Background

- Neurokinin B signaling through NK3 receptors in the median preoptic nucleus (mHPO) has been linked to the occurrence of hot flashes in postmenopausal women (PMW).
- NK3R antagonists have been shown to significantly reduce frequency and severity of hot flashes in PMW in controlled studies.
- Reduction of luteinizing hormone (LH) and testosterone (T) in men recognized as a sensitive biomarker of central NK3 receptor antagonism.
- SJX-653 is a potent and selective small molecule NK3 antagonist in development for the treatment of moderate to severe vasomotor symptoms (VMS) due to menopause.
- We sought to demonstrate clinical proof-of-concept in healthy adult men by measuring changes in plasma LH and T, while also evaluating the pharmacokinetics, safety, and tolerability of SJX-653.

Methods

- Randomized, placebo-controlled, double-blind, single ascending dose study of SJX-653 in 42 healthy men.
- Orally-administered SJX-653 evaluated in dose cohorts of 0.5, 1.5, 4.5, 15, 30, and 90 mg (4 SJX-653: 2 placebo per cohort).
- Confined to Phase 1 unit from Day -1 to 3 with a follow-up visit on Day 8.
- Safety assessments (labs, ECG, vital signs) and serial PK/PD samples were collected pre- and at multiple timepoints up to 48-72 hours post dose.
- Changes in LH and T were calculated as percentage of the baseline (mean of pre-dose time points -1.5, -1.0, -0.5 and 0 hours).

Demographics

- All enrolled subjects completed treatment and the majority were white (64.3% SJX-653 vs 57% placebo).

Pharmacokinetics

- Cmax 6 hours highest peak following dosing and declined gradually with a terminal half-life of 10-13 hours consistent with QD dosing.
- Plasma concentration at 24 hours was about one-third of Cmax.

Table 2: Plasma Pharmacokinetics by Cohort

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Mean (SD)</th>
<th>Median (SD)</th>
<th>Geometric Mean (SD)</th>
<th>Geometric Median (SD)</th>
<th>CV %</th>
</tr>
</thead>
<tbody>
<tr>
<td>SJX-653</td>
<td>8.8 (3.4)</td>
<td>7.1</td>
<td>6.6 (2.1)</td>
<td>6.1 (1.8)</td>
<td>40.1</td>
</tr>
<tr>
<td>0.5 mg</td>
<td>8.2 (3.1)</td>
<td>7.1</td>
<td>6.9 (2.1)</td>
<td>6.0 (1.8)</td>
<td>42.0</td>
</tr>
<tr>
<td>1.5 mg</td>
<td>8.0 (3.0)</td>
<td>7.1</td>
<td>6.8 (2.1)</td>
<td>6.0 (1.8)</td>
<td>43.6</td>
</tr>
<tr>
<td>4.5 mg</td>
<td>7.8 (2.9)</td>
<td>7.1</td>
<td>6.7 (2.1)</td>
<td>6.0 (1.8)</td>
<td>46.6</td>
</tr>
<tr>
<td>15 mg</td>
<td>7.6 (2.8)</td>
<td>7.1</td>
<td>6.5 (2.1)</td>
<td>6.0 (1.8)</td>
<td>47.9</td>
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<tr>
<td>30 mg</td>
<td>7.4 (2.7)</td>
<td>7.1</td>
<td>6.4 (2.1)</td>
<td>6.0 (1.8)</td>
<td>48.8</td>
</tr>
<tr>
<td>60 mg</td>
<td>7.2 (2.6)</td>
<td>7.1</td>
<td>6.3 (2.1)</td>
<td>6.0 (1.8)</td>
<td>49.1</td>
</tr>
<tr>
<td>90 mg</td>
<td>7.0 (2.5)</td>
<td>7.1</td>
<td>6.2 (2.1)</td>
<td>6.0 (1.8)</td>
<td>49.6</td>
</tr>
</tbody>
</table>

Conclusions

- SJX-653, a potent and selective NK3 antagonist, demonstrated clinical proof-of-concept with statistically significant, dose-dependent, and reversible reductions in LH and T in healthy adult men.
- SJX-653 was well tolerated and the PK profile supports once-daily (QD) dosing. SJX-653 exhibits a long plasma half-life and a low ratio of Cmax to C0 consistent with a peak trough ratio of about 3:1 upon repeat dosing.


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