose blood samples were obtained at weeks 1, 2, 4, 8, and 12
- Etrasimod $C_{ss,trough}$ values were determined at each evaluated week and summarized by treatment to confirm achievement of steady-state
- $C_{ss,trough}$ values at each evaluated week were averaged ($C_{ss,avg\ trough}$) and the latter metric summarized by treatment and sex
- The relationship of dose-normalized $C_{ss,avg\ trough}$ values with patient age (range: 21–67 years) and total body weight (range: 47–130 kg) was explored
- The relationship of $C_{ss,trough}$ values with selected clinical response measures at week 12, including change from baseline in modified MCS (range 0–9; includes endoscopy findings, rectal bleeding, and stool frequency) and lymphocyte count was explored

Results

- Dose-proportional arithmetic mean $C_{ss,trough}$ values were observed (**Figure 1**)
- Dose-proportional $C_{ss,avg\ trough}$ values were observed for etrasimod 1 mg and 2 mg (**Table 1**)
  - Moderate between-subject variability was observed
  - Geometric mean $C_{ss,avg\ trough}$ values were higher in females than males by approximately 34% in the etrasimod 1-mg group and 30% in the etrasimod 2-mg group
  - The sex difference is generally consistent with the 20.4% lower overall mean total body weight in females (63.0 kg) vs males (79.1 kg) receiving etrasimod in the study

Results (cont'd)

Figure 1. Etrasimod steady-state trough concentrations were achieved by week 1 and maintained through week 12 in patients treated with (A) etrasimod 1 mg or (B) etrasimod 2 mg



Dashed line, median; solid line within box, mean; upper and lower bounds of box, interquartile range

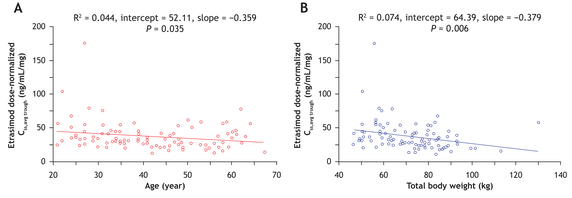
Table 1. Etrasimod $C_{ss,avg\ trough}$ by dose and sex

	Etrasimod 1 mg			Etrasimod 2 mg*		
	Male (n = 30)	Female (n = 22)	Overall (n = 52)	Male (n = 26)	Female (n = 22)	Overall (n = 48)
$C_{ss,avg\ trough}$ (ng/mL)						
Geometric Mean	29.96	40.27	33.96	57.91	75.71	65.48
Geometric CV %	46.80	58.22	53.85	36.59	38.01	39.55

avg, average; CV, coefficient of variation; ss, steady state.
* Two patients treated with etrasimod 2 mg (one male and one female) were excluded from the summary statistics due to missing data/information.

- Statistically significant linear relationships with shallow negative slopes were seen for dose-normalized $C_{ss,avg\ trough}$ values versus patient age (**Figure 2A**) and total body weight (**Figure 2B**)
  - The age effect is generally consistent with the 18.9% higher overall mean total body weight in patients >41 years old (78.8 kg; n = 47) vs patients ≤41 years old (66.3 kg; n = 55) receiving etrasimod in the study

Figure 2. Dose-normalized etrasimod $C_{ss,avg\ trough}$ by (A) age and (B) total body weight



- Compared with the predicted dose-normalized $C_{ss,avg\ trough}$ value of a typical patient 45 years of age receiving etrasimod in this study, relatively modest differences are predicted for the typical patient 15 or 70 years of age (**Table 2**)
- Similarly, compared with the predicted dose-normalized $C_{ss,avg\ trough}$ value for a typical patient with total body weight of 70 kg receiving etrasimod in this study, relatively modest differences are predicted for the typical patient with total body weight of 40 or 100 kg (**Table 3**)

Table 2. Typical predicted dose-normalized etrasimod $C_{ss,avg\ trough}$ for various ages

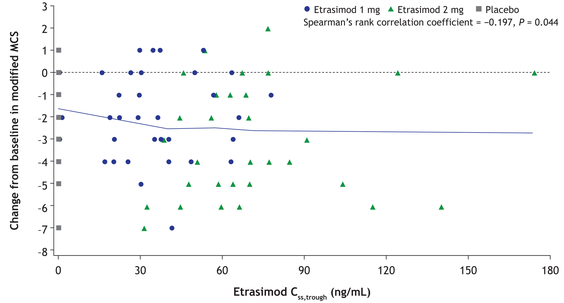
Age (years)	Predicted $C_{ss,avg\ trough}$ (ng/mL/mg)	Ratio versus 45 years of age
15	46.7	1.30
25	43.1	1.20
30	41.3	1.15
40	37.7	1.05
45	**35.9**	**1.00**
50	34.1	0.950
60	30.5	0.850
70	27.0	0.750

Table 3. Typical predicted dose-normalized etrasimod $C_{ss,avg\ trough}$ for various total body weights

Total body weight (kg)	Predicted $C_{ss,avg\ trough}$ (ng/mL/mg)	Ratio versus 70-kg total body weight
40	49.2	1.30
50	45.4	1.20
60	41.6	1.10
70	**37.8**	**1.00**
80	34.1	0.900
90	30.3	0.800
100	26.5	0.699

- At week 12, the exposure-response relationship between etrasimod $C_{ss,trough}$ and change from baseline in modified MCS was statistically significant, and the trend line suggests that the greatest response is typically seen with $C_{ss,trough}$ levels of at least 45–50 ng/mL, which are more commonly achieved with a 2 mg QD dose of etrasimod (**Figure 3**)

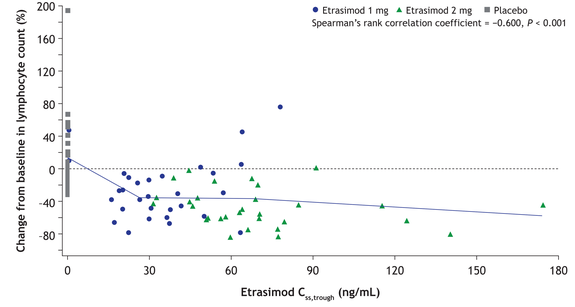
Figure 3. Change from baseline in modified MCS vs etrasimod $C_{ss,trough}$ at week 12



MCS, Mayo Clinic Score.
*Trend line is a locally weighted regression line fit.

- Similarly, the relationship between $C_{ss,trough}$ and percent change from baseline in lymphocyte counts was statistically significant and the trend line suggests that the greatest response is typically seen with $C_{ss,trough}$ levels of at least 30–60 ng/mL, which are more commonly achieved with a 2 mg QD dose of etrasimod (**Figure 4**)

Figure 4. Percentage change from baseline in lymphocyte counts vs etrasimod $C_{ss,trough}$ at week 12



*Trend line is a locally-weighted regression line fit.

Conclusions

- Dose-proportional etrasimod $C_{ss,trough}$ values were achieved and maintained from week 1 to week 12 in patients with moderately-to-severely active UC receiving once-daily oral etrasimod 1 mg or 2 mg
- Only modest sex, age, and total body weight effects were observed
  - Observed effects contributed to variable etrasimod trough exposure, but the effects were not considered clinically meaningful or necessitating any dose adjustments in subsequent adult clinical trials
  - Sex and age effects are likely mainly due to differences in total body weight between sexes and between older and younger adults
- Exploratory exposure-response relationships were consistent with previously reported dose-response relationships
- Demographic effect assessments and exploratory exposure-response relationships support selection of a fixed etrasimod 2-mg QD dosing regimen for phase 3 testing in adult patients with UC
- More extensive evaluations using population pharmacokinetic and pharmacokinetic/pharmacodynamic approaches are planned

References

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Acknowledgements

This study was funded by Arena Pharmaceuticals, Inc., San Diego, CA and was conducted by PPD®, Wilmington, NC. Jennifer Giel, PhD, and Elizabeth Strickland, PhD, of inScience Communications, Springer Healthcare (Philadelphia, PA) provided medical writing support, which was funded by Arena Pharmaceuticals, Inc.

Disclosures

All authors are employees of Arena Pharmaceuticals, Inc.

Presented at the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN)/Council for Pediatric Nutrition Professionals (CPNP)/Association of Pediatric Gastroenterology and Nutrition Nurses (APGNN) Annual Meeting, October 17–19, 2019, Chicago, IL