**Introduction**

Eliptalan (Relpex®) is a potent, selective, 5-HT1B/1D receptor agonist, which is approved as an immediate release (IR) formulation for the acute treatment of migraine with or without aura.

Headache recurrence (HR) within the first 24 hours of treatment was found to be 21-23% after treatment with 40 mg of eliptalan IR and is a classically important issue for migraine patients, occurring in 25-78% of subjects treated with other 5HT1 agonists.

**Objective**

- To develop an integrated PK/PD model to describe the relationship between plasma concentration and both Pain Relief (PR) and Headache Recurrence (HR) in patients with acute migraine with the aim of providing:
  - A target profile to guide the development of a Dual Release (DR) formulation for the treatment of acute migraine (PR) and prevention of HR.
  - Dose response predictions to guide the selection of the optimal IR and MR dose combination for achieving and sustaining Headache Recurrence (SHR).

**Data**

- **Table 1:** Population Parameter estimates from the final pharmacodynamic model

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean</th>
<th>s.e.</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR/IR</td>
<td>0.50</td>
<td>0.10</td>
<td>0.31-0.70</td>
</tr>
<tr>
<td>IR/CR</td>
<td>0.60</td>
<td>0.15</td>
<td>0.35-0.85</td>
</tr>
<tr>
<td>CR/CR</td>
<td>0.70</td>
<td>0.20</td>
<td>0.45-0.95</td>
</tr>
</tbody>
</table>

**Results**

Pain Relief, P(Y=1), and Recurrence, P(T>t), models

- **Pain Relief** model
  - $P(Y=1|X) \propto 1 + e^{-θ_1X}$
  - $θ_1$ = slope factor

- **Recurrence** model
  - $R(t) = R_0 + R_1e^{-θ_2t}$
  - $R_0$ = baseline effect
  - $θ_2$ = slope factor

**Simulation (1): Target Profile**

- To all the development of a DR formulation, simulations were conducted to determine the optimal release characteristics for the MR component of the DR formulation in the prevention of HR. A sigmoidal shape of the cumulative amount released characterized the properties of the types of formulations being investigated.

**Simulation (2): Dose Response**

- The joint model allowed prediction of the dose response for DR.
  - A joint model analyzed the dose response relationship for HR24 and HR48 in a general migraine population. The shape of the dose response relationship for HR24 and HR48 is shown in the figure below.
  - The simulations indicated that the difference in SHR between DR 40/20 and DR 40/40 at 24 and 48 hours would not be substantial.

**Conclusion**

- On the basis of these simulations it is expected that the optimal 40 mg/40 mg DR formulation will provide a relative reduction in headache recurrence of ~33% in comparison 40 mg IR and an increase in sustained response to 48 hours from 30 to 40%.

- The PK/PD model model established using the phase III database for the IR formulation has been used to guide the development and subsequent dose selection for DR formulation being developed for the treatment of acute migraine and prevention of headache recurrence.

**References**