Background

• Sphingosine-1-phosphate (S1P), a membrane-derived lysophospholipid signaling molecule, is implicated in a vast array of physiological and pathophysiological processes.

• Etrasimod is an oral, potent, next-generation S1P modulator in clinical development for modulation, while reducing immunosuppressive side effects and avoiding cardiotoxicity associated with S1P receptor agonists.

• 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 of age, body weight of 50–100 kg, who were not taking any prescription medications.

• Etrasimod was administered once daily for 21 days (Table 1).

• Pharmacokinetic Properties

Pharmacodynamic 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.

• Median maximum absorption occurred between 6–8 hours across all dose levels.

• Mean terminal half-life of etrasimod in plasma was 26.0–32.5 hours.

• Mean terminal half-life of etrasimod was consistent between dosing paradigms: 26.3–28.3 hours.

Safety and Tolerability

• Etrasimod was well tolerated at all doses tested in the study.

• No serious adverse events (SAEs) occurred during the study.

• Adverse events (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.

Table 5. Summary of mean plasma pharmacokinetic parameters* of etrasimod after oral administration from 0.35 to 3.0 mg for 21 days (Cohort 1–3)

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Cmax (ng/mL)</th>
<th>AUC0-24 (ng*h/mL)</th>
<th>AUClast (ng*h/mL)</th>
<th>t1/2Z (h)</th>
<th>CL/F (mL/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.35 mg</td>
<td>307</td>
<td>1140</td>
<td>49700</td>
<td>12.0 (2.0–12.0)</td>
<td>1100 (219)</td>
</tr>
<tr>
<td>1.0 mg</td>
<td>1008</td>
<td>3760</td>
<td>14900</td>
<td>11.7 (0.8–12.0)</td>
<td>994 (266)</td>
</tr>
<tr>
<td>3.0 mg</td>
<td>3500</td>
<td>12160</td>
<td>41800</td>
<td>20.0 (2.0–12.0)</td>
<td>430 (136)</td>
</tr>
</tbody>
</table>

* Cmax, maximum plasma concentration; MRT, mean residence time; NA, not applicable; SD, standard deviation; tmax, time of maximum observed concentration; t1/2Z, terminal half-life; CL/F, apparent systemic clearance.

Table 6. Etrasimod dose proportionality

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Cmax (ng/mL)</th>
<th>AUC0-24 (ng*h/mL)</th>
<th>AUClast (ng*h/mL)</th>
<th>t1/2Z (h)</th>
<th>CL/F (mL/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.35 mg</td>
<td>307</td>
<td>1140</td>
<td>49700</td>
<td>12.0 (2.0–12.0)</td>
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* Cmax, maximum plasma concentration; MRT, mean residence time; NA, not applicable; SD, standard deviation; tmax, time of maximum observed concentration; t1/2Z, terminal half-life; CL/F, apparent systemic clearance.

Conclusions

• Etrasimod exposure increased in a dose proportional manner after a single dose.

• 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 counts with the maximum effects plateauing at the 2.0 mg dose.

• These results support etrasimod’s clinical development at 0.7 mg and 2.0 mg in ulcerative colitis, and potentially other autoimmune indications.

References

4. Lassen are employees of Arena Pharmaceuticals, Inc.; Matilde Sanchez-Kam, Michael Morgan and William Shanahan were employees of Arena Pharmaceuticals, Inc.
5. Acknowledgements

Disclosures

Lassen are employees of Arena Pharmaceuticals, Inc.; Matilde Sanchez-Kam, Michael Morgan and William Shanahan were employees of Arena Pharmaceuticals, Inc. Lassen discloses ownership of Arena Pharmaceuticals, Inc. Other authors disclose no potential conflicts of interest.

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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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Etrasimod is an oral, potent, next-generation S1P modulator in clinical development for the treatment of ulcerative colitis. It is designed to selectively target S1P receptor subtypes 1, 4, and 5 in order to provide systemic and local immune cell modulation, while reducing immunosuppressive side effects and avoiding cardiotoxicity associated with S1P receptor agonists.

The pharmacokinetics were dose-proportional after single doses of 0.7 mg to 2.0 mg. After 21 days of dosing, Cmax and AUC0-24 increased in more than a dose proportional manner (Table 6).