BACKGROUND

XEN901 is a potent and highly selective Na\textsubscript{v}1.6 inhibitor currently in clinical development for the treatment of epilepsy. The objective of this study is to evaluate the safety, tolerability and pharmacokinetics (PK) of single and multiple ascending doses of XEN901 in healthy subjects. XEN901 is expected to have an enhanced safety profile over non-selective inhibitors through potent block of Na\textsubscript{v}1.6, with >100 fold selectivity over Na\textsubscript{v}1.1 (CNS inhibitory) and Na\textsubscript{v}1.5 (cardiac) sodium channels.

METHODS

In this randomized, double blind study, 40 healthy subjects (3:1 active placebo) received single ascending doses (SAD) of XEN901 once daily (QD) and 30 subjects (3:1 active placebo) received multiple ascending doses (MAD) once QD or two times (BID) daily for 7 days. A food effect (FE) cohort received single doses of XEN901 in fed and fasted states in a crossover design. XEN901 was formulated as an immediate release capsule. Safety evaluations throughout the study included adverse event (AE) monitoring, laboratory tests, vital signs, electrocardiograms (EGCs), physical examinations, Columbia Suicide Severity Rating Scale (C SARS) and a brief cognitive assessment. Pilot TMS assessments were done in 50 and 75 mg QD cohorts. The study features an adaptive design and is ongoing.

PHARMACOKINETICS

XEN901’s PK profile displayed a reasonable dose proportional exposure with a mild food effect (1.3-fold increase in \(C_{\text{max}}\), and 1.6-fold in AUC). Typically modest (≤40%) inter-individual variability was observed for the PK parameters. The median \(T_{\text{max}}\) was 1.6 hours across cohorts and typically ranged from 1.7-2.0 hours. The mean \(T_{1/2}\) was 8.1 hours across cohorts and did not change with increasing dose or upon repeated administration. No significant drug accumulation was observed upon 7 days of QD (75 mg) or BID (23 mg x 2; i.e., 46 mg/day) dosing and steady state was achieved by Day 2-3. Significantly higher trough levels were maintained via BID dosing.

PHARMACOKINETICS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>15 mg BID (N=6)</th>
<th>23 mg BID (N=6)</th>
<th>50 mg QD (N=7)</th>
<th>75 mg QD (N=7)</th>
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<tbody>
<tr>
<td>(C_{\text{max}})</td>
<td>1.3</td>
<td>1.2</td>
<td>1.8</td>
<td>1.8</td>
</tr>
<tr>
<td>(T_{\text{max}})</td>
<td>1.6</td>
<td>1.5</td>
<td>1.3</td>
<td>1.3</td>
</tr>
</tbody>
</table>

N = number of subjects; \(C_{\text{max}}\) = maximum plasma concentration; \(T_{\text{max}}\) = time to maximum plasma concentration; \(T_{1/2}\) = terminal half-life

PILOT TMS RESULTS

XEN901’s effects on Transcranial Magnetic Stimulation (TMS) measurements and EEG were assessed in 8 subjects with plasma levels >1100 ng/mL from the 50 and 75 mg QD cohorts and compared to 3 placebo subjects. TMS measures were recorded at baseline and on Day 5/6. In this pilot study XEN901 showed trends for increases in resting and active motor thresholds (RMT/AMT), decrease in amplitude of TMS evoked potential (TEP) at 180 ms (P180) and an increase in delta power in the resting state EEG.

CONCLUSIONS

The results to date suggest that XEN901, a novel, first-in-class Na\textsubscript{v}1.6 inhibitor, is safe and well-tolerated at the doses examined (single doses of up to 80 mg/day and multiple doses of up to 75 mg/day for 7 days).

In addition, XEN901 exhibited linear PK over the dose range examined. The \(T_{1/2}\) of 8 to 11 hours suggests that XEN901 could be compatible with a QD or a BID dosing regimen. No significant accumulation was observed upon repeated dosing and steady state was achieved in 2-3 days.

Changes in TMS/EMG and TMS/EEG parameters suggest XEN901 has effects on corticospinal and cortical excitability.

The favorable PK, tolerability, safety and pilot TMS data support the further clinical development of XEN901 in the treatment of epilepsy.