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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Disclosures: All authors are employees of Arena Pharmaceuticals.

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,tragh}) and their relationship to demographics and clinical responses in patients with ulcerative colitis (UC).

Materials and Methods: Etrasimod C_{ss,tragh} 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,tragh} in pre-dose blood samples drawn at weeks 1, 2, 4, 8, and 12, averaged across weeks (C_{ss,avg,tragh}), and summarized by treatment and gender. We explored relationships of dose-normalized C_{ss,avg,tragh} values with patient age and total body weight (TBW) using linear regression. Exposure-response (E-R) relationships of C_{ss,tragh} 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,tragh} 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,tragh} 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,tragh} was ~30% higher in women than men. Dose-normalized C_{ss,avg,tragh} 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,tragh} and clinical responses were statistically significant; the highest response was seen with C_{ss,tragh} 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,tragh} 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
Table 1: Summary of etrasimod $C_{ss\text{ avg} \text{ trough}}$ by treatment (overall and by gender). Placebo treated patients not shown.

<table>
<thead>
<tr>
<th>Summary Statistic</th>
<th>Treatment Group</th>
<th>Etrasimod 1 mg</th>
<th>Etrasimod 2 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male (N = 30)</td>
<td>Female (N = 22)</td>
<td>Overall (N = 52)</td>
</tr>
<tr>
<td>Geometric Mean</td>
<td>29.96</td>
<td>40.27</td>
<td>33.96</td>
</tr>
<tr>
<td>Geometric % CV</td>
<td>46.80</td>
<td>58.22</td>
<td>53.85</td>
</tr>
</tbody>
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Abbreviation: CV = coefficient of variation.
Figure 1: Scatter plot of change from baseline in modified Mayo Clinic Score vs etrasimod pre-dose concentration ($C_{ss,\text{trough}}$) 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.