A PHASE IIA STUDY INVESTIGATING A γ-SECRETASE MODULATOR IN INDIVIDUALS AT RISK FOR OR AT THE PRODROMAL STAGE OF ALZHEIMER'S DISEASE

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Disclosures

- **RT and TY** are full-time employees of F. Hoffmann-La Roche, Ltd
- **AV, EG, MGVC, FA, TV, LS, SDB, TM, GK, LK, GAK and IG** are full-time employees and stockholders of F. Hoffmann-La Roche, Ltd.
- **DP** and **RC** are full-time employees and stockholders of Roche Products, Ltd
- **KM** is a paid consultant for Roche Products, Ltd

Modulating γ-Secretase is a Compelling Therapeutic Approach

Targeting amyloid precursor protein processing and Aβ-aggregation upstream

γ-secretase modulators alter APP processing without changing the total amount of Aβ

↑ **Non-aggregating $A\beta_{37}$ and $A\beta_{38}$**

↓ **Toxic, aggregating $A\beta_{42}$**

Higher levels of $A\beta_{38}$ are associated with slower cognitive decline in observational cohorts[1]

- **The mechanism of action of γ-Secretase modulators is expected to**
  - slow down or halt amyloid aggregation
  - reduce plaque formation; and
  - delay/prevent cognitive decline

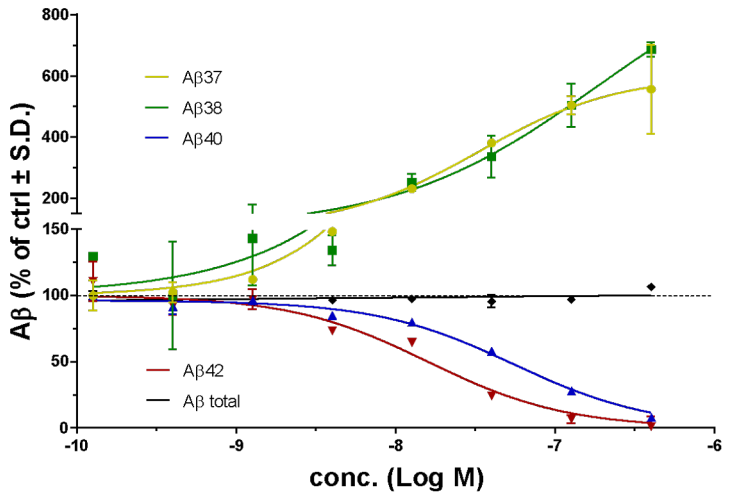
[1]Cullen N, et al. Neurology 2022, 98 (9) e958-e967.
Aβ, amyloid beta; AD, Alzheimer's disease; APP, amyloid precursor protein; GSM, gamma-secretase modulator.

RG6289 Reduces Amylogenic Aβ Species

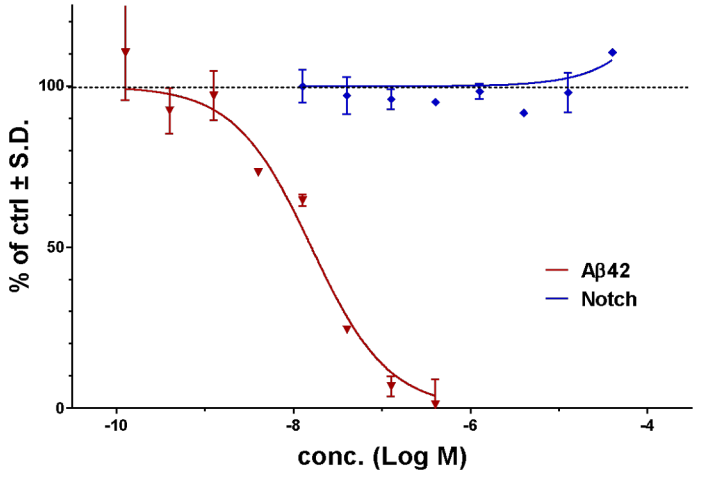
Reduction of Aβ42 and proportional elevation of Aβ38 - Selective for APP with no Effect on Notch

- **Highly potent GSM**
  - IC50 < 10 nM
  - Reduces Aβ42 and Aβ40, proportionally increases Aβ38 and Aβ37
  - No change of enzyme activity - total Aβ peptides remain the same
- **Highly potent GSM**
  - No effect on human Notch-1, no indication for drug effects on processing of other enzyme substrates
  - Selectivity established for broad range of potential targets (enzymes, receptors, ion channels etc.)
- **Expected activity in vivo**
  - Orally bioavailable drug
  - Dose-dependent GSM modulation established in rodents and primates

RG6289 In vitro effect on Aβ fragments[1]



RG6289 In vitro effect on Aβ42 and Notch[1]



[1] Portron et al., Presented at CTAD 2023, Boston, USA.
Aβ, amyloid beta; APP, amyloid precursor protein; ctrl, control; GSM, γ-secretase modulator; SD, standard deviation.

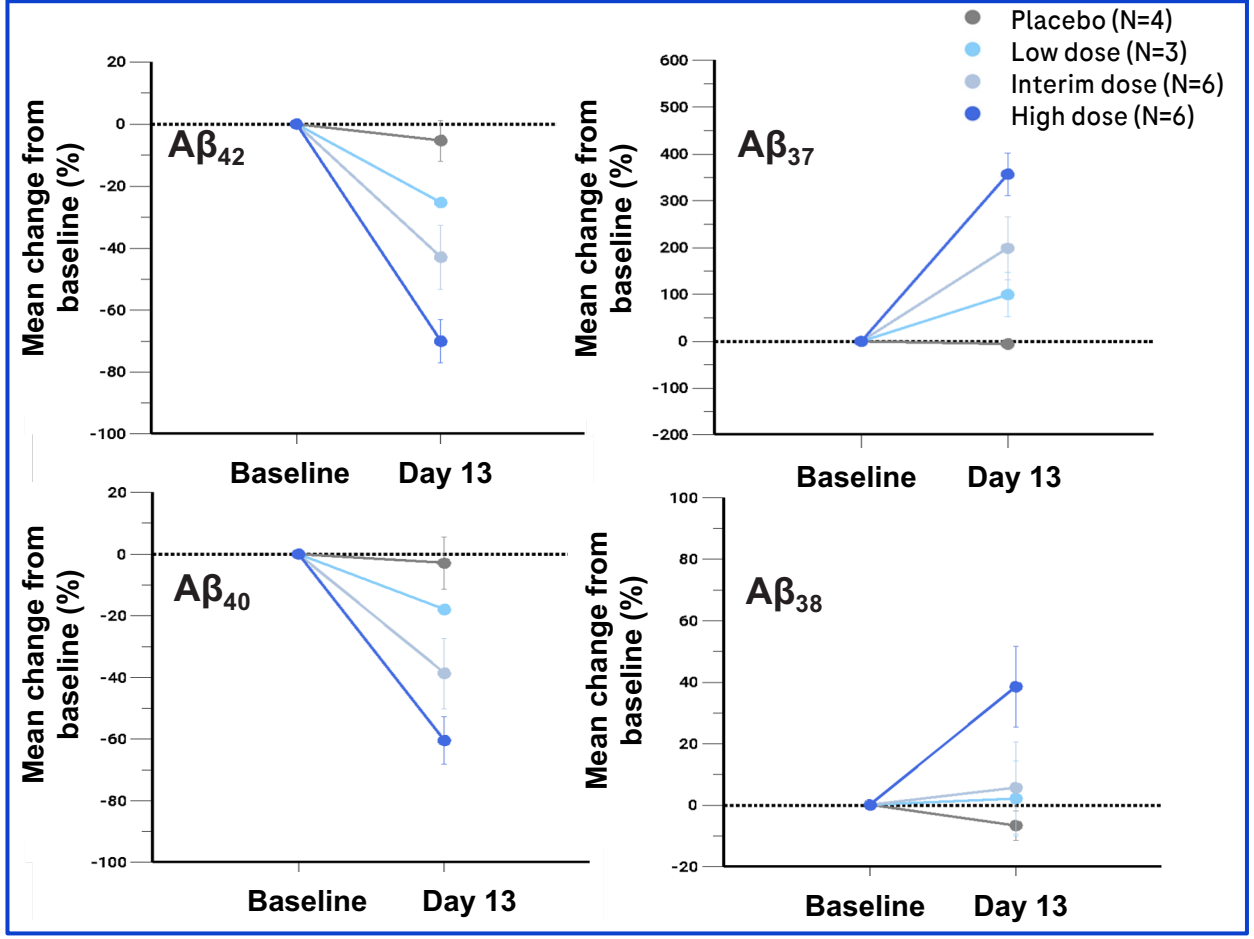
RG6289 Modulates γ-Secretase in Healthy Individuals

Dose-dependent effect of RG6289 on Aβ monomers in CSF

- **Results from the EiH study in young and elderly healthy volunteers showed**
  - Favourable safety and tolerability profile in young and elderly healthy participants
  - Favourable PK profile supporting daily administration and proof of mechanism demonstrated based on the observed dose-dependent γ-secretase modulation

- **Study results support clinical development of RG6289 for the treatment of AD**

PD profile of RG6289 in the EiH Phase I study[1]



[1] Portron et al., Presented at CTAD 2023, Boston, USA.

Arithmetic mean (SD) are displayed. Elecsys® Aβ(1-40), CSF and Aβ(1-37) CSF were measured using the exploratory Roche NeuroToolKit (Roche Diagnostics International Ltd, Rotkreuz, Switzerland).

Aβ, amyloid-beta; EiH, entry-in-human .

GABriella Tests RG6289 Safety and Effects on AD-Related Biomarkers

In a population of individuals at risk for or at the prodromal stage of AD

Study rationale

GABriella will investigate over 18 months:

- Safety and tolerability
- Effects on multiple disease-related biomarkers:
  - Amyloid-PET; Aβ42, Aβ40, Aβ38, Aβ37; Aβ oligomers; p-tau species; markers of neurodegeneration, synaptic integrity, inflammation

Selected study population

Baseline amyloid burden optimized for high amyloid accumulation rate[1]:

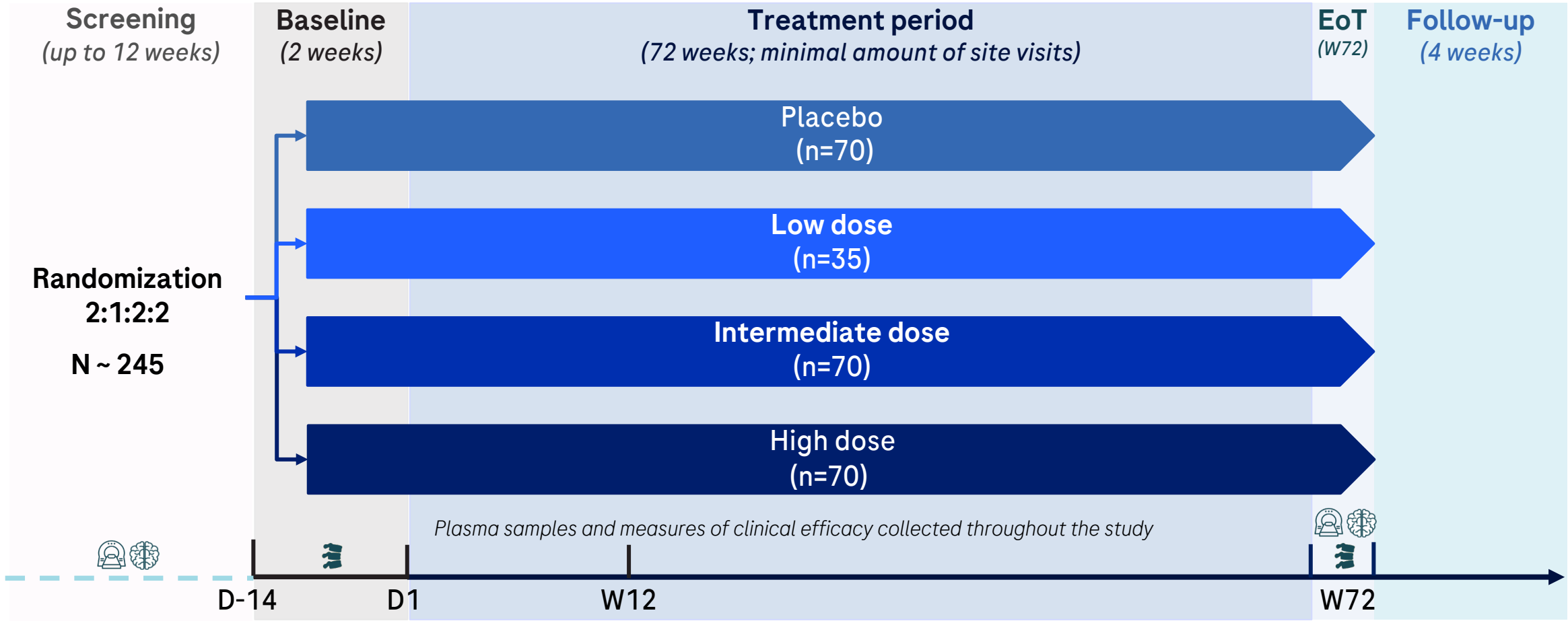
- ≥24 CL cut-off
- >100 CL will be allowed only for ~15% of the total sample
- Cognitively unimpaired or with diagnosis of MCI due to AD per NIA-AA criteria[2]
- CDR-GS= 0 or 0.5

[1] Jagust WJ, et al. Neurology 2021, 2;96(9):e1347-e1357; [2] Jack CR Jr, et al. Alzheimers Dementia 2018, 14(4):535-562.
Aß, amyloid-beta; AD, Alzheimer's disease; CL, Centiloids; *MCI, mild cognitive impairment; NDG, neurodegeneration; PET, positron emission tomography ; p-tau; phosphorylated tau;*

GABriella is a Phase IIa study starting to recruit in H1 2024

Double blind, parallel-group, randomised, placebo controlled study design with 4 cohorts

A total of 78 sites in Canada, Chile, Denmark, France, Germany, Italy, Poland, South Korea, Spain, UK and US



D, day; EoT, end-of-treatment; PO, orally; W, week; MRI; Amyloid PET; lumbar puncture.

GABriella study endpoints

Safety and biomarkers

Primary - Evaluate safety, tolerability and effect on amyloid accumulation of RG6289

Safety: Nature, frequency, severity, and timing of AEs

Brain amyloid accumulation: Change from BL in amyloid PET

Secondary - Evaluate PK and PD of RG6289

PK: Plasma and CSF concentration at different timepoints

PD: Change from BL in Aβ monomers in CSF and blood

Exploratory: clinical efficacy and additional PD effects

PD: Change from baseline in CSF and plasma biomarkers, and MRI sequences

Clinical: Change from baseline in the Cogstate Cognitive Test Battery and CDR-SB

Aß, amyloid-beta; AE, adverse events; BL, base line; CDR-SB, Clinical Dementia Rating scale-Sum of Boxes; CSF, cerebral spinal fluid; DLAE, dose-limiting adverse event; MRI, magnetic resonance imaging; PD, pharmacodynamic; PET, positron emission tomography; PK, pharmacokinetic..

GABriella study: Key inclusion and exclusion criteria

Key Inclusion criteria

- 60-85 years of age
- Cognitively unimpaired or with diagnosis of MCI due to AD per NIA-AA criteria[1]
- CDR-GS= 0 or 0.5
- Positive amyloid PET scan (cut-off: ≥24 CL); >100 CL will be allowed only for ~15% of the total sample
- Stable dose of AD medication ≥8 weeks prior to baseline
- Study partner

Key exclusion criteria

- ANY condition other than AD that may affect cognition
- Major psychiatric disorders
- Active inflammatory bowel disease
- AF, CVD, uncontrolled hypertension
- Impaired hepatic function or chronic kidney disease or poorly controlled
- Diabetes
- Cancer, unless cured or currently not needing treatment
- Fazekas score of 3 and ≥20 mm at the MRI scan
- Inability to tolerate MRI scan or contraindication to MRI scan, LP or PET scan

[1] *Jack CR Jr, et al. Alzheimers Dement. 2018*

AD, Alzheimer's disease; AF, atrial fibrillation; APOE, apolipoprotein; BMI, body mass index; CDR-GS, clinical dementia rating scale-global score; CL, Centiloid units; CNS, central nervous system; CVD, cardiovascular disease; LP, lumbar puncture; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; NIA-AA, National Institute on Aging-Alzheimer's Association; PET, positron emission tomography

Commitment to inclusive research and diversity

Patient representatives contributed to the design of the GABriella study

- Addressing the scientific and medical questions
- Measuring meaningful outcomes
- Considering the impact of trial participation in people's lives

Proactive community engagements to include people that represent the populations most affected by Alzheimer's disease

- Community outreach and relationship-building
- Availability of culturally appropriate language for study materials
- Identifying and addressing barriers to clinical study participation

Summary

GABriella is the first Phase II study investigating a γ- secretase modulator in individuals at risk for or at the prodromal stage of Alzheimer's disease

- Recruitment starting in H1 2024

GABriella will investigate safety, tolerability and the effects of RG6289 on AD-related biomarkers

GABriella follows a patient-inclusive approach to increase diversity

GABriella will inform the clinical development of RG6289 in Alzheimer's disease

AD, Alzhweimer's disease.

Acknowledgements to everyone involved in the study

We thank

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GABriella