SKYLINE study design: Efficacy and safety of gantenerumab in participants at risk for or at the earliest stages of Alzheimer’s disease

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Disclosures

- Szofia Bullain, Macarena Garcia-Valdecasas Colell, Jakub Wojtowicz, Claire J. Lansdall, Caroline Giacobino, Paul Delmar, Monika Baudler-Klein, and Susanne Ostrowitzki are full-time employees of and own stock/stock options in F. Hoffmann-La Roche Ltd.
- Gesine Respondek is a full-time employee of F. Hoffmann-La Roche Ltd.
- Reisa Sperling reports consulting fees for AC Immune, Genentech, F. Hoffmann-La Roche Ltd, Ionis, Janssen, NervGen, Prothena and Shionogi
- Eric M. Reiman reports compensation as a scientific advisor to Aural Analytics, Denali, Green Valley, Retromer Therapeutics, and Vaxxinity, and funding from several NIH grants. Co-founder and shareholder in ALZPath
- Paul Aisen reports research agreements with Janssen, Lilly, Eisai, and F. Hoffmann-La Roche Ltd; grants from NIA, the Alzheimer's Association and FNIH; and consulting fees from Biogen, Merck, AbbVie, Immunobrain Checkpoint, Rainbow Medical and Shionogi
- Keith A. Johnson reports consulting fees for Novartis and Janssen
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- Pierre N. Tariot reports consulting fees from Acadia, AC Immune, Avanir, Axsome, BioXcel, CME Outfitters, Eisai, Otuska & Astex, Syneos, T3D; consulting fees and research support from AbbVie, Biogen, Cortexyme, Genentech, Lilly, Merck & Co. Roche; research support only from Novartis; and owns stock in Adamas Pharmaceuticals
- Tobias Bittner and Rachelle S. Doody are employees of F. Hoffmann-La Roche Ltd. and Genentech Inc., part of F. Hoffmann-La Roche Ltd, and own stock/stock options in F. Hoffmann-La Roche Ltd.
- Elizabeth Ashford is an employee of Roche Products Ltd and owns stock/stock options in F. Hoffmann-La Roche Ltd.
- Courtney Schiffman is an employee of Genentech Inc., part of F. Hoffmann-La Roche Ltd. and owns stock in F. Hoffmann-La Roche Ltd.
SKYLINE: Study context

- Gantenerumab is a fully human IgG1 monoclonal antibody which promotes Fcγ receptor-mediated microglial phagocytosis of aggregated Aβ\(^1.2\)

- Gantenerumab has demonstrated significant amyloid removal and effects on downstream biomarkers\(^2.3\)

- Subcutaneous gantenerumab is under investigation in early AD (including GRADUATE I & II)\(^4.5\) and in familial AD (DIAN-TU)\(^6.7\)

**SKYLINE** – secondary prevention study to investigate slowing of cognitive and functional decline in amyloid-positive, cognitively unimpaired participants at risk for or at the earliest stages of AD (preclinical AD)\(^8\)

Aβ, beta-amyloid; AD, Alzheimer’s disease; MCI, mild cognitive impairment.

Figure adapted for illustration and may not reflect medical accuracy. Figure reprinted from The Lancet Neurology, Hypothetical model of dynamic biomarkers of the Alzheimer’s pathological cascade, Clifford R Jack Jr, David S Knopman, William J Jagust, Leslie M Shaw, Paul S Aisen, Michael W Weiner, Ronald C Petersen, John Q Trojanowski, 2010; 9: 119-128, Copyright (2022), with permission from Elsevier.

SKYLINE: Global Phase III, multi-centre, randomised, parallel-group, double-blind, placebo-controlled study to evaluate the efficacy and safety of gantenerumab in participants at risk for or at the earliest stages of AD¹

- Participant-centric, flexible dosing options: SC Q1W or Q2W dosing by self-administration, study partner and/or HCP-administration, in-clinic and/or at home
- Blood-based biomarker prescreening to enrich the main screening population for amyloid positivity²
- Routine MRI monitoring and predefined dose intervention strategy to minimise and mitigate ARIA risk
- Initiation of gantenerumab treatment following progression to MCI or dementia due to AD

Study design developed in planned public-private collaboration with Banner Alzheimer’s Institute, University of Southern California and Massachusetts General Hospital.²

¹Blinding to treatment assignment at randomisation maintained. ²Optional BBBM prescreening test availability depends on local country / regulatory approval.

AD, Alzheimer’s disease; ARIA, amyloid-related imaging abnormalities; BBBM; blood-based biomarker; HCP, healthcare practitioner; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; Q1W, every 1 week; Q2W, every 2 weeks; SC, subcutaneous.
SKYLINE: Key inclusion and exclusion criteria¹

**INCLUSION**

- Age: 60–80 years
- Cognitively unimpaired
  - CDR-GS = 0
  - RBANS DMI ≥80
- Evidence of cerebral amyloid accumulation
  - CSF pTau$_{181}$/Aβ$_{42}$ ratio > 0.04 or
  - Amyloid PET visual read positive

**EXCLUSION**

- Concomitant neurodegenerative disease or cerebrovascular disease that may lead to cognitive impairment
- Contraindication to MRI
- Predefined cerebral abnormalities on MRI

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Aβ, beta-amyloid; CDR-GS, Clinical Dementia Rating–Global Score; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; PET, positron emission tomography; pTau, phosphorylated tau; RBANS DMI, Repeatable Battery for the Assessment of Neuropsychological Status Delayed Memory Index.
Elecsys® plasma assays are investigational and availability depends on local country / regulatory approval. Elecsys® β-Amyloid (1-42) CSF and Elecsys® Phospho-Tau (181P) CSF are currently available in CE-mark accepting countries. Aβ, beta-amyloid; APOE ε4, apolipoprotein E ε4; CSF, cerebrospinal fluid; pTau, phosphorylated tau.

SKYLINE: Endpoints

**Primary Endpoint**

- **PACC-5**
  - Composite endpoint to assess cognition in asymptomatic AD\(^1,2\)

**Logical Memory from the WMS\(^1,3\)**

- **FCSRT\(^1,3\)**

- **Coding from the WAIS-IV\(^1,3\)**

- **MMSE\(^1,3\)**

- **Category Fluency Test\(^3\)**

**Secondary Endpoints**

- CFla
- A-IADL-Q-SV
- Time to clinical progression
- CDR-SB
- Safety: MRI, AEs, C-SSRS, ECGs, ADAs

**Additional Endpoints**

- Blood-based biomarkers, vMRI, amyloid and tau PET, CSF biomarkers
- Pharmacokinetics

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AD, Alzheimer's Disease; ADAs, anti-drug antibodies; AE, adverse event; A-IADL-Q-SV, Amsterdam Instrumental Activities of Daily Living Questionnaire Short Version; CDR-SB, Clinical Dementia Rating–Sum of Boxes; CFla, Cognitive Function Instrument acute; CSF, cerebrospinal fluid; C-SSRS, Columbia-Suicide Severity Rating Scale; DSST, Digit Symbol Substitution Test; ECG, electrocardiogram; FCSRT, Free and Cued Selective Reminding Test; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; PACC-5, Preclinical Alzheimer's Cognitive Composite-5; PET, positron emission tomography; vMRI, volumetric MRI; WAIS, Wechsler Adult Intelligence Scale; WMS, Wechsler Memory Scale.

SKYLINE: Initiation of gantenerumab treatment following progression to MCI or dementia due to AD

**4-YEAR DOUBLE-BLIND DOSING PERIOD**

- **Screening**
- **Titration**
- **Target dose (1,020 mg monthly SC Q1W or Q2W) to Week 211**
- **Safety Follow-up**
- **Randomisation 1:1**
- **Progression to MCI or dementia due to AD**
- **Post-progression titration**

**Placebo switch**
- Participants on placebo uptitrare to gantenerumab target dose

**Gantenerumab mock uptitrate**
- Participants on gantenerumab continue on target dose

*a*Blinding to treatment assignment at randomisation maintained

AD, Alzheimer’s disease; MCI, mild cognitive impairment; Q1W, every 1 week; Q2W, every 2 weeks; SC, subcutaneous.
SKYLINE: Participant-centric, flexible dosing options

Dosing frequency

Participants can choose by Week 25
• Q1W frequency at target dose or
• Q2W frequency at target dose

Administration

There are options for
• self-administration or study partner administration in the clinic and/or at the participant’s home or other suitable location after adequate training by the site
• home administration by a mobile nurse

Subcutaneous gantenerumab allows flexibility in dosing frequency and administration
SKYLINE: Summary

- Global Phase III, double-blind, placebo-controlled, 4-year secondary prevention study to assess the efficacy and safety of gantenerumab in preclinical AD
- Blood-based biomarker prescreening to enrich the main screening population for amyloid positivity
- Initiation of gantenerumab treatment following progression to MCI or dementia due to AD
- Subcutaneous gantenerumab offers flexibility of self-, study partner and/or HCP administration in the clinic and/or at home with choice of Q1W or Q2W dosing frequency

AD, Alzheimer’s disease; HCP, healthcare professional; MCI, mild cognitive impairment; Q1W, every 1 week; Q2W, every 2 weeks.
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