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.
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- **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 Aβ_{37} and Aβ_{38} → Toxic, aggregating Aβ_{42}

Higher levels of Aβ_{38} are associated with slower cognitive decline in observational cohorts

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

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1Cullen 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

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1 Porton 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

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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.
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:

- ≥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
- CDR-GS= 0 or 0.5

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Aβ, 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

Treatment period (72 weeks; minimal amount of site visits)

- Placebo (n=70)
- Low dose (n=35)
- Intermediate dose (n=70)
- High dose (n=70)

Follow-up (4 weeks)

Screening (up to 12 weeks)

Baseline (2 weeks)

Randomization 2:1:2:2

N ~ 245

Plasma samples and measures of clinical efficacy collected throughout the study

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 \( \text{A}\beta \) 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

\( \text{A}\beta \), amyloid-beta; \( \text{AE} \), adverse events; \( \text{BL} \), base line; \( \text{CDR-SB} \), Clinical Dementia Rating scale-Sum of Boxes; \( \text{CSF} \), cerebral spinal fluid; \( \text{DLAE} \), dose-limiting adverse event; \( \text{MRI} \), magnetic resonance imaging; \( \text{PD} \), pharmacodynamic; \( \text{PET} \), positron emission tomography; \( \text{PK} \), 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
- 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

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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
Acknowledgements to everyone involved in the study

We thank
the investigators, and site staff
for their time and commitment to prepare for
GABriella