Brainshuttle AD: A Phase Ib/IIa Multiple Ascending Dose Study to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of RG6102 in Participants with Prodromal or Mild-to-moderate Alzheimer’s Disease

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Disclosures

• Luka Kulic, Annamarie Vogt, Fabian Alcaraz, Gregory Klein, Ruth Croney, David Agnew, and Hanno Svoboda are full-time employees of and own stock/stock options/shares in F. Hoffmann-La Roche Ltd.

• Maddalena Marchesi, João A. Abrantes, and Paul Jordan are full time employees of F. Hoffmann-La Roche Ltd and may own company stock/stock options

• Philip Barrington is a contractor of F. Hoffmann-La Roche Ltd.
Gantenerumab

An anti-Aβ compound to treat Alzheimer’s disease (AD) patients

Brain beta-amyloid (Aβ) plaque

• Aβ is a classic biological hallmark of AD, and is a prime suspect of memory loss and cognitive decline in the early phase of AD⁰¹
• Emerging evidence from several independent amyloid clearing mAbs has identified a relationship between Aβ plaque reduction and an improvement in cognition⁰¹,²

Gantenerumab

• Fully human, anti-Aβ monoclonal IgG1 antibody binding with high affinity to aggregated Aβ³
• Currently in Phase III clinical trials⁴

Amyloid plaque removal⁵

PET SUVR reduction following 1 year of gantenerumab treatment

Aβ, beta-amyloid; AD, Alzheimer’s disease; IgG, immunoglobulin G; mAbs, monoclonal antibodies; PET, positron emission tomography; SUVR, standard uptake value ratio.
RG6102 structure and mechanism of entry

Active receptor-mediated shuttling across the blood–brain barrier into the brain

Aβ, beta-amyloid; BBB, blood–brain barrier; Tf, Transferrin; TfR1, Transferrin receptor 1.
RG6102 substantially higher exposure due to shuttling

Six- to 42-fold higher brain (tissue) exposure in nonhuman primates

Increased exposure especially in deep brain regions in nonhuman primates (RG6102 vs gantenerumab)

Brain immunohistochemistry confirms exposure in cortex 24 h after injection

Single IV dose: 10 mg/kg RG6102 vs 20 mg/kg gantenerumab.

No target (amyloid plaques) in the brain.

The Brainshuttle AD study may establish whether more extensive and homogenous brain penetration, with faster amyloid plaque clearance, can be achieved through active TfR1 receptor-mediated transcytosis

AUC, area under the curve; Cmax, maximum observed concentration; DAPI, 46-diamidino-2-phenylindole; IgG, immunoglobulin; IV, intravenous; Kp, partition coefficient.

First-in-human (Ph Ia) study of RG6102 in healthy volunteers

SAD study design and objectives

Dose escalation scheme

- **Primary objectives:**
  - Safety and tolerability
- **Secondary objectives:**
  - PK in plasma
  - CSF penetration
  - Immunogenicity

- Parallel-group study design
- 36 healthy male volunteers (18–40 years)
- Intravenous administration
- Adaptive dose and sample size selection

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**Dose 1**
0.1 mg/kg
RG6102/placebo

**Dose 2**
0.4 mg/kg
RG6102/placebo

**Dose 3**
1.2 mg/kg
RG6102/placebo

**Dose 4**
3.6 mg/kg
RG6102/placebo

**Dose 5**
7.2 mg/kg
RG6102/placebo

- 4 active / 2 placebo
- 6 active / 2 placebo

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CSF, cerebrospinal fluid; Ph, phase; PK, pharmacokinetic; SAD, single ascending dose.
Phase Ia single ascending dose study results

Plasma PK and CSF/plasma ratio

- A dose-proportional increase in plasma PK with RG6102
- Eight-fold increase in CSF/plasma ratio compared with conventional IgG mAbs

Safety and tolerability

- RG6102 doses from 0.1–3.6 mg/kg were generally well tolerated
  - All observed AEs were classified as either Grade 1 or Grade 2 in intensity and were resolved
  - No Grade 3–5 AEs
- Most frequent AEs considered related to study treatment were infusion-related reactions, headache, and nausea
- No serious AEs (including with fatal outcome) were reported up to the maximally tested dose level of 7.2 mg/kg

AE; adverse event; CSF, cerebrospinal fluid; IgG, immunoglobulin G; mAbs, monoclonal antibodies; PK, pharmacokinetic; SAD, single ascending dose.

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Phase Ib/IIa Brainshuttle AD study design

- Randomized, global multicenter, double-blind, placebo-controlled, parallel-group Phase Ib/IIa study
- The study uses a staggered, parallel-group design, with 4 initial sequential cohorts planned\(^a\)

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**Phase Ib/IIa Brainshuttle AD study design**

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\(^a\)Sentinel dosing will be applied to each cohort to avoid simultaneous exposure of all participants to a given ascending dose. The initial dose of 0.2 mg/kg of RG6102 will be administered to participants randomized to active treatment in Cohort 1. A Dose Decision Committee (DDC) will select subsequent dose levels in an adaptive manner during study conduct based on emerging safety, tolerability, and available pharmacokinetic data.

AD, Alzheimer's disease; IV, intravenous; Q4W, every 4 weeks

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An initial 10 participants with prodromal or mild-to-moderate AD will be randomized per cohort (\(n = 8\) RG6102, \(n = 2\) placebo)

Up to a maximum of 120 participants may be enrolled

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*Screening up to 12 weeks*

**Parallel-group, double-blind treatment period** 28 weeks

- Cohort 1: 0.2 mg/kg IV (Q4W)
- Cohort 2: 0.6 mg/kg IV (Q4W)
- Cohort 3: 1.8 mg/kg IV (Q4W)
- Cohort 4: 3.6 mg/kg IV (Q4W)

**Follow-up** 28 weeks

**W28 primary endpoint**

**D1 Start of treatment**
Key inclusion and exclusion criteria

- Recruitment for the Brainshuttle AD study launched in December 2020 and is ongoing

<table>
<thead>
<tr>
<th>Key inclusion criteria</th>
<th>Key exclusion criteria</th>
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<tbody>
<tr>
<td>Prodromal or mild-to-moderate AD (NIA-AA criteria)</td>
<td>Evidence of a relevant neurological condition</td>
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<td>• MMSE score 18–28</td>
<td>Other relevant medical conditions (including hematological, ophthalmologic, cardiovascular, kidney, hepatic, thyroid)</td>
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<td>• CDR-GS score = 0.5, 1, or 2</td>
<td>MRI exclusion criteria</td>
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<tr>
<td>50 to 85 years of age</td>
<td>• &gt;2 lacunar infarcts, territorial infarct &gt;1 cm³, white matter lesion ≥3 Fazekas score</td>
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<tr>
<td>Amyloid pathology confirmed by amyloid PET^a</td>
<td>• &gt;5 combined microhemorrhages and leptomeningeal hemosiderosis or &gt;3 leptomeningeal hemosiderosis</td>
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<tr>
<td>Study partner with sufficient contact with the patient, capable of providing consent to participate throughout the study</td>
<td>• ARIA-E</td>
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^aCentiloid score >50
AD, Alzheimer’s disease; CDR-GS, Clinical Dementia Rating Scale – Global Score; CNS, central nervous system; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; NIA-AA, National Institute on Aging-Alzheimer’s Association; PET, positron emission tomography.
Objectives and endpoints

<table>
<thead>
<tr>
<th>Primary Objective</th>
<th>Endpoints</th>
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<tr>
<td>Evaluate safety and tolerability of multiple-ascending IV doses of RG6102</td>
<td>Nature, frequency, severity, and timing of AEs, including laboratory assessments, vital signs, physical and neurological examination, ECG, and brain MRI</td>
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<th>Secondary Objectives</th>
<th>Endpoints</th>
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<td>Pharmacodynamics</td>
<td>Change from baseline in amyloid by amyloid PET (Week 28, additional measure at Week 12 for Cohorts 3 and 4)</td>
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<td>Pharmacokinetics</td>
<td>Concentration of RG6102 in plasma (up to 32 weeks) and CSF (baseline, Week 25)</td>
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<td>Immunogenicity</td>
<td>Incidence and titer of anti-drug antibodies (up to 56 weeks)</td>
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<th>Exploratory Objectives</th>
<th>Endpoints</th>
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<td>Clinical efficacy</td>
<td>Change from baseline in CDR and MMSE (baseline, Weeks 28 and 40)</td>
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<td>Cerebral perfusion</td>
<td>Change from baseline in PET and ASL-MRI</td>
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<td>Neuroimaging biomarkers</td>
<td>Change from baseline volumetric changes, fMRI, DTI-MRI</td>
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<td>Blood &amp; CSF biomarker</td>
<td>Change from baseline Aβ1-42, tTau, pTau, neurogranin, NfL, and sTREM2 amongst others (Blood: baseline, Weeks 11, 24, 25, and 26; CSF: baseline, Week 25)</td>
</tr>
</tbody>
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Aβ, beta-amyloid; ASL-MRI, arterial spin labeling magnetic resonance imaging; CDR, Clinical Dementia Rating Scale; CSF, cerebrospinal fluid; DTI-MRI, diffusion tensor imaging magnetic resonance imaging; ECG, electrocardiogram; fMRI, functional magnetic resonance imaging; IV, intravenous; MMSE, Mini-Mental State Examination; NfL, neurofilament light protein; PET, positron emission tomography; pTau, phosphorylated tau; PK, pharmacokinetic; sTREM2, Soluble triggering receptor expressed on myeloid cells 2; tTau, total tau.
Conclusions

RG6102 is a bispecific 2+1 monoclonal anti-Aβ antibody with a TfR1 binding module

In preclinical models, TfR1-mediated brain shuttling led to a substantially increased and homogenous brain penetration, including in deeper brain structures

The ongoing Phase Ib/IIa Brainshuttle AD study is evaluating the safety and tolerability profile of RG6102 in people with prodromal or mild-to-moderate AD

The Brainshuttle AD study may establish whether more extensive and homogenous brain penetration, with faster amyloid plaque clearance, can be achieved through active TfR1 receptor-mediated transcytosis

Aβ, beta-amyloid; AD, Alzheimer’s disease; mAbs, monoclonal antibodies; TfR1, transferrin receptor 1
Acknowledgments

We would like to thank all the participants and their families, the investigators and site staff, and the entire study team for their time and commitment to the Brainshuttle AD study.

This study was sponsored by F. Hoffmann-La Roche Ltd, Basel, Switzerland.

Editorial support in the development of this presentation was provided by Chris Ackroyd, MBiochem, of Health Interactions, funded by F. Hoffmann-La Roche Ltd.

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