Clinical trial results:
A Phase II, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Efficacy, and Safety Study of MTAU9937a in Patients With Moderate Alzheimer's Disease

Summary

EudraCT number	2018-003398-87
Trial protocol	ES
Global end of trial date	30 August 2023

Results information

Result version number	v3 (current)
This version publication date	14 September 2024
First version publication date	31 July 2022
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	GN40040

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03828747
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	30 August 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 August 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this trial was to evaluate the clinical efficacy, safety, pharmacokinetics, and pharmacodynamics of semorinemab in participants with moderate AD.

Protection of trial subjects:

All study subjects were required to read and sign and Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 January 2019
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	3 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 22
Country: Number of subjects enrolled	Poland: 43
Country: Number of subjects enrolled	Spain: 36
Country: Number of subjects enrolled	United States: 171
Worldwide total number of subjects	272
EEA total number of subjects	101

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)	49

From 65 to 84 years	209
85 years and over	14

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 49 centers in 4 countries.

Pre-assignment

Screening details:

A total of 272 participants were enrolled at 49 centers. 5 participants did not receive blinded treatment.

Period 1

Period 1 title	Double-Blind Treatment 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	Semorinemab

Arm description:

Semorinemab was administered intravenously in the double-blind treatment period and was administered intravenously in the optional open-label extension period.

Arm type	Experimental
Investigational medicinal product name	Semorinemab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants will receive semorinemab every 2 weeks (Q2W) for the first three doses of the double-blind treatment period and every 4 weeks (Q4W) thereafter during the double-blind treatment period. Semorinemab will be administered Q4W in the OLE period.

Investigational medicinal product name	[18F]GTP1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

[18F]GTP1 was administered as a solution for intravenous (IV) use, as part of positron emission tomography (PET) imaging.

Arm title	Placebo

Arm description:

Placebo was administered intravenously in the double-blind treatment period and semorinemab was administered intravenously in the optional open-label extension.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received placebo Q2W for the first three doses of the double-blind treatment period and

Q4W thereafter during the double-blind treatment period.

Investigational medicinal product name	[18F]GTP1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

[18F]GTP1 was administered as a solution for IV use, as part of PET imaging.

Number of subjects in period 1	Semorinemab	Placebo
Started	136	136
Cohort 1	92 [1]	99 [2]
Cohort 2	43 [3]	33 [4]
Completed	106	102
Not completed	30	34
Consent withdrawn by subject	17	19
Physician decision	1	4
Adverse Event	6	6
Death	1	1
Various reasons	5	3
Lost to follow-up	-	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: We are showing the number or participants, per cohort who started in each arm to be consistent with the clinicaltrials.gov posting
[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: We are showing the number or participants, per cohort who started in each arm to be consistent with the clinicaltrials.gov posting
[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: We are showing the number or participants, per cohort who started in each arm to be consistent with the clinicaltrials.gov posting
[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: We are showing the number or participants, per cohort who started in each arm to be consistent with the clinicaltrials.gov posting

Period 2

Period 2 title	Open-Label Extension
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Semorinemab

Arm description:

Semorinemab was administered intravenously in the double-blind treatment period and was administered intravenously in the optional open-label extension period.

Arm type	Experimental
Investigational medicinal product name	[18F]GTP1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

[18F]GTP1 was administered as a solution for intravenous (IV) use, as part of positron emission tomography (PET) imaging.

Investigational medicinal product name	Semorinemab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received semorinemab every 2 weeks (Q2W) for the first three doses of the double-blind treatment period and every 4 weeks (Q4W) thereafter during the double-blind treatment period. Semorinemab was administered Q4W in the OLE period.

Arm title	Placebo

Arm description:

Placebo was administered intravenously in the double-blind treatment period and semorinemab will be administered intravenously in the optional open-label extension.

Arm type	Placebo
Investigational medicinal product name	[18F]GTP1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

[18F]GTP1 was administered as a solution for IV use, as part of PET imaging.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received placebo Q2W for the first three doses of the double-blind treatment period and Q4W thereafter during the double-blind treatment period.

Number of subjects in period 2[5]	Semorinemab	Placebo
Started	102	97
Completed	48	52
Not completed	54	45
Physician decision	6	2
Consent withdrawn by subject	31	30
Adverse Event	9	7
Death	-	2
Various reasons	4	4
Lost to follow-up	4	-

Notes:

[5] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: The number of participants starting this period differs from those that completed the previous period as this was an optional open-label extension for participants to join.

Baseline characteristics

Reporting groups	
Reporting group title	Semorinemab
Reporting group description:	
Semorinemab was administered intravenously in the double-blind treatment period and was administered intravenously in the optional open-label extension period.	
Reporting group title	Placebo
Reporting group description:	
Placebo was administered intravenously in the double-blind treatment period and semorinemab was administered intravenously in the optional open-label extension.	

Reporting group values	Semorinemab	Placebo	Total
Number of subjects	136	136	272
Age Categorical Units: Participants			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	30	19	49
From 65-84 years	100	109	209
85 years and over	6	8	14
Age Continuous Units: years			
arithmetic mean	71.6	73.0	
standard deviation	± 8.2	± 8.0	-
Gender Categorical Units: Participants			
Female	92	84	176
Male	44	52	96
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	4	3	7
Not Hispanic or Latino	117	115	232
Unknown or Not Reported	15	18	33
Race (NIH/OMB) Units: Subjects			
Asian	1	0	1
Black or African American	4	5	9
White	122	119	241
Unknown or Not Reported	9	12	21

Subject analysis sets

Subject analysis set title	Semorinemab (Modified ITT)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The modified intent-to-treat population included all randomized participants who received at least one dose of study drug and had at least one baseline and one postbaseline ADAS-Cog11 score. For ADCS-ADL, CDR-SB and MMSE, participants also had the respective score at the given time point.

Subject analysis set title	Placebo (Modified ITT)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The modified intent-to-treat population included all randomized participants who received at least one dose of study drug and had at least one baseline and one postbaseline ADAS-Cog11 score. For ADCS-ADL, CDR-SB and MMSE, participants also had the respective score at the given time point.

Subject analysis set title	Semorinemab (Open-Label Extension)
Subject analysis set type	Per protocol

Subject analysis set description:

An optional OLE period was available to those participants who completed the double-blind period, and who the investigator thought would potentially benefit from open-label treatment.

Reporting group values	Semorinemab (Modified ITT)	Placebo (Modified ITT)	Semorinemab (Open-Label Extension)
Number of subjects	123	115	199
Age Categorical Units: Participants			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	29	17	
From 65-84 years	89	92	
85 years and over	5	6	
Age Continuous Units: years			
arithmetic mean	71.2	72.8	
standard deviation	± 8.2	± 8.2	±
Gender Categorical Units: Participants			
Female	84	70	
Male	39	45	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	4	2	
Not Hispanic or Latino	104	97	
Unknown or Not Reported	15	16	
Race (NIH/OMB) Units: Subjects			
Asian	1	0	
Black or African American	4	4	
White	109	101	

Unknown or Not Reported	9	10	

End points

End points reporting groups

Reporting group title	Semorinemab
Reporting group description:	
Semorinemab was administered intravenously in the double-blind treatment period and was administered intravenously in the optional open-label extension period.	
Reporting group title	Placebo
Reporting group description:	
Placebo was administered intravenously in the double-blind treatment period and semorinemab was administered intravenously in the optional open-label extension.	
Reporting group title	Semorinemab
Reporting group description:	
Semorinemab was administered intravenously in the double-blind treatment period and was administered intravenously in the optional open-label extension period.	
Reporting group title	Placebo
Reporting group description:	
Placebo was administered intravenously in the double-blind treatment period and semorinemab will be administered intravenously in the optional open-label extension.	
Subject analysis set title	Semorinemab (Modified ITT)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The modified intent-to-treat population included all randomized participants who received at least one dose of study drug and had at least one baseline and one postbaseline ADAS-Cog11 score. For ADCS-ADL, CDR-SB and MMSE, participants also had the respective score at the given time point.	
Subject analysis set title	Placebo (Modified ITT)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The modified intent-to-treat population included all randomized participants who received at least one dose of study drug and had at least one baseline and one postbaseline ADAS-Cog11 score. For ADCS-ADL, CDR-SB and MMSE, participants also had the respective score at the given time point.	
Subject analysis set title	Semorinemab (Open-Label Extension)
Subject analysis set type	Per protocol
Subject analysis set description:	
An optional OLE period was available to those participants who completed the double-blind period, and who the investigator thought would potentially benefit from open-label treatment.	

Primary: Change From Baseline to Last Visit of Double-Blind Treatment Period in Cognitive Function as Measured by the Alzheimer’s Disease Assessment Scale, Cognitive Subscale, 11-Item Version (ADAS-Cog11)

End point title	Change From Baseline to Last Visit of Double-Blind Treatment Period in Cognitive Function as Measured by the Alzheimer’s Disease Assessment Scale, Cognitive Subscale, 11-Item Version (ADAS-Cog11)
End point description:	
The Alzheimer’s Disease Assessment Scale, Cognitive Subscale, 11-Item Version (ADAS-Cog11) is an 11 item cognitive subscale used to quantify the areas of cognitive function most often affected in Alzheimer's disease. The total score ranges from 0-70 with lower scores indicating better cognitive function.	
End point type	Primary
End point timeframe:	
Baseline to Week 49 for Cohorts 1 and 2, and Baseline to Week 61 for Cohort 2	

End point values	Semorinemab (Modified ITT)	Placebo (Modified ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	123	115		
Units: Units on a scale				
least squares mean (standard error)				
Baseline	23.93 (± 0.533)	24.09 (± 0.589)		
Change from Baseline at Week 49 (Cohort 1 and 2)	3.96 (± 0.658)	6.85 (± 0.643)		
Change from Baseline at Week 61 (only Cohort 2)	5.71 (± 0.907)	8.47 (± 0.965)		

Statistical analyses

Statistical analysis title	Week 49
Comparison groups	Semorinemab (Modified ITT) v Placebo (Modified ITT)
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0008
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-2.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.56
upper limit	-1.21
Variability estimate	Standard error of the mean
Dispersion value	0.849

Statistical analysis title	Week 61
Comparison groups	Semorinemab (Modified ITT) v Placebo (Modified ITT)
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0351
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-2.75

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.31
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	1.287

Primary: Change From Baseline to Last Visit of Double-Blind Treatment Period in Functional Capacities as Measured by the Alzheimer's Disease Cooperative Study-Daily Living Inventory (ADCS-ADL)

End point title	Change From Baseline to Last Visit of Double-Blind Treatment Period in Functional Capacities as Measured by the Alzheimer's Disease Cooperative Study-Daily Living Inventory (ADCS-ADL)

End point description:

A scale used to quantify performance of activities of daily living. Scores on the ADCS-ADL range from 0-78, with higher scores indicating better ADL function.

End point type	Primary

End point timeframe:

Baseline to Week 49 for Cohorts 1 and 2, and Baseline to Week 61 for Cohort 2

End point values	Semorinemab (Modified ITT)	Placebo (Modified ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	123	115		
Units: Units on a scale				
least squares mean (standard error)				
Baseline	62.03 (± 0.764)	59.74 (± 0.842)		
Change from Baseline at Week 49 (Cohort 1 and 2)	-7.63 (± 1.002)	-6.80 (± 0.974)		
Change from Baseline at Week 61 (only Cohort 2)	-9.29 (± 1.343)	-7.57 (± 1.462)		

Statistical analyses

Statistical analysis title	Week 61
Comparison groups	Semorinemab (Modified ITT) v Placebo (Modified ITT)
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3704
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-1.72

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.5
upper limit	2.07
Variability estimate	Standard error of the mean
Dispersion value	1.911

Statistical analysis title	Week 49
Comparison groups	Semorinemab (Modified ITT) v Placebo (Modified ITT)
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5207
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.39
upper limit	1.72
Variability estimate	Standard error of the mean
Dispersion value	1.295

Secondary: Change From Baseline to Last Visit of Double-Blind Treatment Period on the Clinical Dementia Rating-Sum of Boxes (CDR-SB)

End point title	Change From Baseline to Last Visit of Double-Blind Treatment Period on the Clinical Dementia Rating-Sum of Boxes (CDR-SB)

End point description:

A scale used to quantify the severity of symptoms of dementia. The CDR-SB is obtained through interviews of patients and informants, and disease severity is rated in 6 domains of functioning: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Each domain is rated on a 5-point scale of functioning as follows: 0, no impairment; 0.5, questionable impairment; 1, mild impairment; 2, moderate impairment; and 3, severe impairment (personal care is scored on a 4-point scale without a 0.5 rating available). The CDR-SB score is obtained by summing each of the domain box scores, with scores ranging from 0 to 18, with the higher values representing more severe impairment.

End point type	Secondary

End point timeframe:

Baseline to Week 49 for Cohorts 1 and 2, and Baseline to Week 61 for Cohort 2

End point values	Semorinemab (Modified ITT)	Placebo (Modified ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	123	115		
Units: Units on a scale				
least squares mean (standard error)				
Baseline	6.23 (± 0.156)	6.51 (± 0.182)		
Change from Baseline at Week 49 (Cohort 1 and 2)	1.80 (± 0.217)	1.54 (± 0.214)		
Change from Baseline at Week 61 (only Cohort 2)	2.45 (± 0.367)	2.28 (± 0.393)		

Statistical analyses

Statistical analysis title	Week 61
Comparison groups	Semorinemab (Modified ITT) v Placebo (Modified ITT)
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7431
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.87
upper limit	1.22
Variability estimate	Standard error of the mean
Dispersion value	0.525

Statistical analysis title	Week 49
Comparison groups	Semorinemab (Modified ITT) v Placebo (Modified ITT)
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3501
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	0.82
Variability estimate	Standard error of the mean
Dispersion value	0.282

Secondary: Change From Baseline to Last Visit of Double-Blind Treatment Period on the Mini-Mental State Examination (MMSE)

End point title	Change From Baseline to Last Visit of Double-Blind Treatment Period on the Mini-Mental State Examination (MMSE)

End point description:

The Mini Mental State Examination (MMSE) is a brief clinical cognitive examination commonly used to screen for dementia and other cognitive deficits that has a total score of 0-30. Higher scores indicate better cognitive function.

End point type	Secondary

End point timeframe:

Baseline to Week 49 for Cohorts 1 and 2, and Baseline to Week 61 for Cohort 2

End point values	Semorinemab (Modified ITT)	Placebo (Modified ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	123	115		
Units: Units on a scale				
least squares mean (standard error)				
Baseline	18.38 (± 0.182)	18.15 (± 0.197)		
Change from Baseline at Week 49 (Cohort 1 and 2)	-2.86 (± 0.330)	-3.12 (± 0.325)		
Change from Baseline at Week 61 (only Cohort 2)	-3.14 (± 0.429)	-4.22 (± 0.466)		

Statistical analyses

Statistical analysis title	Week 49
Comparison groups	Semorinemab (Modified ITT) v Placebo (Modified ITT)
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5366
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.58
upper limit	1.11
Variability estimate	Standard error of the mean
Dispersion value	0.429

Statistical analysis title	Week 61
Comparison groups	Semorinemab (Modified ITT) v Placebo (Modified ITT)
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0851
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	2.3
Variability estimate	Standard error of the mean
Dispersion value	0.618

Secondary: Percentage of Participants with Adverse Events

End point title	Percentage of Participants with Adverse Events

End point description:

An Adverse Event is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as adverse events.

End point type	Secondary

End point timeframe:

Baseline up to end of study (approximately 4 years and 7 months)

End point values	Semorinemab	Placebo	Semorinemab (Open-Label Extension)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	135	132	199	
Units: Percentage of Participants				
number (not applicable)	83.0	81.1	85.4	

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentration of RO7105705 at Specified Timepoints

End point title	Serum Concentration of RO7105705 at Specified Timepoints

End point description:

The pharmacokinetic(PK)-evaluable population included all safety-evaluable participants with at least 1 post-dose serum PK sample. 9999999=not reportable as study drug hadn't been administered yet.

End point type	Secondary

End point timeframe:

Weeks 1,3,5,9,13,25,37,49, and at treatment discontinuation (up to Week 48) for Cohort 1. Weeks 1,3,5,9,13,25,37,49,61, and at treatment discontinuation (up to Week 60) for Cohort 2.

End point values	Semorinemab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	0[1]		
Units: Microgram per milliliter (µg/ml)				
geometric mean (geometric coefficient of variation)				
Week 1 predose (n=130,0)	9999999 (± 9999999)	()		
Week 1 postdose (n=129,0)	1610 (± 27.9)	()		
Week 3 predose (n=127,0)	546 (± 32.1)	()		
Week 3 postdose (n=128,0)	1980 (± 32.6)	()		
Week 5 predose (n=127,0)	951 (± 30.4)	()		
Week 5 postdose (n=125,0)	2260 (± 47.0)	()		
Week 9 predose (n=116,0)	935 (± 32.2)	()		
Week 9 postdose (n=117,0)	2520 (± 27.2)	()		
Week 13 predose (n=118,0)	943 (± 32.9)	()		
Week 13 postdose (n=114,0)	2480 (± 31.2)	()		
Week 25 predose (n=110,0)	996 (± 37.1)	()		
Week 25 postdose (n=108,0)	2420 (± 37.9)	()		
Week 37 predose (n=107,0)	981 (± 45.4)	()		
Week 37 postdose (n=107,0)	2430 (± 31.1)	()		
Week 49 predose (n=101,0)	1020 (± 35.2)	()		
Week 49 postdose (n=36,0)	2650 (± 34.2)	()		
Week 61 (n=40,0)	1100 (± 26.8)	()		

Notes:

[1] - Only participants that received Semorinemab were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of anti-drug antibodies (ADAs) during the study relative to the prevalence of ADAs at baseline

End point title	Incidence of anti-drug antibodies (ADAs) during the study relative to the prevalence of ADAs at baseline

End point description:

Participants with at least one predose and one postdose ADA assessment were included in this analysis. 9999999=Participants in the placebo arm weren't analyzed for ADA's post-baseline

End point type	Secondary

End point timeframe:

Weeks 1,13,25,37,49, and at treatment discontinuation (up to Week 48) for Cohort 1. Weeks 1,13,25,37,49,61, and at treatment discontinuation (up to Week 60) for Cohort 2.

End point values	Semorinemab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	132		
Units: Participants				
number (not applicable)				
Baseline (BL) - positive sample (n=133,129)	0	1		
BL - negative sample (n=133,129)	133	128		
Post-BL - positive TE-ADA (n=128,0)	0	9999999		
Post-BL - negative TE-ADA (n=128,0)	128	9999999		

Statistical analyses

No statistical analyses for this end point

Secondary: Relationship between ADA Status and Percentage of Participants with Adverse Events

End point title	Relationship between ADA Status and Percentage of Participants with Adverse Events

End point description:

Descriptive statistics will be used for assessment. Participants with at least one predose and one postdose ADA assessment were included in this analysis. 9999999=Since there were no participants with ADAs, this relationship is not possible to establish.

End point type	Secondary

End point timeframe:

Up to 57 weeks for Cohort 1, and up to 69 weeks for Cohort 2.

End point values	Semorinemab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	132		
Units: Percentage of Participants				
number (not applicable)	9999999	9999999		

Statistical analyses

No statistical analyses for this end point

Secondary: Relationship Between ADA Status and Change From Baseline to Last

Visit of Double-Blind Treatment Period in Cognitive Function as Measured by the Alzheimer's Disease Assessment Scale, Cognitive Subscale, 11-Item Version (ADAS-Cog11)

End point title	Relationship Between ADA Status and Change From Baseline to Last Visit of Double-Blind Treatment Period in Cognitive Function as Measured by the Alzheimer's Disease Assessment Scale, Cognitive Subscale, 11-Item Version (ADAS-Cog11)

End point description:

Descriptive statistics will be used for assessment.

A 70-point scale used to quantify the areas of cognitive function most often affected in Alzheimer's disease. Lower scores indicate better cognitive function.

Participants with at least one predose and one postdose ADA assessment were included in this analysis.

9999999=Since there were no participants with ADAs, this relationship is not possible to establish.

End point type	Secondary

End point timeframe:

Baseline to Week 49 for Cohort 1, and Baseline to Week 61 for Cohort 2

End point values	Semorinemab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	132		
Units: Percentage of Participants				
number (not applicable)	9999999	9999999		

Statistical analyses

No statistical analyses for this end point

Secondary: Relationship Between ADA Status and Change From Baseline to Last Visit of Double-Blind Treatment Period in Functional Capacities as Measured by the Alzheimer's Disease Cooperative Study-Daily Living Inventory (ADCS-ADL)

End point title	Relationship Between ADA Status and Change From Baseline to Last Visit of Double-Blind Treatment Period in Functional Capacities as Measured by the Alzheimer's Disease Cooperative Study-Daily Living Inventory (ADCS-ADL)

End point description:

Descriptive statistics will be used for assessment.

A scale used to quantify performance of activities of daily living. Scores on the ADCS-ADL range from 0-78, with higher scores indicating better ADL function.

Participants with at least one predose and one postdose ADA assessment were included in this analysis.

9999999=Since there were no participants with ADAs, this relationship is not possible to establish.

End point type	Secondary

End point timeframe:

Baseline to Week 49 for Cohort 1, and Baseline to Week 61 for Cohort 2

End point values	Semorinemab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	132		
Units: Percentage of Participants				
number (not applicable)	9999999	9999999		

Statistical analyses

No statistical analyses for this end point

Secondary: Relationship Between ADA Status and Change From Baseline to Last Visit of Double-Blind Treatment Period on the Clinical Dementia Rating-Sum of Boxes (CDR-SB)

End point title	Relationship Between ADA Status and Change From Baseline to Last Visit of Double-Blind Treatment Period on the Clinical Dementia Rating-Sum of Boxes (CDR-SB)

End point description:

Descriptive statistics will be used for assessment.

A scale used to quantify the severity of symptoms of dementia. The CDR-SB is obtained through interviews of patients and informants, and disease severity is rated in 6 domains of functioning: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Each domain is rated on a 5-point scale of functioning as follows: 0, no impairment; 0.5, questionable impairment; 1, mild impairment; 2, moderate impairment; and 3, severe impairment (personal care is scored on a 4-point scale without a 0.5 rating available). The CDR-SOB score is obtained by summing each of the domain box scores, with scores ranging from 0 to 18, with the higher values representing more severe impairment.

Participants with at least one predose and one postdose ADA assessment were included in this analysis.

9999999=Since there were no participants with ADAs, this relationship is not possible to establish.

End point type	Secondary

End point timeframe:

Baseline to Week 49 for Cohort 1, and Baseline to Week 61 for Cohort 2

End point values	Semorinemab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	132		
Units: Percentage of Participants				
number (not applicable)	9999999	9999999		

Statistical analyses

No statistical analyses for this end point

Secondary: Relationship Between ADA Status and Change From Baseline to Last Visit of Double-Blind Treatment Period on the Mini-Mental State Examination (MMSE)

End point title	Relationship Between ADA Status and Change From Baseline to Last Visit of Double-Blind Treatment Period on the Mini-Mental State Examination (MMSE)

End point description:

Descriptive statistics will be used for assessment.

The Mini Mental State Examination (MMSE) is a brief clinical cognitive examination commonly used to screen for dementia and other cognitive deficits that has a total score of 0-30. Higher scores indicate better cognitive function.

Participants with at least one predose and one postdose ADA assessment were included in this analysis.

9999999=Since there were no participants with ADAs, this relationship is not possible to establish.

End point type	Secondary

End point timeframe:

Baseline to Week 49 for Cohort 1, and Baseline to Week 61 for Cohort 2

End point values	Semorinemab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	132		
Units: Percentage of Participants				
number (not applicable)	9999999	9999999		

Statistical analyses

No statistical analyses for this end point

Secondary: Relationship Between ADA Status and Serum Concentration of RO7105705 at Specified Timepoints

End point title	Relationship Between ADA Status and Serum Concentration of RO7105705 at Specified Timepoints

End point description:

Descriptive statistics will be used for assessment.

Participants with at least one predose and one postdose ADA assessment were included in this analysis.

9999999=Since there were no participants with ADAs, this relationship is not possible to establish.

End point type	Secondary

End point timeframe:

Weeks 1,13,25,37,49, and at treatment discontinuation (up to Week 48) for Cohort 1. Weeks 1,13,25,37,49,61, and at treatment discontinuation (up to Week 60) for Cohort 2.

End point values	Semorinemab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	132		
Units: Percentage of Participants				
number (not applicable)	9999999	99999999		

Statistical analyses

No statistical analyses for this end point

Secondary: Relationship Between ADA Status and Incidence of Anti-Drug Antibodies (ADAs) During the Study Relative to the Prevalence of ADAs at Baseline

End point title	Relationship Between ADA Status and Incidence of Anti-Drug Antibodies (ADAs) During the Study Relative to the Prevalence of ADAs at Baseline

End point description:

Descriptive statistics will be used for assessment.

Participants with at least one predose and one postdose ADA assessment were included in this analysis.

9999999=Since there were no participants with ADAs, this relationship is not possible to establish.

End point type	Secondary

End point timeframe:

Weeks 1,13,25,37,49, and at treatment discontinuation (up to Week 48) for Cohort 1. Weeks 1,13,25,37,49,61, and at treatment discontinuation (up to Week 60) for Cohort 2.

End point values	Semorinemab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	132		
Units: Percentage of Participants				
number (not applicable)				
Positive Sample at Baseline (n=135,132)	0	1		
Positive Sample post BL (n=135,132)	9999999	9999999		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to end of study (approximately 4 years and 7 months)

Adverse event reporting additional description:

The safety population included all randomized participants who received at least one dose of either semorinemab or placebo.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo was administered intravenously in the double-blind treatment period and semorinemab was administered intravenously in the optional open-label extension.

Reporting group title	Semorinemab (Double Blind)

Reporting group description:

Semorinemab was administered intravenously in the double-blind treatment period

Reporting group title	Semorinemab (OLE)

Reporting group description:

Semorinemab was administered intravenously in the optional open-label extension period.

Serious adverse events	Placebo	Semorinemab (Double Blind)	Semorinemab (OLE)
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 132 (16.67%)	23 / 135 (17.04%)	37 / 199 (18.59%)
number of deaths (all causes)	3	1	2
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Transitional cell carcinoma recurrent			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	1 / 199 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma metastatic			

subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal neoplasm			
subjects affected / exposed	1 / 132 (0.76%)	0 / 135 (0.00%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cancer			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	0 / 132 (0.00%)	0 / 135 (0.00%)	1 / 199 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung cancer metastatic			
subjects affected / exposed	0 / 132 (0.00%)	0 / 135 (0.00%)	1 / 199 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	1 / 132 (0.76%)	0 / 135 (0.00%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery thrombosis			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			

subjects affected / exposed	0 / 132 (0.00%)	0 / 135 (0.00%)	1 / 199 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery aneurysm			
subjects affected / exposed	0 / 132 (0.00%)	0 / 135 (0.00%)	1 / 199 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 132 (0.00%)	0 / 135 (0.00%)	1 / 199 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 132 (0.76%)	1 / 135 (0.74%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	1 / 132 (0.76%)	0 / 135 (0.00%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypothermia			
subjects affected / exposed	0 / 132 (0.00%)	0 / 135 (0.00%)	1 / 199 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	0 / 132 (0.00%)	0 / 135 (0.00%)	1 / 199 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Scrotal oedema			
subjects affected / exposed	0 / 132 (0.00%)	0 / 135 (0.00%)	1 / 199 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Prostatitis			
subjects affected / exposed	0 / 132 (0.00%)	0 / 135 (0.00%)	1 / 199 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 132 (0.76%)	0 / 135 (0.00%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Agitation			
subjects affected / exposed	3 / 132 (2.27%)	0 / 135 (0.00%)	3 / 199 (1.51%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aggression			
subjects affected / exposed	0 / 132 (0.00%)	0 / 135 (0.00%)	1 / 199 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
SARS-CoV-2 test positive			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	2 / 132 (1.52%)	0 / 135 (0.00%)	4 / 199 (2.01%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			

subjects affected / exposed	1 / 132 (0.76%)	0 / 135 (0.00%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patella fracture			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Craniocerebral injury			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain contusion			
subjects affected / exposed	0 / 132 (0.00%)	0 / 135 (0.00%)	1 / 199 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 132 (0.00%)	0 / 135 (0.00%)	1 / 199 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical vertebral fracture			
subjects affected / exposed	0 / 132 (0.00%)	0 / 135 (0.00%)	1 / 199 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 132 (0.00%)	0 / 135 (0.00%)	5 / 199 (2.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			

subjects affected / exposed	0 / 132 (0.00%)	0 / 135 (0.00%)	1 / 199 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 132 (0.76%)	0 / 135 (0.00%)	1 / 199 (0.50%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stress cardiomyopathy			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	0 / 132 (0.00%)	0 / 135 (0.00%)	1 / 199 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus node dysfunction			
subjects affected / exposed	0 / 132 (0.00%)	0 / 135 (0.00%)	1 / 199 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Upper motor neurone lesion			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			

subjects affected / exposed	1 / 132 (0.76%)	1 / 135 (0.74%)	3 / 199 (1.51%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	1 / 132 (0.76%)	0 / 135 (0.00%)	1 / 199 (0.50%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 132 (0.76%)	1 / 135 (0.74%)	2 / 199 (1.01%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysarthria			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	1 / 199 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	0 / 132 (0.00%)	0 / 135 (0.00%)	1 / 199 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebellar infarction			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 132 (0.00%)	0 / 135 (0.00%)	1 / 199 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Leukocytosis			

subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Inguinal hernia strangulated			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hernial eventration			
subjects affected / exposed	1 / 132 (0.76%)	0 / 135 (0.00%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	2 / 132 (1.52%)	0 / 135 (0.00%)	1 / 199 (0.50%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 132 (0.00%)	0 / 135 (0.00%)	1 / 199 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 132 (0.00%)	0 / 135 (0.00%)	1 / 199 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 132 (0.76%)	0 / 135 (0.00%)	1 / 199 (0.50%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			

subjects affected / exposed	0 / 132 (0.00%)	0 / 135 (0.00%)	1 / 199 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary fistula			
subjects affected / exposed	0 / 132 (0.00%)	0 / 135 (0.00%)	1 / 199 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	1 / 132 (0.76%)	0 / 135 (0.00%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	1 / 132 (0.76%)	0 / 135 (0.00%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anuria			
subjects affected / exposed	0 / 132 (0.00%)	0 / 135 (0.00%)	1 / 199 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19			
subjects affected / exposed	2 / 132 (1.52%)	1 / 135 (0.74%)	2 / 199 (1.01%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Pneumonia			
subjects affected / exposed	2 / 132 (1.52%)	0 / 135 (0.00%)	2 / 199 (1.01%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			

subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	2 / 199 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 132 (0.76%)	0 / 135 (0.00%)	1 / 199 (0.50%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	0 / 132 (0.00%)	0 / 135 (0.00%)	1 / 199 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Escherichia bacteraemia			
subjects affected / exposed	0 / 132 (0.00%)	0 / 135 (0.00%)	1 / 199 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epididymitis			
subjects affected / exposed	0 / 132 (0.00%)	0 / 135 (0.00%)	1 / 199 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 132 (0.00%)	0 / 135 (0.00%)	1 / 199 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	1 / 132 (0.76%)	1 / 135 (0.74%)	1 / 199 (0.50%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic metabolic decompensation			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	Semorinemab (Double Blind)	Semorinemab (OLE)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	74 / 132 (56.06%)	78 / 135 (57.78%)	122 / 199 (61.31%)
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	5 / 132 (3.79%)	14 / 135 (10.37%)	14 / 199 (7.04%)
occurrences (all)	9	30	16
Fall			
subjects affected / exposed	19 / 132 (14.39%)	14 / 135 (10.37%)	37 / 199 (18.59%)
occurrences (all)	28	20	64
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 132 (3.79%)	8 / 135 (5.93%)	5 / 199 (2.51%)
occurrences (all)	5	10	5
Nervous system disorders			
Dizziness			
subjects affected / exposed	9 / 132 (6.82%)	8 / 135 (5.93%)	7 / 199 (3.52%)
occurrences (all)	11	8	8
Headache			
subjects affected / exposed	9 / 132 (6.82%)	11 / 135 (8.15%)	10 / 199 (5.03%)
occurrences (all)	10	14	13
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	5 / 132 (3.79%)	7 / 135 (5.19%)	10 / 199 (5.03%)
occurrences (all)	6	7	10
Psychiatric disorders			

Agitation			
subjects affected / exposed	8 / 132 (6.06%)	8 / 135 (5.93%)	18 / 199 (9.05%)
occurrences (all)	5	8	19
Insomnia			
subjects affected / exposed	3 / 132 (2.27%)	7 / 135 (5.19%)	13 / 199 (6.53%)
occurrences (all)	3	7	13
Depression			
subjects affected / exposed	7 / 132 (5.30%)	10 / 135 (7.41%)	6 / 199 (3.02%)
occurrences (all)	7	11	6
Anxiety			
subjects affected / exposed	12 / 132 (9.09%)	9 / 135 (6.67%)	11 / 199 (5.53%)
occurrences (all)	12	11	11
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 132 (3.03%)	8 / 135 (5.93%)	11 / 199 (5.53%)
occurrences (all)	4	8	12
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	16 / 132 (12.12%)	11 / 135 (8.15%)	27 / 199 (13.57%)
occurrences (all)	19	14	36
Nasopharyngitis			
subjects affected / exposed	3 / 132 (2.27%)	9 / 135 (6.67%)	5 / 199 (2.51%)
occurrences (all)	3	10	5
COVID-19			
subjects affected / exposed	0 / 132 (0.00%)	0 / 135 (0.00%)	36 / 199 (18.09%)
occurrences (all)	0	0	36

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 April 2020	This protocol was amended to address feedback from the European Health Authorities.
16 April 2020	The following updates were made: [1] The study design was revised to assign randomized participants to one of up to three cohorts; [2] Endpoints, statistical consideration and analysis plans were updated; [3] For participants in Cohorts 2 and 3, study drug administration was revised for those who missed 2 or more infusions; [4] During the double-blind treatment period, additional clinical outcome assessments (COAs) could be administered remotely due to the COVID-19 pandemic; [5] End of study and length of study were updated; [6] Due to COVID-19 travel restrictions, some study activities could be performed in the participants home or alternate location; [6] Guidance was provided for monitoring participant's signs or symptoms suggestive of new clinically significant neurologic abnormalities; [7] Schedules of activities for the double-blind treatment period and OLE period were added for Cohorts 2 and 3; [8] Mandatory cerebrospinal fluid collection by lumbar puncture was removed.
29 June 2020	The following updates were made; [1] Participants who completed blinded study drug treatment through Week 45 without any missed doses of study drug were eligible to revert to the Cohort 1 Schedule of Activities continue to OLE. Participants who were active in the double-blind treatment period when Protocol Version 4 was implemented who either completed the Cohort 2 Week 49 visit, continued in Cohort 2; [2] Up to 100 participants could be recruited into the study; [3] The option to administer study drug infusion in the participant's home or in an approved alternate location during the COVID-19 pandemic was clarified; [4] Approval by the Medical Monitor for daily treatment with medications from selected drug classes could be permitted during the OLE.
14 December 2021	The following updates were made; [1] Cohort 3 was removed; [2] The option to enroll up to 100 additional participants was removed as it was deemed unnecessary; [3] [18F]GTP1 PET was removed during the OLE at Week 145 for Cohort 1, Week 157 for Cohort 2, and at treatment discontinuation visit (for both cohorts); [4] OLE COAs, with the exception of the Columbia-Suicide Severity Rating Scale, were removed at Week 121 for Cohort 1 and Week 133 for Cohort 2; [5] The collection of serum PK and ADA samples was reduced to only once during the OLE, at Week 97 for Cohort 1 and Week 109 for Cohort 2; [6] The Medical Monitor changed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported