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 AD offering convenient treatment options with broad access.
- The safety and tolerability profile of RG6298 was favorable in the Entry-into-Human study in healthy participants.
- Population PK-PD modeling was instrumental to support dose selection for an upcoming Phase II study in early AD.

Conclusions

- Exposure and plasma Aβ42 lowering were well characterized in a population PK-PD analysis of EiH study data.
- RG6289 can be equally dosed in fed and fasted condition.
- Higher exposure and slightly larger Aβ42 lowering is 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.

Background

- Recent clinical trial results from anti-Aβ antibodies provide evidence that Aβ is a valid therapeutic target for AD. This insight supports the search for disease-modifying treatments with improved efficacy, safety, and convenience [1,2].
- RG6289 is a novel, potent and selective, orally bioavailable γ-secretase modulator (GSM) with good CNS drug-like properties.
- The Entry-into-Human (EiH) study was designed to assess the safety and tolerability, and to characterize the pharmacokinetics (PK) and pharmacodynamics (PD) following single and multiple ascending oral dosing of healthy participants.
- The degree of Aβ42 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 Aβ42 lowering was developed using data from the EiH study (Table 1).
- RG6289 concentrations were measured with a validated LC-MS/MS assay. Aβ42 was quantified using a validated immunoassay. Realtime analysis results (generated during study conduct) were used for modeling.
- Model development aimed to characterize:
  - The population-typical (i.e., the average) behaviour;
  - Differences between individuals, i.e., the inter-individual variability (IIV);
  - The impact of subject- and study-specific characteristics (i.e., covariates).
- Model selection was based on numerical criteria and graphical evaluations[4].
- The assessed covariates were age, sex, body weight, creatinine clearance, dose, and food intake. For PK, an automated covariate search was conducted using COSSAC[5]. 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 modelling in Monolix v.2023R1[6]. Simulx v. 2023R1 [7] was used for simulations. Data visualization was carried out using R v. 4.1.2. [8]

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

Study part	Cohort	N (active: placebo)	Population	Food intake
Part 1a (SAD)	A1 A2 A3 A4 A5 A6 A7	6 (4:2) 6 (4:2) 8 (6:2) 8 (6:2) 8 (6:2) 8 (6:2) 8 (6:2)	Healthy young participants (18-45 years)	Fasted
Part 1b (Food effect)	A8	8 (8:0)		Fasted / fed (high-fat meal[b])
Part 2 (cCSF)	B1 B2 B3	4 (3:1) 4 (3:1) 4 (3:1)	Healthy participants (40-70 years)	Fasted
Part 3a (MAD)	C1 C2 C3	8 (6:2) 12 (9:3) 12 (9:3)	Healthy young participants (18-64 years)	Fed (standard meal)
Part 3b (MAD)	C4	8 (6:2)	Healthy elderly participants (65-85 years)	Fed (standard meal)
Part 4 (DDI[a])	D1	14 (14:0)	Healthy young participants (18-64 years)	Fed (standard meal)

cCSF: continuous cerebrospinal fluid; DDI: drug-drug interaction; MAD: multiple ascending dose; PD: pharmacodynamics; PK: pharmacokinetic(s); SAD: single ascending dose.
[a] DDI with midazolam and caffeine; [b] high-fat meal according to FDA guidance [3].

Results

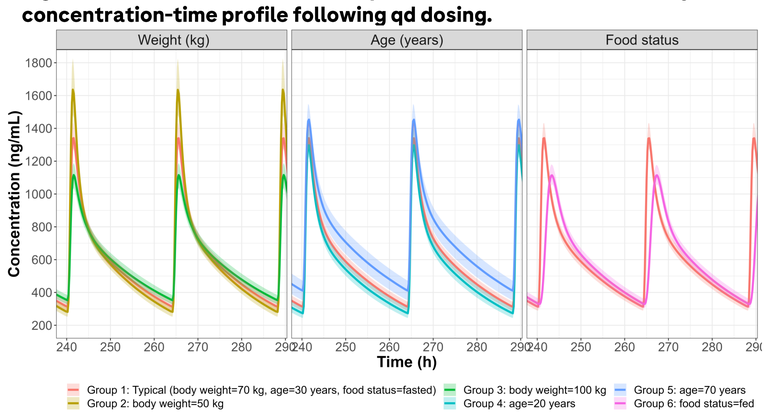
Data set

- A total of 2794 plasma PK (N=99 participants on RG6289) and 2560 plasma Aβ42 (N=85 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 I_{max} on the Aβ42 production rate.
- The following covariate effects were identified (Figure 1):
  - Food intake showed an impact on absorption resulting in a later T_{max} and a lower C_{max} without any relevant effect on steady-state (ss) AUC;
  - Higher body weight was associated with a higher volume of distribution translating into a lower C_{max} for heavier individuals with no impact on ss AUC;
  - Higher age was associated with lower clearance leading to slightly higher ss exposure (C_{max} and AUC) for older individuals;
  - No covariates were identified to impact the PK-PD relationship.

Figure 1. PK model simulations - Impact of covariates on the steady-state concentration-time profile following qd dosing.



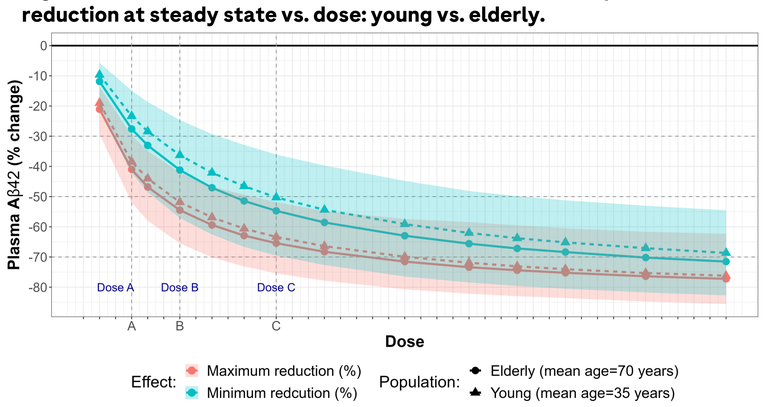
Shaded areas represent parameter estimation uncertainty based on 250 replicates
Typical/reference individual: body weight=70 kg, age=30 years, food condition=fasted

- The majority of model parameters were precisely estimated with relative standard errors below 30%. Descriptive and predictive model performance were good.

Model simulations

- Simulation setup:
  - Doses: Wide dose range with qd dosing for 14 days assuming full compliance.
  - Population (N=500): Young (mean age=35 years) & elderly (mean age=70 years).

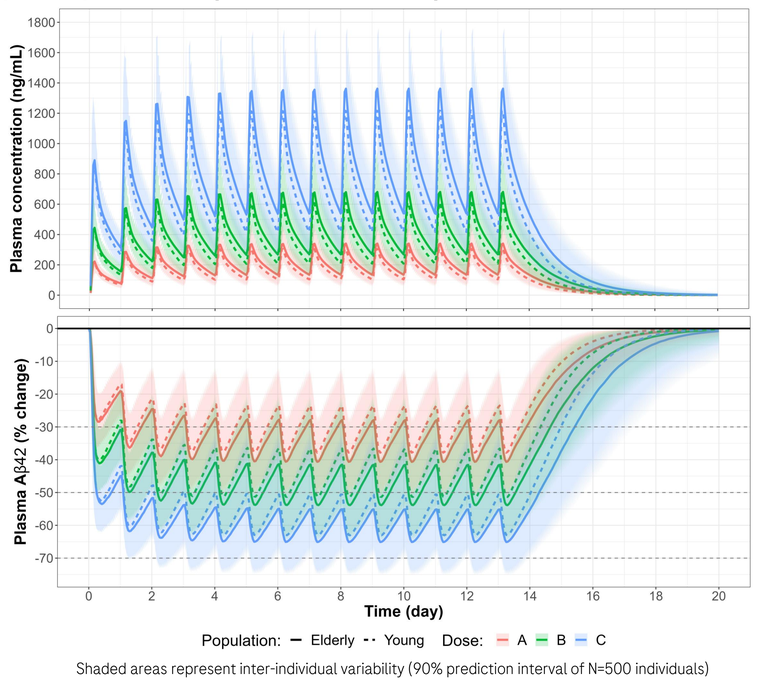
Figure 2. PK-PD model simulations: Minimum and maximum plasma Aβ42 reduction at steady state vs. dose: young vs. elderly.



Shaded areas represent inter-individual variability (5th to 95th percentile based on N=500 per group)

- Steep relationship between RG6289 dose and Aβ42 reduction up to Dose B. Between Dose B and Dose C, an additional reduction of 10% is predicted. Flattening of the dose-response relationship for doses higher than Dose C.
- Slightly larger effect in the elderly population due to, on average, higher exposure.

Figure 3. Median predicted RG6289 concentration (top) and plasma Aβ42 (bottom) versus time profiles for different qd doses.



Shaded areas represent inter-individual variability (90% prediction interval of N=500 individuals)

- Plasma Aβ42 lowering (min. to max. reduction) of 27-41%, 41-54%, and 55-66% was predicted following doses A, B, and C qd in an elderly population.
- These doses are expected to describe the dose-response relationship well, to lead to a separation of the concentration-time profile for the different doses, and to provide a positive benefit-to-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 at 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.

Further information

- Further data from the RG6289 EiH trial will be presented @CTAD in the oral session on Phase I Clinical Trials on Friday 27 October (afternoon session).

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Disclosures

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