Background

- The amyloid beta peptide (Aβ) plays a pivotal role in Alzheimer's disease (AD) pathogenesis. The Aβ peptide is generated from Amyloid precursor protein, APP, via the sequential cleavages by β- and γ-secretase.

- γ-secretase inhibitors (GSIs) have reached late stage clinical trials, of which none has resulted in significant improvement for the patients.

- GSIs have a complex impact on Aβ levels which makes it difficult to interpret their net impact on CNS Aβ levels.

Objectives and Approach

- To get a better understanding on what effect clinical GSIs have had on brain Aβ levels in clinical trials by performing a quantitative meta pharmacokinetic-pharmacodynamic (PKPD) analysis on Aβ biomarkers from published GSI clinical trials.

- To investigate if preclinical data on GSI pharmacology could be used to predict CNS and plasma Aβ production in man.

Data sources & Methods

- Time course of (pre)clinical data on Aβ biomarkers and drug exposure were digitized from the public domain (see refs) for Semagacestat, Avagacestat, Begaacestat, PF3084014. Additional preclinical Aβ inhibition data was generated in house.

- A model-based meta PKPD analysis was undertaken with mean time-concentration-effect observations using a descriptive modeling approach using a composite Emax model, combined with a turnover model to describe the biphasic effects. Systems parameters were kept constant between compounds, whereas the drug parameters were allowed to differ.

- From the population parameter estimates, the exposure giving 50% inhibition from baseline (IC50%) was derived and used for interspecies comparison.

Results: Human Analysis

- Bi-phasic effects in plasma Aβ were observed for all compounds which resulted in averaged increase over time, rather than the anticipated decrease (Table 1).

- No significant effects on CSF Aβ levels for Semagacestat, Begaacestat, PF3084014 were observed for clinically relevant doses, whereas 200 mg Avagacestat seem to reduce CSF Aβ40 levels after single dose (placebo baseline drift).

- Avagacestat doses below 100 mg are being used in continued clinical testing and seem not to reduce Aβ40 (see figure 2 and ref 11).

Table 1. Prediction of the average plasma Aβ40 effect over 24h after single dose of GSI tested in long term clinical trials.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Single dose</th>
<th>Mean effect 0-24 h</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semagacestat</td>
<td>140 mg</td>
<td>+17%</td>
<td>3</td>
</tr>
<tr>
<td>Avagacestat</td>
<td>200 mg</td>
<td>+26%</td>
<td>1</td>
</tr>
</tbody>
</table>

Can preclinical data predict human observations?

- Human predictions on plasma Aβ40 were made based on mouse and GP in vivo potency estimates with observed human PK and human Aβ turnover estimates.

- The mouse predicts the plasma Aβ40 effect within a 3-fold range, whereas GP seems to overpredict.

- Both mouse & GP would predict small CNS effects for clinically used doses of Semagacestat assuming brain/plasma ratio is similar between species (mean reduction of 10-25% reduction from baseline).

Conclusions

- The observed inhibition on CNS Aβ production in clinical trials conducted so far has been very limited both in size and duration.

- The limited information on clinical CNS Aβ levels does not indicate a significant reduction in Aβ levels at intended therapeutic doses. Variability in observations and change in placebo might mask modest CSF effects.

- We see similar (qualitative) but not identical (quantitative) Aβ effects between man, mouse and guinea pig.

- Comparing clinical plasma and CSF data with animal plasma, CSF and brain Aβ data in response to the same GSIs, suggests that biphasic plasma effects with no net lowering over 24 h could have been predicted from in vivo results and that modest inhibition of CNS Aβ levels were expected (10-25% reduction in brain Aβ40 for Semagacestat).

- More efficacious Aβ production targeting drugs that lower Aβ substantially over the dosing interval period should be tested in clinical trials to prove or disprove whether these drug targets are efficacious in mild AD.

Table 2. Unbound plasma concentration estimates (nM) giving 50% inhibition (IC50%) of Aβ40 levels in human, mouse and GP from the population PKPD analysis

<table>
<thead>
<tr>
<th>Compound</th>
<th>Aβ40</th>
<th>Human</th>
<th>Mouse WT</th>
<th>Guinea-Pig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semagacestat</td>
<td>plasma</td>
<td>1167</td>
<td>925</td>
<td>294</td>
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<tr>
<td></td>
<td>CSF</td>
<td>-</td>
<td>1572</td>
<td>1244</td>
</tr>
<tr>
<td>Avagacestat</td>
<td>plasma</td>
<td>10</td>
<td>47</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>CSF</td>
<td>-</td>
<td>10</td>
<td>1.0</td>
</tr>
</tbody>
</table>

References: