A Comparison of XP23829 With DMF, the Active Ingredient of BG-12

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Introduction

- Fumaric acid ester (FAE) formulations have demonstrated efficacy in the treatment of psoriasis and relapsing-remitting multiple sclerosis (RRMS).
- Monomethyl fumarate (MMF) is thought to be the active moiety in circulation after oral treatment with dimethyl fumarate (DMF).

Results

- XP23829 demonstrated greater efficacy in the EAE mouse model.
- XP23829 caused less stomach irritation than DMF in rats.

Conclusions

- In the EAE mouse model of MS, XP23829 given orally produced similar or greater reductions in clinical score compared with DMF.
- 14-day GI side effect studies suggest that the observed effects are local in nature and not correlated with systemic MMF exposure.
- In rat doses of XP23829 that produced higher blood levels of MMF could be tolerated without evidence of GI irritation compared with DMF.
- Similar results have been observed in monkey studies and will be reported in the future.
- Based upon these preclinical studies, XP23829 may provide a potential new treatment option for patients with RRMS.
- XenoPort has filed an IND for XP23829 and plans to initiate Phase 1 clinical studies in the second half of 2012.

Methods

Mouse experimental autoimmune encephalomyelitis (EAE) model
- Female C57BL/6 mice were injected subcutaneously with MOG35-55. Pertussis toxin was injected on days 0 and 2. Mice were dosed twice daily with either XP23829 or DMF. Daily EAE clinical scores were recorded on a standard 5-point scale.

- 14-day rat stomach irritation model
  - Rats (6/group/dose) were treated with three different doses of XP23829 or DMF for 2 weeks and PK samples were collected on day 14. Signs of stomach irritation were evaluated at necropsy. The dosages were selected to produce roughly equivalent MMF blood levels.

Summary of EAE results

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose (mg/kg)</th>
<th>% Decrease in Clinical Score vs Vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMF</td>
<td>14</td>
<td>39% (p &lt; 0.01)</td>
</tr>
<tr>
<td>XP23829</td>
<td>11</td>
<td>57% (p &lt; 0.01)</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>60% (p &lt; 0.01)</td>
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</tbody>
</table>

References

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Disclosure
All co-authors and acknowledged contributors were employees at XenoPort, Inc. during this work.