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

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Background/Aims: Etrasimod is a once-daily, oral, selective, sphingosine-1-phosphate receptor modulator in development for immune-mediated inflammatory disorders. We examined etrasimod steady-state plasma trough concentrations ($C_{ss,trough}$) and their relationship to demographics and clinical responses in patients with ulcerative colitis (UC).

Materials and Methods: Etrasimod $C_{ss,trough}$ and clinical responses were evaluated from the randomized, double-blind, parallel-group, 12-week, Phase 2 OASIS study of once-daily etrasimod 1 mg (n=52 [30 males]), 2 mg (n=50 [27 males]), or placebo (n=54 [32 males]) in patients with moderately-to-severely active UC (modified Mayo Clinic Score [mMCS] 4–9, endoscopic subscore ≥2, rectal bleeding subscore ≥1). We measured etrasimod $C_{ss,trough}$ in pre-dose blood samples drawn at weeks 1, 2, 4, 8, and 12, averaged across weeks ($C_{ss,avg\ trough}$), and summarized by treatment and gender. We explored relationships of dose-normalized $C_{ss,avg\ trough}$ values with patient age and total body weight (TBW) using linear regression. Exposure-response (E-R) relationships of $C_{ss,trough}$ with clinical responses (change from baseline [BL] in mMCS and lymphocyte count at week 12) were assessed using Spearman's correlation and locally weighted regression line fit.

Results: Arithmetic mean $C_{ss,trough}$ was similar across time points (range: 31.8–42.5 ng/mL and 64.1–71.1 ng/mL for 1 mg and 2 mg, respectively), indicating that steady-state was achieved in week 1. $C_{ss,avg\ trough}$ values were dose-proportional (geometric mean [GM]: 33.96 and 65.48 ng/mL, respectively), with moderate intersubject variability (Table 1). The GM $C_{ss,avg\ trough}$ was ~30% higher in women than men. Dose-normalized $C_{ss,avg\ trough}$ values negatively correlated with age (slope −0.359, P = 0.035) and TBW (slope −0.379, P = 0.006). Exploratory E-R relationships between $C_{ss,trough}$ and clinical responses were statistically significant; the highest response was seen with $C_{ss,trough}$ levels of ≥45–50 ng/mL for mMCS (Fig. 1) and ≥30–60 ng/mL for lymphocyte count (Fig. 2).

Conclusion: Dose-proportional etrasimod $C_{ss,trough}$ levels were achieved and maintained from weeks 1 to 12 in patients with moderately-to-severely active UC. Modest gender, age, and TBW effects contributed to variability in trough exposure which was not clinically meaningful. Exploratory E-R relationships were consistent with previously reported dose-response relationships in the Phase 2 study and support an etrasimod 2-mg once-daily dosing regimen for Phase 3. ClinicalTrial.gov: NCT02447302

Tables/Figures:

Summary Statistic $C_{ss\ avg\ trough}$ (ng/mL)	Treatment Group					
	Etrasimod 1 mg			Etrasimod 2 mg		
	Male (N = 30)	Female (N = 22)	Overall (N = 52)	Male (N = 26)	Female (N = 22)	Overall (N = 48)
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

Abbreviation: CV = coefficient of variation.

Table 1: Summary of etrasimod $C_{ss\ avg\ trough}$ by treatment (overall and by gender). Placebo treated patients not shown.

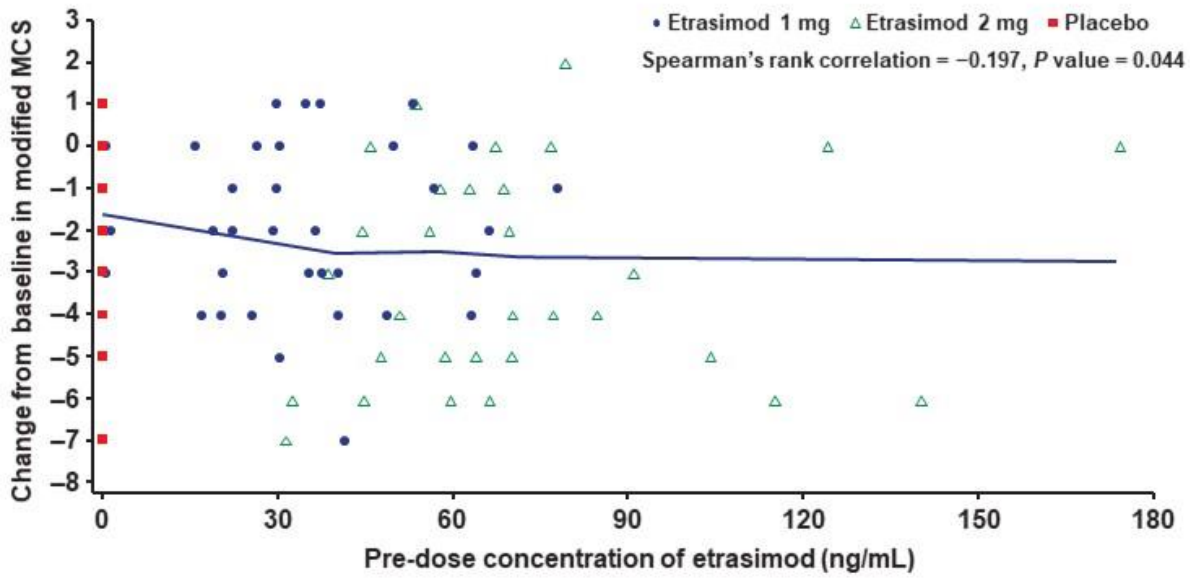

Figure 1: Scatter plot of change from baseline in modified Mayo Clinic Score vs etrasimod pre-dose concentration ($C_{ss,trough}$) at week 12. Line shown is a locally weighted regression fit.

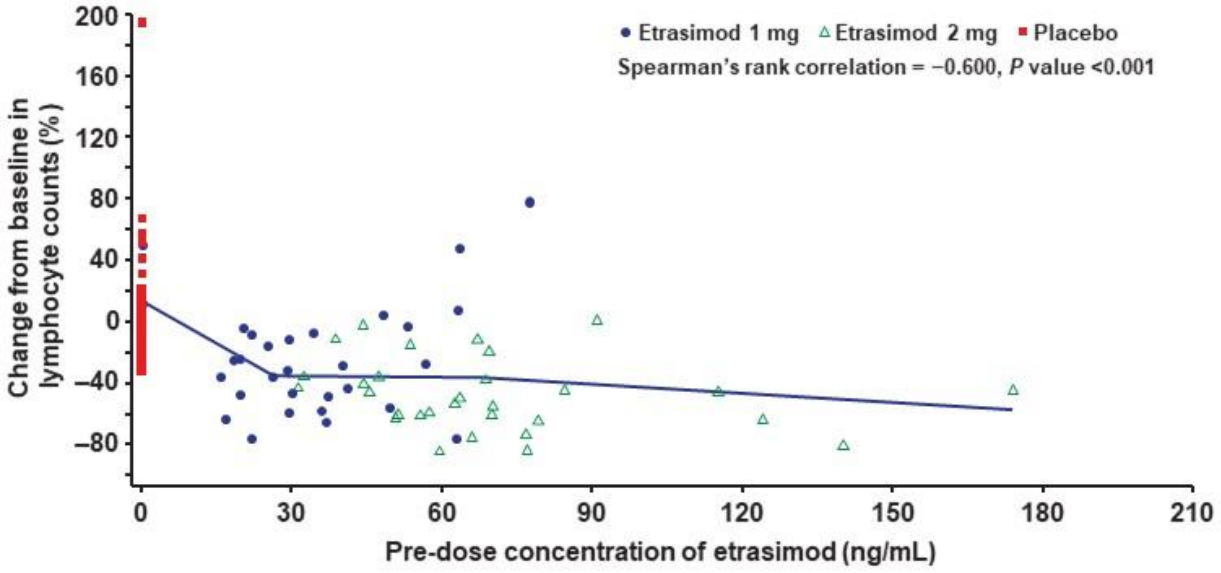

Figure 2: Scatter plot of percentage change from baseline in lymphocyte counts (%) vs etrasimod pre-dose concentration ($C_{ss,trough}$) at week 12. Line shown is a locally weighted regression fit.