Conclusions

- Etrasimod was well tolerated at all single and multiple doses up to 3.0 mg. There were no clinically significant changes in ocular exams, liver and pulmonary function tests.
- Treatment with etrasimod produces a dose-dependent, significant and sustained decrease in lymphocyte count with the 2.0 mg dose, with complete lymphocyte recovery after 7 days.
- These results support the further clinical development of etrasimod in autoimmune and inflammatory diseases.

Introduction

- Sphingosine-1-phosphate (S1P) is a membrane-derived lysophospholipid signaling molecule involved in many physiological and pathophysiological processes.⁴
- Non-selective S1P modulators have been associated with potentially serious adverse events (AEs)⁵.
- Etrasimod is an oral, potent, next-generation S1P modulator with an optimised S1P receptor affinity profile in Phase 2 clinical development for ulcerative colitis.
- Etrasimod selectively targets S1P receptor subtypes 1, 4, and 5 to reduce inflammation and modulate lymphocyte trafficking, while potentially reducing immunosuppressive side effects and avoiding adverse side effects associated with subtypes 2 and 3⁶.

Objectives

- To investigate safety, tolerability and pharmacodynamic properties of single- and multiple ascending doses of etrasimod in healthy adults.

Methods

- Two Phase I, randomised, double-blind studies evaluated safety and pharmacodynamics of etrasimod in:
  - Single-ascending study:
    - 0.1, 0.35, 1.0, 3.0 or 5.0 mg (n=6 per cohort) or placebo (n=10)
    - Multiple ascending dose study (Figure 1) 1.0, 1.35 or 2.0 mg (n=10 per cohort) or placebo (n=10), for 21 days
- Subjects included healthy adults (18–45 years; 50–100 kg) who were non-smokers and not taking prescription medications.

Results

- Single-ascending study
  - All 40 subjects completed the study.
  - Safety and tolerability:
    - Etrasimod was well tolerated at doses ≤3.0 mg.
    - Most commonly reported AEs were headache (0.1 mg: 1/6; 0.35 mg: 1/6; 1.0 mg: 5/6; 3.0 mg: 3/6; placebo: 2/10) and contact dermatitis (0.35 mg: 1/6; 1.0 mg: 2/6; 3.0 mg: 1/6; placebo: 2/10).
    - In the highest dose, 5.0 mg:
      - One subject had asymptomatic first and second degree atrioventricular (AV) block with bradycardia.
      - Two subjects had first degree AV block, one associated with bradycardia.
    - Further dose escalation was discontinued.
    - There were no serious AEs reported.

- Multiple ascending dose study
  - 60 subjects were enroled, 59 completed (1 withdrew consent for personal reasons).
  - Safety and tolerability:
    - Etrasimod was well tolerated at all tested doses (non-titrated 0.7, 1.35, 2.0 mg as well as one-step titration from 0.35 mg to 2.0 mg and from 0.5 to 3.0 mg).
    - AEs occurring in one or more subjects are shown in Table 1.
    - Most AEs were mild and not dose-responsive (except leukopenia, which occurred only in the 0.5/3.0 mg dose group).
    - Three subjects developed first degree AV block defined as PR >200 ms:
      - one subject in the placebo group, one in the 2.0 mg dose group and one in the 0.3/0.3 mg dose group.
    - No second degree or higher AV block was observed.
    - There were no serious AEs reported; no discontinuations due to AEs.
    - There were no clinically significant changes in ocular exams, liver and pulmonary function tests over 21 days of treatment.

Pharmacodynamic responses

- Treatment with etrasimod produced a dose-dependent and sustained decrease in lymphocyte count, with potent lymphocyte-lowering at 2.0 mg (Figure 2).
- Etrasimod 2.0 mg reduced lymphocyte counts by 69% from baseline to day 21.
- Lymphocyte counts returned to baseline within 7 days of discontinuation (Figure 2).

Table 1. Summary of treatment-emergent AEs reported by ≥1 subject (n=60) receiving etrasimod or placebo for 21 days in the multiple ascending dose study

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Placebo, once daily</th>
<th>Etrasimod once daily, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.7 mg</td>
<td>0.7, 1.35, 2.0</td>
<td>0.35/2.0/2.0* 0.5/3.0**</td>
</tr>
<tr>
<td>Subject, n (%)</td>
<td>10/10/10/10/10</td>
<td>10/10/10/10/10</td>
</tr>
<tr>
<td>AEs, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatitis contact</td>
<td>6 (60)</td>
<td>1 (10) 7 (70) 5 (50) 5 (50) 2 (20)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (40)</td>
<td>2 (20) 1 (10) 1 (10) 1 (10) 3 (30)</td>
</tr>
<tr>
<td>Constipation</td>
<td>0</td>
<td>2 (20) 3 (30) 3 (30) 2 (20) 0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (10)</td>
<td>3 (30) 2 (20) 0 2 (20) 0</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (20)</td>
<td>1 (10) 3 (30) 1 (10) 0 0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2 (20)</td>
<td>0 0 1 (10) 3 (30) 0</td>
</tr>
<tr>
<td>Back pain</td>
<td>0</td>
<td>2 (20) 2 (20) 0 0 1 (10)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>0</td>
<td>0 0 0 2 (20) 0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0</td>
<td>0 0 0 2 (20) 0</td>
</tr>
<tr>
<td>Ear discomfort</td>
<td>0</td>
<td>0 1 (10) 0 0 1 (10)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>0 0 2 (20) 0 0</td>
</tr>
<tr>
<td>Laceration</td>
<td>0</td>
<td>0 0 1 (10) 0 0</td>
</tr>
<tr>
<td>Menstrual disorder</td>
<td>0</td>
<td>0 0 0 2 (20) 0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0</td>
<td>1 (10) 0 1 (10) 0</td>
</tr>
</tbody>
</table>

*The dose 0.35 mg was taken daily for 7 days, followed by 2.0 mg daily dose for 14 days.
**The dose 0.5/3.0 mg was taken daily for 7 days, followed by 3.0 mg daily dose for 14 days.

All adverse events are shown, regardless of relationship to the study medication.

Figure 1. Multiple ascending dose study design

Figure 2. Multiple ascending dose study: mean observed lymphocyte counts* in subjects (n=60) receiving etrasimod without a titration scheme or placebo

References


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Disclosures


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Safety, tolerability and lymphocyte-lowering properties of etrasimod (APD334), an oral, potent, next-generation, selective S1P receptor modulator, after dose escalation in healthy volunteers

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