**Abstract**

Posiphen is in clinical development as an oral treatment for Alzheimer’s disease (AD). In cell cultures, normal, transgenic and inflammatory conditions, Posiphen reduces the rate of synthesis of amyloid-β (Aβ) peptide and plaques. Posiphen is a potent inhibitor of precursor protein (APP) and thereby, lowers levels of Aβ and other neurotoxic peptides generated from APP processing. We conducted a clinical trial in mild cognitive impaired (MCI) patients to confirm the mechanism of action (a reduction in the rate of Aβ synthesis) in humans and correlate it to pharmacokinetics of the drug and its metabolites in CSF.

**Introduction**

Major hallmarks of Alzheimer’s disease (AD) are synaptic loss, brain shrinkage and plaques. The plaques are deposits of the Aβ peptide and neurofibrillary tangles, current AD drugs on the market provide symptomatic relief and improve quality of life. Posiphen is a novel compound that acts as an amyloid-β (Aβ) precursor protein (APP) inhibitor and provides symptomatic relief and improve cognition. Posiphen has a mechanism of action that is studied at the molecular level in the laboratory of Jack Rogers (Mass General Hospital, Charlestown, MA). Iron influx increases the translation of APP via an iron-responsive element (IRE) RNA in neurons, which generates the substrate that forms toxic Aβ plaques and neuronal cell death.

**Methods**

Recent reports suggest high endogenous variability of Aβ production that may be altered by dietary fluxes and/or by fed vs. fasted states. The patients tolerated the procedure well. The same subjects were dosed for 10 days. The patients tolerated the procedure well.

**Conclusion**

The human PK of Posiphen and metabolites confirmed that Posiphen appears to be a promising experimental drug for AD as it reduces brain levels of APP by reducing mRNA APP translation in all species tested1,9,10 including humans. Additionally it inhibits tau and phospho-tau.

**Human PD**

- Posiphen steadily enters the brain in mice and rats with brain levels ranging from 7 to 9 times higher than concurrent plasma levels. Comparison of robust CSF, brain and plasma levels with human CSF and plasma levels allowed us to infer a log-linear dose response for once a day dosing as well as 4 times a day dosing (Figure 5).

**Comparison with Healthy Volunteers**

- Posiphen lowers sAPPβ and tau levels back to the levels found in healthy volunteers (Figure 6).

**Table 1: Differential Action of Posiphen on APP and sAPPβ in MCI patients**

<table>
<thead>
<tr>
<th>Table</th>
<th>Normal Control</th>
<th>MCI 0 Day</th>
<th>MCI 11 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>APP</td>
<td>100%</td>
<td>120%</td>
<td>60%</td>
</tr>
<tr>
<td>sAPPβ</td>
<td>100%</td>
<td>120%</td>
<td>40%</td>
</tr>
</tbody>
</table>

**Figure 3: Posiphen Increases Inhibitory IRE Response in Cultured Neurons**

- Posiphen increases the rate of APP mRNA translation at 3% of control (Figure 2). Aβ binds to DR6 receptors and induces nerve cell death.

**Table 2: Posiphen Affects Biomarkers in CSF**

<table>
<thead>
<tr>
<th>All AD</th>
<th>Posiphen A/B Posiphen C/D Posiphen E/F</th>
<th>Posiphen A/B Posiphen C/D Posiphen E/F</th>
<th>Normal Control</th>
<th>MCI 0 Day</th>
<th>MCI 0 Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>APP</td>
<td>-34%</td>
<td>-33%</td>
<td>-36%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sAPPβ</td>
<td>-45%</td>
<td>-38%</td>
<td>-31%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 4: Mechanism of Action of Posiphen**

- Posiphen inhibits the activity of the N-terminus of APP mRNA translation.

**Figure 5: Plasma, CSF and Extrapolated Brain Levels of Posiphen and” MCI patients”**

<table>
<thead>
<tr>
<th>CSF</th>
<th>MCI 0 Day</th>
<th>MCI 0 Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>APP</td>
<td>100%</td>
<td>120%</td>
</tr>
<tr>
<td>sAPPβ</td>
<td>100%</td>
<td>120%</td>
</tr>
</tbody>
</table>

**Figure 6: Tau/AB 42 Ratio Elevated CSF levels of tau and decreased concentrations of 42 are considered to be a pathological biomarker signature diagnostic for AD. The ratio Tau/AB is used to estimate progression to AD. Posiphen shifts this ratio toward non-AD subjects.**

**Figure 7: Summary of Results**

- The primary end point was an estimate of progression to AD. Posiphen reduces sAPPβ and tau levels back to the levels found in healthy volunteers (Figure 6).

**Support**

Supported by QR Pharma Inc.

**Contact Info**

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**References**


