RG6289, a new γ-secretase modulator for the treatment of Alzheimer’s disease: Dose selection for a Phase II trial based on population PK/PD modeling

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What does this mean for the AD community?
- RG6289 is a novel γ-secretase modulator with the potential to become the first oral disease-modifier for early Alzheimer’s disease.
- Population PK/PD modeling was instrumental to support dose selection for an upcoming Phase II trial in early AD.

Background
- Recent clinical trial results from anti-AP antibodies provide evidence that AP is a valid therapeutic target for AD. This insight supports the search for disease-modifying treatments with improved efficacy, safety, and convenience.
- RG6289 is a novel, potent and selective, orally bioavailable γ-secretase modulator (GSM) with good CNS drug-like properties.
- The entry-into-Human (EH) study was designed to assess the safety and tolerability, and to characterize the pharmacokinetic (PK) and pharmacodynamics (PD) following single and multiple ascending oral doses of healthy participants.
- The degree of AP lowering required to impact the AD disease course is unknown and requires studying RG6289 in individuals with early stages of AD.
- A Phase II study to investigate safety, tolerability, PK, and PD of RG6289 is scheduled for 2024 and doses were selected using PK/PD model simulations.

Methodology
- A population PK/PD model characterizing the relationship between PK and plasma RG6289 lowering was developed using data from the EH study (Table 1).
- RG6289 concentrations were measured with a validated LC/MS/MS assay. RG6289 was quantified using a validated immunoassay. Realtime analysis results (generated during study conduct) were used for modeling.
- Model development aimed to characterize:
  - The population-specific (i.e., the average) behaviour:
    - Differences between individuals, i.e., the inter-individual variability (IV);
    - The impact of subject- and study-specific characteristics (i.e., covariates).
- Model selection was based on numerical criteria and graphical evaluations.
- The assessed covariates were age, sex, body weight, creatinine clearance, dose, and food intake. For PK, an automated covariate search was conducted using COSSAC®. PD covariate analysis was exploratory.
- Simulations were performed to predict PK and PD at steady state for different RG6289 doses (including doses not yet tested clinically) to achieve Aβ42 reductions of 30-70% in the planned Phase II study.
- Model development applied nonlinear mixed-effects modeling in Monolix v.2023R1. SimuLx 2023R1 was used for simulations. Data visualization was carried out using R v. 4.1.2.

Table 1. Overview of the Entry-into-Human study.

<table>
<thead>
<tr>
<th>Study part</th>
<th>Cohort</th>
<th>n (active/ placebo)</th>
<th>Population</th>
<th>Food intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Part 1a (SAD)</td>
<td>A1</td>
<td>6 (4/2)</td>
<td>Healthy young participants (18-45 years)</td>
<td>Fed</td>
</tr>
<tr>
<td></td>
<td>A2</td>
<td>6 (4/2)</td>
<td>Healthy young participants (18-45 years)</td>
<td>Fed</td>
</tr>
<tr>
<td></td>
<td>A3</td>
<td>8 (6/2)</td>
<td>Healthy young participants (18-45 years)</td>
<td>Fed</td>
</tr>
<tr>
<td></td>
<td>A4</td>
<td>8 (6/2)</td>
<td>Healthy young participants (18-45 years)</td>
<td>Fed</td>
</tr>
<tr>
<td></td>
<td>A5</td>
<td>8 (6/2)</td>
<td>Healthy young participants (18-45 years)</td>
<td>Fed</td>
</tr>
<tr>
<td></td>
<td>A6</td>
<td>8 (6/2)</td>
<td>Healthy young participants (18-45 years)</td>
<td>Fed</td>
</tr>
<tr>
<td></td>
<td>A7</td>
<td>8 (6/2)</td>
<td>Healthy young participants (18-45 years)</td>
<td>Fed</td>
</tr>
<tr>
<td></td>
<td>A8</td>
<td>8 (6/2)</td>
<td>Healthy young participants (18-45 years)</td>
<td>Fed</td>
</tr>
<tr>
<td>Part 1b (Food effect)</td>
<td>B1</td>
<td>8 (4/4)</td>
<td>Healthy young participants (18-45 years)</td>
<td>Fed/fed (high-fat meal)</td>
</tr>
<tr>
<td></td>
<td>B2</td>
<td>8 (4/4)</td>
<td>Healthy young participants (18-45 years)</td>
<td>Fed/fed (high-fat meal)</td>
</tr>
<tr>
<td></td>
<td>B3</td>
<td>8 (4/4)</td>
<td>Healthy young participants (18-45 years)</td>
<td>Fed/fed (high-fat meal)</td>
</tr>
<tr>
<td>Part 2a (CSF)</td>
<td>C1</td>
<td>12 (9/3)</td>
<td>Healthy young participants (18-65 years)</td>
<td>Fed (standard meal)</td>
</tr>
<tr>
<td></td>
<td>C2</td>
<td>12 (9/3)</td>
<td>Healthy young participants (18-65 years)</td>
<td>Fed (standard meal)</td>
</tr>
<tr>
<td></td>
<td>C3</td>
<td>12 (9/3)</td>
<td>Healthy young participants (18-65 years)</td>
<td>Fed (standard meal)</td>
</tr>
<tr>
<td></td>
<td>C4</td>
<td>8 (6/2)</td>
<td>Healthy elderly participants (65-85 years)</td>
<td>Fed (standard meal)</td>
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<tr>
<td>Part 2b (MAD)</td>
<td>D1</td>
<td>14 (10/4)</td>
<td>Healthy young participants (18-65 years)</td>
<td>Fed (standard meal)</td>
</tr>
</tbody>
</table>

Data set
- A total of 2794 plasma PK (N=99 participants on RG6289 and 2560 plasma Aβ42 (N=45 participants on RG6289) observations were available.
- Participants had a median age of 32 years (18 to 72 years) and a median body weight of 77.6 kg (54.6 to 110.2 kg).

Final PK/PD model
- The final PK/PD model is a 2-compartment disposition model with transit compartment absorption and linear clearance coupled to an indirect-response model with drug effect implementation as relative T0.24 on the Aβ42 production rate.
- The following covariate effects were identified (Figure 1):
  - Food intake showed an impact on absorption resulting in a later T0.24 and a lower Cmax without any relevant effect on steady-state (ss) AUC;
  - Higher body weight was associated with a higher volume of distribution translating into a lower Cmax for heavier individuals with no impact on ss AUC;
  - Higher age was associated with lower clearance leading to slightly higher ss exposure (Cmax and AUC) for older individuals.
- No covariates were identified to impact the PK-PD relationship.

Figure 1. PK/PD model simulations: Minimum and maximum plasma Aβ42 reduction at steady state vs. dose: young vs. elderly.

Results
- Exposure and plasma Aβ42 lowering were well characterized in a population PK/PD analysis of EH study data.
- RG6289 can be equally dosed in fed and fasted condition.
- Higher exposure and slightly larger Aβ42 lowering was predicted for older individuals, which is relevant for the treatment of an elderly AD population. Aβ42 lowering in plasma and CSF at steady state were strongly correlated.
- Doses for Phase II were selected using model-based simulations considering the benefit-risk ratio.

Discussion
- The PK of RG6289 was well characterized by PK modeling. Age was a relevant covariate on drug clearance/elimination. Food intake delayed absorption but did not affect steady state. AUC such that RG6289 can be equally dosed in fed and fasted condition without any relevant effect on the PD.
- Simulations were used to characterize the dose-exposure-response profile. The model will be re-assessed once more data become available.
- Plasma Aβ42 reduction was considered a proxy for changes in CSF since the observed effects in CSF and plasma correlated well at through steady state following repeated dosing.
- The selected doses for Phase II are covering a broad range of Aβ42 lowering that is expected to be therapeutically relevant in early AD.

Conclusions
- Exposure and plasma Aβ42 lowering were well characterized in a population PK/PD analysis of EH study data.
- RG6289 can be equally dosed in fed and fasted condition.
- Higher exposure and slightly larger Aβ42 lowering was predicted for older individuals, which is relevant for the treatment of an elderly AD population. Aβ42 lowering in plasma and CSF at steady state were strongly correlated.
- Doses for Phase II were selected using model-based simulations considering the benefit-risk ratio.

Further information
- Further data from the RG6289 EH trial will be presented at CTAD in the oral session on Phase I Clinical Trials on Friday 27 October, 2023.

Table 2. Median predicted RG6289 concentration (top) and plasma Aβ42 (bottom) versus time profiles for different qd doses.

<table>
<thead>
<tr>
<th>Dose (qd)</th>
<th>Median Aβ42 concentration (μM)</th>
<th>Median RG6289 concentration (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mg</td>
<td>0.53</td>
<td>16.2</td>
</tr>
<tr>
<td>3 mg</td>
<td>1.57</td>
<td>48.6</td>
</tr>
<tr>
<td>5 mg</td>
<td>2.61</td>
<td>75.9</td>
</tr>
</tbody>
</table>

Acknowledgements
- We would like to thank all study participants, study partners, investigators, and site staff for past and future engagement on the GMD2 program.
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References

Disclosures
- NB: There may be associated costs for downloading data. These costs may vary depending on your service provider and may be high in low-income countries.
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