Clinical trial results:
A Phase III, Multicenter, Randomized, 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 Alzheimer's Disease

Summary

EudraCT number	2021-001184-25
Trial protocol	ES SE IT
Global end of trial date	13 March 2023

Results information

Result version number	v2 (current)
This version publication date	27 July 2024
First version publication date	24 March 2024
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	WN42444

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05256134
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 March 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 March 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The objective of this study was to evaluate the efficacy, safety, pharmacodynamics and pharmacokinetics of gantenerumab treatment compared with placebo in cognitively unimpaired participants, at risk for or at the earliest stages of Alzheimer's Disease (AD).

Protection of trial subjects:

All study participants and the study partners were required to read and sign an informed consent form (ICF).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 April 2022
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	United States: 22
Worldwide total number of subjects	25
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	1
From 65 to 84 years	24

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in this study at 12 investigative centers in Australia, Canada, and the United States from 19 April 2022 to 13 March 2023.

Pre-assignment

Screening details:

A total of 25 amyloid-positive, cognitively unimpaired participants at risk for or at the earliest stages of AD were randomized in a 1:1 ratio to receive either gantenerumab or placebo in this study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received placebo subcutaneous (SC) injection for a maximum of 191 days. Participants had the option to choose between every week (Q1W) or every two weeks (Q2W) dosing regimens for the target dose. A gradual up titration was performed. Participants who chose the Q1W dosing regimen received placebo, SC every 4 weeks (Q4W) six times, and then Q2W six times, prior to reaching the target dose of Q1W. Participants who chose the Q2W dosing regimen received placebo, SC Q4W nine times, prior to reaching the target dose of Q2W. By the time the study was terminated, none of the participants had reached the target dose.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo SC injection administered for a maximum of 191 days. Participants had the option to choose between Q1W or Q2W dosing regimens for the target dose. A gradual up titration was performed. Participants who chose the Q1W dosing regimen received placebo, SC Q4W six times, and then Q2W six times, prior to reaching the target dose of Q1W. Participants who chose the Q2W dosing regimen received placebo, SC Q4W nine times, prior to reaching the target dose of Q2W. By the time the study was terminated, none of the participants had reached the target dose.

Arm title	Gantenerumab

Arm description:

Participants received gantenerumab SC injection for a maximum of 172 days. Participants had the option to choose between Q1W or Q2W dosing regimens for the target dose. A gradual up titration was performed. Participants who chose the Q1W dosing regimen received a dose of gantenerumab 120 milligrams (mg) SC Q4W three times, 255 mg SC Q4W three times, and 255 mg SC Q2W six times, prior to reaching the target dose of 255 mg Q1W (i.e., 1020 mg per month). Participants who chose the Q2W dosing regimen received a dose of gantenerumab 120 mg SC Q4W three times, 255 mg SC Q4W three times, and 510 mg SC Q4W three times, prior to reaching the target dose of 510 mg Q2W (i.e., 1020 mg per month). By the time the study was terminated, none of the participants had reached the target dose.

Arm type	Experimental

Investigational medicinal product name	Gantenerumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Gantenerumab SC injection administered for a maximum of 172 days. Participants had the option to choose between Q1W or Q2W dosing regimens for the target dose. A gradual up titration was performed. Participants who chose the Q1W dosing regimen received a dose of gantenerumab 120 mg SC Q4W three times, 255 mg SC Q4W three times, and 255 mg SC Q2W six times, prior to reaching the target dose of 255 mg Q1W (i.e., 1020 mg per month). Participants who chose the Q2W dosing regimen received a dose of gantenerumab 120 mg SC Q4W three times, 255 mg SC Q4W three times, and 510 mg SC Q4W three times, prior to reaching the target dose of 510 mg Q2W (i.e., 1020 mg per month). By the time the study was terminated, none of the participants had reached the target dose.

Number of subjects in period 1	Placebo	Gantenerumab
Started	12	13
Completed	0	0
Not completed	12	13
Withdrawal by Subject	1	3
Study Terminated by Sponsor	11	10

Baseline characteristics

Reporting groups	
Reporting group title	Placebo

Reporting group description:

Participants received placebo subcutaneous (SC) injection for a maximum of 191 days. Participants had the option to choose between every week (Q1W) or every two weeks (Q2W) dosing regimens for the target dose. A gradual up titration was performed. Participants who chose the Q1W dosing regimen received placebo, SC every 4 weeks (Q4W) six times, and then Q2W six times, prior to reaching the target dose of Q1W. Participants who chose the Q2W dosing regimen received placebo, SC Q4W nine times, prior to reaching the target dose of Q2W. By the time the study was terminated, none of the participants had reached the target dose.

Reporting group title	Gantenerumab

Reporting group description:

Participants received gantenerumab SC injection for a maximum of 172 days. Participants had the option to choose between Q1W or Q2W dosing regimens for the target dose. A gradual up titration was performed. Participants who chose the Q1W dosing regimen received a dose of gantenerumab 120 milligrams (mg) SC Q4W three times, 255 mg SC Q4W three times, and 255 mg SC Q2W six times, prior to reaching the target dose of 255 mg Q1W (i.e., 1020 mg per month). Participants who chose the Q2W dosing regimen received a dose of gantenerumab 120 mg SC Q4W three times, 255 mg SC Q4W three times, and 510 mg SC Q4W three times, prior to reaching the target dose of 510 mg Q2W (i.e., 1020 mg per month). By the time the study was terminated, none of the participants had reached the target dose.

Reporting group values	Placebo	Gantenerumab	Total
Number of subjects	12	13	25
Age Categorical Units: participants			
Age Continuous Units: years			
arithmetic mean	70.9	72.7	
standard deviation	± 3.2	± 4.7	-
Gender Categorical Units: participants			
Female	8	9	17
Male	4	4	8
Ethnicity Units: Subjects			
Hispanic or Latino	0	2	2
Not Hispanic or Latino	10	7	17
Unknown or Not Reported	2	4	6
Race Units: Subjects			
White	10	9	19
Not Reported	2	4	6
Baseline of Preclinical Alzheimer's Cognitive Composite-5 (PACC-5)			

PACC-5=average of z-scores of 5 cognitive measures: Wechsler Memory Scale (WMS Logical Memory[LM] I-II)-Total Score LM II Delayed Recall; Free & Cued Selective Reminding Test -Immediate & Delayed Recall-Trials 1-3: Total Recall; Wechsler Adult Intelligence Scale-IV Coding-Total Raw Score; Mini Mental State Examination - Total Score; Category Fluency Test-3 categories-Vegetables, Fruits & Animals-Total Admissible Words. z-score=difference between assessment &mean of baseline assessments, divided by SD of baseline assessments. Z-scores range= -3to+3. Higher scores=better

cognitive performance.			
Units: score on a scale			
arithmetic mean	0.110	-0.101	
standard deviation	± 0.7339	± 0.5286	-

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received placebo subcutaneous (SC) injection for a maximum of 191 days. Participants had the option to choose between every week (Q1W) or every two weeks (Q2W) dosing regimens for the target dose. A gradual up titration was performed. Participants who chose the Q1W dosing regimen received placebo, SC every 4 weeks (Q4W) six times, and then Q2W six times, prior to reaching the target dose of Q1W. Participants who chose the Q2W dosing regimen received placebo, SC Q4W nine times, prior to reaching the target dose of Q2W. By the time the study was terminated, none of the participants had reached the target dose.

Reporting group title	Gantenerumab

Reporting group description:

Participants received gantenerumab SC injection for a maximum of 172 days. Participants had the option to choose between Q1W or Q2W dosing regimens for the target dose. A gradual up titration was performed. Participants who chose the Q1W dosing regimen received a dose of gantenerumab 120 milligrams (mg) SC Q4W three times, 255 mg SC Q4W three times, and 255 mg SC Q2W six times, prior to reaching the target dose of 255 mg Q1W (i.e., 1020 mg per month). Participants who chose the Q2W dosing regimen received a dose of gantenerumab 120 mg SC Q4W three times, 255 mg SC Q4W three times, and 510 mg SC Q4W three times, prior to reaching the target dose of 510 mg Q2W (i.e., 1020 mg per month). By the time the study was terminated, none of the participants had reached the target dose.

Primary: Change from Baseline in PACC-5 Score

End point title	Change from Baseline in PACC-5 Score[1]

End point description:

PACC-5 is computed as the average of z-scores of following cognitive measures: 1. WMS LM I-II - Total Score LM II Delayed Recall; 2. Free & Cued Selective Reminding Test (FCSRT) -Immediate & Delayed Recall - Trials 1-3: Total Recall; 3. Wechsler Adult Intelligence Scale (WAIS) -IV Coding - Total Raw Score; 4. Mini Mental State Examination (MMSE) - Total Score; 5. Category Fluency Test (CFT) - 3 categories - Vegetables, Fruits & Animals - Total Admissible Words. z-score was defined as difference between the assessment and the mean of baseline assessments, divided by standard deviation of baseline assessments. Z-scores range from -3to+3 with higher scores indicating better cognitive performance. Intent-to-Treat (ITT) Population included all participants randomly assigned to study treatment. Participants were grouped into two arms (placebo or gantenerumab) according to treatment assigned at randomization. Overall number analyzed=number of participants with data available for analyses.

End point type	Primary

End point timeframe:

Baseline to early termination visit (up to 225 days from start of treatment)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics were planned to be analyzed for this study.

End point values	Placebo	Gantenerumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	11		
Units: score on a scale				
arithmetic mean (standard deviation)	-0.052 (± 0.5790)	-0.119 (± 0.6038)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time from Randomization to Clinical Progression to Mild Cognitive Impairment (MCI) or Dementia due to AD

End point title	Time from Randomization to Clinical Progression to Mild Cognitive Impairment (MCI) or Dementia due to AD

End point description:

Time from randomization to clinical progression to mild cognitive impairment or dementia due to Alzheimer's disease was based on the diagnosis of the independent Clinical Adjudication Committee (iCAC). 9999 = Data was not estimable as none of the participants met the diagnosis criteria for clinical progression i.e., No participant progressed to mild cognitive impairment or dementia due to Alzheimer's disease based on the diagnosis of the iCAC.

End point type	Secondary

End point timeframe:

Randomization to early termination visit (up to 225 days from start of treatment)

End point values	Placebo	Gantenerumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	13		
Units: weeks				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Onset of Confirmed Clinical Progression

End point title	Time to Onset of Confirmed Clinical Progression

End point description:

Time to onset of confirmed clinical progression=time from randomization to first occurrence of two consecutive visits (approx. 6 months apart)with a Clinical Dementia Rating Global Score(CDR-GS) of >0. CDR=clinician reported (ClinRO)measure for staging severity of AD dementia based on semi-structured interview with participant &reliable informant. CDR characterizes participant's level of cognitive &functional impairment across six domains (memory/orientation/judgment &problem solving/community affairs/home &hobbies/personal care) on 5-point rating. CDR-GS is calculated using Washington University CDR-assignment algorithm &characterizes a participant's level of global impairment/stage of dementia according to following categories: 0=normal;0.5=very mild dementia;1=mild dementia;2=moderate dementia;3=severe dementia. Score range=0 to 3. High score=high disease severity. 9999=Data was not estimable as no participants had two consecutive visits (approx. 6 months apart) with a CDR-GS >0.

End point type	Secondary

End point timeframe:

Randomization to early termination visit (up to 225 days from start of treatment)

End point values	Placebo	Gantenerumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	13		
Units: weeks				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Cognitive Function Instrument Acute (CFIa) Participant Version

End point title	Change from Baseline in the Cognitive Function Instrument Acute (CFIa) Participant Version

End point description:

The CFIa is an outcome measure developed to assess memory-related cognitive and functional decline in non-demented elderly individuals. The CFIa is a modified version of the original CFI and differs in terms of recall period and item response options. The CFIa is computed as the sum of 14 items, rated on a 5-point Likert scale ranging from Never=0 to Always=4 and referring to the participant's current ability (most recent experience). Total scores range from 0 to 56. Higher scores indicate greater cognitive impairment. Negative change from baseline indicates improvement. The participant (PRO) and study partner (ObsRO) versions of the CFIa were used in this study. ITT Population included all participants randomly assigned to study treatment. Participants were grouped into two arms (placebo/gantenerumab) according to treatment assigned at randomization. Overall number analyzed is the number of participants with data available for analyses.

End point type	Secondary

End point timeframe:

Baseline to early termination visit (up to 225 days from start of treatment)

End point values	Placebo	Gantenerumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	11		
Units: score on a scale				
arithmetic mean (standard deviation)	0.3 (± 4.52)	0.9 (± 4.70)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Amsterdam Instrumental Activities of Daily Living Questionnaire Short Version (A-IADL-Q-SV)

End point title	Change from Baseline in the Amsterdam Instrumental Activities of Daily Living Questionnaire Short Version (A-IADL-Q-SV)

End point description:

A-IADL-Q-SV=observer reported measure assessing ability to perform instrumental activities of daily living(household/leisure activities,use of household appliances,management of finances,etc.).A-IADL-Q-

SV had 30 items rated by study partner. Each item is divided into 2 questions(Q),Q1 was if activity was performed during past 4 weeks(Yes/No/Don't know).If performed,Q2 captures level of difficulty while performing the activity on 5-point Likert scale(no difficulty to no longer able to perform the activity).If not performed,Q2 captures why activity was not performed(never done before, no longer able to do so due to physical problems, no longer able to do so due to difficulties with memory,planning/thinking/other including free text response).A-IADL-Q-SV=average of all scored responses multiplied by 25.Score range=0-100.Higher scores=better functioning. Negative change from baseline=worsening.ITT Population.Overall number analyzed=number of participants with data available for analyses.

End point type	Secondary

End point timeframe:

Baseline to early termination visit (up to 225 days from start of treatment)

End point values	Placebo	Gantenerumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	11		
Units: score on a scale				
arithmetic mean (standard deviation)	-1.3 (± 3.93)	-0.4 (± 1.29)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events (AEs), Serious Adverse Events (SAEs), and Adverse Events of Special Interest (AESIs)

End point title	Number of Participants with Adverse Events (AEs), Serious Adverse Events (SAEs), and Adverse Events of Special Interest (AESIs)

End point description:

An AE is any untoward medical occurrence in a patient or clinical study participant temporally associated with the use of a study treatment, whether or not considered related to the study treatment. A SAE is defined as any untoward medical occurrence that, at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent disability or incapacity, and leads to congenital anomaly or birth defect. An AESI included drug induced liver injury and suspected transmission of infectious agent via medicinal products. Safety Evaluable Population included all participants randomly assigned to study treatment and who received at least 1 dose of study drug. Participants were grouped according to the treatment they received at first exposure.

End point type	Secondary

End point timeframe:

Day 1 to safety follow-up visit (up to 310 days from start of treatment)

End point values	Placebo	Gantenerumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	13		
Units: participants				
AEs	6	5		
SAEs	0	0		

AESIs	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Anti-Drug Antibodies (ADAs) to Gantenerumab

End point title	Number of Participants with Anti-Drug Antibodies (ADAs) to Gantenerumab[2]

End point description:

The number of ADA-positive participants after drug administration were determined for participants exposed to gantenerumab. For determining post-baseline incidence, participants were considered to be ADA-positive if they were ADA-negative or had missing data at baseline but developed an ADA response following study drug exposure, or if they were ADA-positive at baseline and the titer of 1 or more post-baseline samples was at least 4-fold higher in comparison to the titer at the baseline. As prespecified in the protocol, this outcome measure was applicable only to participants exposed to gantenerumab. Safety Evaluable Population included all participants randomly assigned to study treatment and who received at least 1 dose of study drug. Participants were grouped according to the treatment they received at first exposure.

End point type	Secondary

End point timeframe:

Day 1 to early termination visit (up to 216 days from start of treatment)

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: As prespecified in the protocol, this outcome measure was applicable only to participants in the gantenerumab arm group.

End point values	Gantenerumab			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: participants	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the CFIa Study Partner Version

End point title	Change from Baseline in the CFIa Study Partner Version

End point description:

The CFIa is an outcome measure developed to assess memory-related cognitive and functional decline in non-demented elderly individuals. The CFIa is a modified version of the original CFI and differs in terms of recall period and item response options. The CFIa is computed as the sum of 14 items, rated on a 5-point Likert scale ranging from Never=0 to Always=4 and referring to the participant’s current ability (most recent experience). Total scores range from 0 to 56. Higher scores indicate greater cognitive impairment. Negative change from baseline indicates improvement. The PRO and ObsRO versions of the CFIa were used in this study. ITT Population included all participants randomly assigned to study treatment. Participants were grouped into two arms (placebo/gantenerumab) according to treatment assigned at randomization. Overall number analyzed is the number of participants with data

available for analyses.

End point type	Secondary

End point timeframe:

Baseline to early termination visit (up to 225 days from start of treatment)

End point values	Placebo	Gantenerumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	10		
Units: score on a scale				
arithmetic mean (standard deviation)	-0.8 (± 3.24)	0.2 (± 5.14)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Clinical Dementia Rating Sum of Boxes (CDR-SB)

End point title	Change from Baseline in the Clinical Dementia Rating Sum of Boxes (CDR-SB)

End point description:

CDR is a ClinRO measure used to stage the severity of AD dementia based on a semi-structured interview with the participant & a reliable informant. CDR characterizes participant's level of cognitive and functional impairment across six domains (memory, orientation, judgment & problem solving, community affairs, home & hobbies, & personal care) on a 5-point rating scale in which 0=None, 0.5=questionable, 1=mild, 2=moderate, 3=severe (with exception of personal care, which is rated on a 4-point rating scale & excludes questionable impairment level). CDR-SB is calculated by summing the ratings across each of the six domains (total score=0-18). Higher scores=greater impairment. Negative change from baseline=improvement. ITT Population=all participants randomly assigned to study treatment. Participants were grouped into two arms (placebo or gantenerumab) according to treatment assigned at randomization. Overall number analyzed=number of participants with data available for analyses.

End point type	Secondary

End point timeframe:

Baseline to early termination visit (up to 225 days from start of treatment)

End point values	Placebo	Gantenerumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	10		
Units: score on a scale				
arithmetic mean (standard deviation)	0.29 (± 0.498)	-0.05 (± 0.158)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Brain Amyloid Load Over Time as Measured by Amyloid Positron Emission Tomography (PET) in a Subset of Participants

End point title	Change in Brain Amyloid Load Over Time as Measured by Amyloid Positron Emission Tomography (PET) in a Subset of Participants

End point description:

Brain amyloid load over time was planned to be assessed using [18F] florbetaben or [18F] flutemetamol tracers. These are PET radioligand selective to amyloid. Amyloid PET burden is measured in a composite region of interest (ROI) by using standardized uptake value ratio (SUVR) mapped to the centiloid scale. The weighted composite target region are composed of (both left and right side): frontal lobe, parietal lobe, temporal lobe lateral, cingulum posterior and anterior cingulate gyrus. The reference region used to normalize the composite region is the whole cerebellum. The centiloid scale anchor points are 0 and 100, where 0 represents a high-certainty amyloid negative scan and 100 represents the amount of global amyloid deposition found in a typical AD scan. Data is not reported as no postbaseline samples were collected due to early termination of study by the sponsor.

End point type	Secondary

End point timeframe:

Baseline

End point values	Placebo	Gantenerumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[3]	0[4]		
Units: Centiloid				
arithmetic mean (standard deviation)	()	()		

Notes:

[3] - Data is not reported as no postbaseline samples were collected.

[4] - Data is not reported as no postbaseline samples were collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Abnormal Magnetic Resonance Imaging (MRI) Findings: Amyloid-related Imaging Abnormalities – Edema/Effusion (ARIA-E) and ARIA-Hemosiderin Deposition (ARIA-H)

End point title	Number of Participants with Abnormal Magnetic Resonance Imaging (MRI) Findings: Amyloid-related Imaging Abnormalities – Edema/Effusion (ARIA-E) and ARIA-Hemosiderin Deposition (ARIA-H)

End point description:

ARIA are an identified risk with anti-amyloid antibodies, including gantenerumab. These changes can be identified on brain MRI. In ARIA-E, (E for edema or effusion), edema can be seen in different areas of the brain on MRI, representing fluid leakage into the brain parenchyma or sulcal spaces. ARIA-H (H for hemosiderosis) are small foci of signal loss observed on MRI sequences sensitive for paramagnetic tissue properties and comprise cerebral microbleeds (small foci of bleeding in the brain parenchyma) and leptomeningeal hemosiderosis (small foci of bleeding on the surface of the brain). These changes also occur sporadically in AD. Safety Evaluable Population included all participants randomly assigned to study treatment and who received at least 1 dose of study drug. Participants were grouped according to the treatment they received at first exposure.

End point type	Secondary

End point timeframe:

Day 1 to early termination visit (up to 248 days from start of treatment)

End point values	Placebo	Gantenerumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	13		
Units: participants				
ARIA-E	0	0		
ARIA-H	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Post-baseline Suicidal Behaviors and Ideations as Assessed by Columbia-Suicide Severity Rating Scale (C-SSRS) Score

End point title	Number of Participants With Post-baseline Suicidal Behaviors and Ideations as Assessed by Columbia-Suicide Severity Rating Scale (C-SSRS) Score

End point description:

C-SSRS=assessment tool used to assess lifetime suicidality of a participant (at baseline) &any new instances of suicidality(since last visit).Structured interview prompts recollection of suicidal ideation(SI), including intensity of ideation, behavior, &attempts with actual/potential lethality. Categories have binary responses (yes/no) &include: Wish to be Dead; Non-specific Active Suicidal Thoughts; Active SI with Any Methods(Not Plan) Without Intent to Act; Active SI with Some Intent to Act, Without Specific Plan; Active SI with Specific Plan & Intent, Preparatory Acts & Behavior; Aborted Attempt; Interrupted Attempt; Actual Attempt(non-fatal);Completed Suicide.SI/behavior is indicated as "yes" answer to any of the listed categories. Score of 0=if no suicide risk is present. A score of 1 or higher=SI/behavior. Categories with at least 1 participant with event are reported. Safety Evaluable Population. Overall Number analyzed=number of participants with data available for analyses.

End point type	Secondary

End point timeframe:

Day 1 to safety follow-up visit (up to 310 days from start of treatment)

End point values	Placebo	Gantenerumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	11		
Units: participants				
SI: Non-specific Active Suicidal Thoughts	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Injection-site Reactions (ISRs)

End point title	Number of Participants with Injection-site Reactions (ISRs)

End point description:

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational product or other protocol-imposed intervention, regardless of attribution. Local injection reactions (or injection-site reactions) are defined as AEs related to the injection site that occur during or within 24 hours after study drug administration that are judged to be related to the study drug injection. Safety Evaluable Population included all participants randomly assigned to study treatment and who received at least 1 dose of study drug. Participants were grouped according to the treatment they received at first exposure.

End point type	Secondary

End point timeframe:

Day 1 to safety follow-up visit (up to 310 days from start of treatment)

End point values	Placebo	Gantenerumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	13		
Units: participants	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in CSF Neurofilament Light (NFL) Over Time in a Subset of Participants

End point title	Change in CSF Neurofilament Light (NFL) Over Time in a Subset of Participants

End point description:

NFL is a neuronal cytoplasmic protein highly expressed in large, myelinated axons. Its levels increase in CSF proportionally to the degree of axonal damage in a variety of neurological disorders, including AD. Data is not reported as no postbaseline samples were collected due to early termination of study by the sponsor.

End point type	Secondary

End point timeframe:

Baseline

End point values	Placebo	Gantenerumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[5]	0[6]		
Units: pg/mL				
arithmetic mean (standard deviation)	()	()		

Notes:

[5] - Data is not reported as no postbaseline samples were collected.

[6] - Data is not reported as no postbaseline samples were collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in CSF Amyloid Peptide: Aβ 1-40 Over Time in a Subset of Participants

End point title	Change in CSF Amyloid Peptide: Aβ 1-40 Over Time in a Subset of Participants

End point description:

Amyloid beta is a peptide fragment of the amyloid precursor protein. Data is not reported as no postbaseline samples were collected due to early termination of study by the sponsor.

End point type	Secondary

End point timeframe:

Baseline

End point values	Placebo	Gantenerumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[7]	0[8]		
Units: pg/mL				
arithmetic mean (standard deviation)	()	()		

Notes:

[7] - Data is not reported as no postbaseline samples were collected.

[8] - Data is not reported as no postbaseline samples were collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Cerebrospinal Fluid (CSF) Amyloid (A) Peptide beta (β): Aβ 1-42 Over Time in a Subset of Participants

End point title	Change in Cerebrospinal Fluid (CSF) Amyloid (A) Peptide beta (β): Aβ 1-42 Over Time in a Subset of Participants

End point description:

Amyloid beta is a peptide fragment of the amyloid precursor protein. Data is not reported as no postbaseline samples were collected due to early termination of study by the sponsor.

End point type	Secondary

End point timeframe:

Baseline

End point values	Placebo	Gantenerumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[9]	0[10]		
Units: pg/mL				
arithmetic mean (standard deviation)	()	()		

Notes:

[9] - Data is not reported as no postbaseline samples were collected.

[10] - Data is not reported as no postbaseline samples were collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Brain Tau Load Over Time as Measured by Tau PET in a Subset of Participants

End point title	Change in Brain Tau Load Over Time as Measured by Tau PET in a Subset of Participants

End point description:

Change in tau load represents how much neurofibrillary tau pathology is present in brain assessed using PET scan. For the longitudinal tau PET assessment, [18F]-MK-6240 was used. Tau load is measured using SUVR in four composite target ROIs: Temporal composite target region included (both left & right) anterior & posterior superior temporal gyrus, posterior temporal lobe, fusiform gyrus, & middle and inferior temporal gyrus; Medial temporal composite region not including hippocampus included (both left & right): amygdala, parahippocampus & anterior medial & lateral temporal lobe; Frontal lobe (both left & right) & Parietal lobe (both left & right). Inferior cerebellar grey matter = reference region for calculating median SUVRs for all four target regions. Data is not reported as no postbaseline samples were collected due to early termination of study by the sponsor.

End point type	Secondary

End point timeframe:

Baseline

End point values	Placebo	Gantenerumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[11]	0[12]		
Units: SUVR				
arithmetic mean (standard deviation)	()	()		

Notes:

[11] - Data is not reported as no postbaseline samples were collected.

[12] - Data is not reported as no postbaseline samples were collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in CSF Phosphorylated Tau (pTau) Over Time in a Subset of Participants

End point title	Change in CSF Phosphorylated Tau (pTau) Over Time in a Subset of Participants

End point description:

CSF pTau is an indicator of neuronal injury and neurodegeneration. An elevation in levels specific pTau species, is thought to be a marker for progressive cellular degeneration in AD. Data is not reported as no postbaseline samples were collected due to early termination of study by the sponsor.

End point type	Secondary

End point timeframe:

Baseline

End point values	Placebo	Gantenerumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[13]	0[14]		
Units: pg/mL				
arithmetic mean (standard deviation)	()	()		

Notes:

[13] - Data is not reported as no postbaseline samples were collected.

[14] - Data is not reported as no postbaseline samples were collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in CSF Total Tau (tTau) Over Time in a Subset of Participants

End point title	Change in CSF Total Tau (tTau) Over Time in a Subset of Participants

End point description:

CSF biomarker tTau has been considered as a general marker of neurodegeneration. An elevation in levels of tau, is thought to be a marker for progressive cellular degeneration in AD. Data is not reported as no postbaseline samples were collected due to early termination of study by the sponsor.

End point type	Secondary

End point timeframe:

Baseline

End point values	Placebo	Gantenerumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[15]	0[16]		
Units: pg/mL				
arithmetic mean (standard deviation)	()	()		

Notes:

[15] - Data is not reported as no postbaseline samples were collected.

[16] - Data is not reported as no postbaseline samples were collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Total Ventricular Volume Over Time as Determined by MRI in a Subset of Participants

End point title	Change in Total Ventricular Volume Over Time as Determined by MRI in a Subset of Participants

End point description:

Total Ventricular Volume is measured by vMRI. Volumetric imaging is a 3D technique where all the MRI signals are collected from the entire tissue sample and imaged as a whole entity, therefore providing a high signal to noise ratio. Total ventricular volume represents a summary measure of total including right and left lateral ventricles, third ventricle and fourth ventricle of brain. Data is not reported as no postbaseline samples were collected due to early termination of study by the sponsor.

End point type	Secondary

End point timeframe:

Baseline

End point values	Placebo	Gantenerumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[17]	0[18]		
Units: mm^3				
arithmetic mean (standard deviation)	()	()		

Notes:

[17] - Data is not reported as no postbaseline samples were collected.

[18] - Data is not reported as no postbaseline samples were collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Whole Brain Volume Over Time as Determined by MRI in a Subset of Participants

End point title	Change in Whole Brain Volume Over Time as Determined by MRI in a Subset of Participants

End point description:

Whole brain volume is measured by volumetric (vMRI). Volumetric imaging is a three dimensional (3D) technique where all the MRI signals are collected from the entire tissue sample and imaged as a whole entity, therefore providing a high signal to noise ratio. Whole brain volume represents a summary measure of total brain parenchyma which includes the cerebrum, basal ganglia, diencephalon, and cerebellum. Data is not reported as no postbaseline samples were collected due to early termination of study by the sponsor.

End point type	Secondary

End point timeframe:

Baseline

End point values	Placebo	Gantenerumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[19]	0[20]		
Units: cubic millimeter (mm^3)				
arithmetic mean (standard deviation)	()	()		

Notes:

[19] - Data is not reported as no postbaseline samples were collected.

[20] - Data is not reported as no postbaseline samples were collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Blood NFL Over Time in All Participants

End point title	Change in Blood NFL Over Time in All Participants

End point description:

NFL is a neuronal cytoplasmic protein highly expressed in large, myelinated axons. Its levels increase in blood proportionally to the degree of axonal damage in AD.

End point type	Secondary

End point timeframe:

Baseline to safety follow-up visit (up to 310 days from start of treatment)

End point values	Placebo	Gantenerumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[21]	0[22]		
Units: pg/mL				
arithmetic mean (standard deviation)	()	()		

Notes:

[21] - No analyses were conducted due to limited data collected at the time of study termination.

[22] - No analyses were conducted due to limited data collected at the time of study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Hippocampal Volume Over Time as Determined by MRI in a Subset of Participants

End point title	Change in Hippocampal Volume Over Time as Determined by MRI in a Subset of Participants

End point description:

Total hippocampal volume is measured by vMRI. Volumetric imaging is a 3D technique where all the MRI signals are collected from the entire tissue sample and imaged as a whole entity, therefore providing a high signal to noise ratio. Total hippocampal volume is calculated by summing up right and left hippocampal volumes. Data is not reported as no postbaseline samples were collected due to early termination of study by the sponsor.

End point type	Secondary

End point timeframe:

Baseline

End point values	Placebo	Gantenerumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[23]	0[24]		
Units: mm^3				
arithmetic mean (standard deviation)	()	()		

Notes:

[23] - Data is not reported as no postbaseline samples were collected.

[24] - Data is not reported as no postbaseline samples were collected.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in Blood Aβ 1-42 Over Time in All Participants

End point title	Change in Blood Aβ 1-42 Over Time in All Participants

End point description:

Amyloid beta is a peptide fragment of the amyloid precursor protein.

End point type	Other pre-specified

End point timeframe:

Baseline to safety follow-up visit (up to 310 days from start of treatment)

End point values	Placebo	Gantenerumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[25]	0[26]		
Units: pg/mL				
arithmetic mean (standard deviation)	()	()		

Notes:

[25] - No analyses were conducted due to limited data collected at the time of study termination.

[26] - No analyses were conducted due to limited data collected at the time of study termination.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in Blood pTau Over Time in All Participants Over Time

End point title	Change in Blood pTau Over Time in All Participants Over Time

End point description:

End point type	Other pre-specified

End point timeframe:

Baseline to safety follow-up visit (up to 310 days from start of treatment)

End point values	Placebo	Gantenerumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[27]	0[28]		
Units: pg/mL				
arithmetic mean (standard deviation)	()	()		

Notes:

[27] - No analyses were conducted due to limited data collected at the time of study termination.

[28] - No analyses were conducted due to limited data collected at the time of study termination.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in Blood Aβ 1-40 Over Time in All Participants

End point title	Change in Blood Aβ 1-40 Over Time in All Participants

End point description:

Amyloid beta is a peptide fragment of the amyloid precursor protein.

End point type	Other pre-specified

End point timeframe:

Baseline to safety follow-up visit (up to 310 days from start of treatment)

End point values	Placebo	Gantenerumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[29]	0[30]		
Units: pg/mL				
arithmetic mean (standard deviation)	()	()		

Notes:

[29] - No analyses were conducted due to limited data collected at the time of study termination.

[30] - No analyses were conducted due to limited data collected at the time of study termination.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 to safety follow-up visit (up to 310 days from start of treatment)

Adverse event reporting additional description:

Safety evaluable population included all participants randomly assigned to study treatment and who received at least 1 dose of study drug. Participants were grouped according to the treatment they received at first exposure.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Gantenerumab

Reporting group description:

Participants received gantenerumab SC injection for a maximum of 172 days. Participants had the option to choose between Q1W or Q2W dosing regimens for the target dose. A gradual up titration was performed. Participants who chose the Q1W dosing regimen received a dose of gantenerumab 120 mg SC Q4W three times, 255 mg SC Q4W three times, and 255 mg SC Q2W six times, prior to reaching the target dose of 255 mg Q1W (i.e., 1020 mg per month). Participants who chose the Q2W dosing regimen received a dose of gantenerumab 120 mg SC Q4W three times, 255 mg SC Q4W three times, and 510 mg SC Q4W three times, prior to reaching the target dose of 510 mg Q2W (i.e., 1020 mg per month). By the time the study was terminated, none of the participants had reached the target dose.

Reporting group title	Placebo

Reporting group description:

Participants received placebo SC injection for a maximum of 191 days. Participants had the option to choose between Q1W or Q2W dosing regimens for the target dose. A gradual up titration was performed. Participants who chose the Q1W dosing regimen received placebo, SC Q4W six times, and then Q2W six times, prior to reaching the target dose of Q1W. Participants who chose the Q2W dosing regimen received placebo, SC Q4W nine times, prior to reaching the target dose of Q2W. By the time the study was terminated, none of the participants had reached the target dose.

Serious adverse events	Gantenerumab	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Gantenerumab	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 13 (38.46%)	6 / 12 (50.00%)	
Investigations			

Cardiac murmur			
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Skin abrasion			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Skin laceration			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Arthropod bite			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Muscle strain			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Fall			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 13 (15.38%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Vaccination site reaction			
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Pain			

subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Injection site reaction			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Endocrine disorders			
Thyroid disorder			
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 13 (7.69%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Urinary tract infection			
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Viral infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 November 2021	Protocol WN42444 was amended to address a health authority (HA) requirement. Substantive changes made to the protocol are: 1. Updates made to address a HA requirement to include a COVID-19 vaccination risk assessment. 2. Updates made to clarify the MRI safety monitoring schedule for each study period (initial dose escalation, maintenance dosing, and post-progression dose escalation periods) and dosing schedule (every week [Q1W], every 2 weeks [Q2W], Q4W). 3. Updates made to clarify timing of MRIs related to amyloid-related imaging abnormality (ARIA) management for each study period and dosing schedule. 4. Footnotes were added to tables to clarify the assessment schedule during and following the post-progression dose escalation. 5. Text was updated to clarify that, before a participant entered the post-progression dose escalation period based on having clinically progressed, they need to be on target dose; it was also clarified that, in order to conclude on clinical progression, the change in diagnostic classification must be confirmed on a second visit, approximately 6 months later so that the diagnosis could be considered stable. 6. Pharmacokinetic samples at Week 131 and Week 183 added in schedule of assessment. 7. The process for rescreening was clarified

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
11 November 2022	Decision to terminate development of gantenerumab for treatment of prodromal/mild/early stage of Alzheimer disease (AD) as well as in people at risk for or at the earliest stages of AD following results of a pre-planned analysis of the safety and efficacy of gantenerumab in Graduate I&II (WN29922/WN39658).	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

SKYLINE study was terminated early & limited data could be collected & analyzed. Hence, no conclusions can be made on effectiveness of gantenerumab in treatment of people at risk for or at earliest stages of AD.

Notes: