



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 | |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 |
| This version publication date | 31 July 2022 |
| First version publication date | 31 July 2022 |

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 | Interim |
| Date of interim/final analysis | 20 July 2021 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 20 July 2021 |
| Global end of trial reached? | 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. These 267 participants represented the Safety Analysis population and data for this population is presented here.

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 will be administered intravenously in the double-blind treatment period and will be 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 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.

| | |
|------------------|---------|
| 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 | 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^[1] | Semorinemab | Placebo |
|---|-------------|---------|
| Started | 135 | 132 |
| Completed | 104 | 96 |
| Not completed | 31 | 36 |
| Consent withdrawn by subject | 19 | 21 |
| Physician decision | - | 3 |
| Adverse Event | 6 | 6 |
| Death | 1 | 2 |
| Various reasons | 5 | 3 |
| Lost to follow-up | - | 1 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 5 participants didn't receive blinded treatment.

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 will be administered intravenously in the double-blind treatment period and will be 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 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.

| | |
|------------------|---------|
| 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^[2] | Semorinemab | Placebo |
|---|-------------|---------|
| Started | 104 | 95 |
| Completed | 0 | 0 |
| Not completed | 104 | 95 |
| Consent withdrawn by subject | 19 | 16 |
| Adverse Event | 3 | 4 |
| Death | - | 2 |
| Various reasons | 1 | 1 |
| Lost to follow-up | 4 | - |
| Continuing on study | 77 | 72 |

Notes:

[2] - 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 will be administered intravenously in the double-blind treatment period and will be 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. | |

| Reporting group values | Semorinemab | Placebo | Total |
|--|-------------|---------|-------|
| Number of subjects | 135 | 132 | 267 |
| 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 | 18 | 48 |
| From 65-84 years | 99 | 106 | 205 |
| 85 years and over | 6 | 8 | 14 |
| Age Continuous Units: years | | | |
| arithmetic mean | 71.6 | 73.1 | - |
| standard deviation | ± 8.2 | ± 8.0 | - |
| Gender Categorical Units: Participants | | | |
| Female | 93 | 80 | 173 |
| Male | 42 | 52 | 94 |
| Ethnicity (NIH/OMB) Units: Subjects | | | |
| Hispanic or Latino | 4 | 3 | 7 |
| Not Hispanic or Latino | 116 | 111 | 227 |
| Unknown or Not Reported | 15 | 18 | 33 |
| Race (NIH/OMB) Units: Subjects | | | |
| Asian | 1 | 0 | 1 |
| Black or African American | 4 | 5 | 9 |
| White | 121 | 115 | 236 |
| 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.

| Reporting group values | Semorinemab (Modified ITT) | Placebo (Modified ITT) | |
|--|----------------------------|------------------------|--|
| Number of subjects | 123 | 115 | |
| 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 will be administered intravenously in the double-blind treatment period and will be 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. | |
| Reporting group title | Semorinemab |
| Reporting group description: Semorinemab will be administered intravenously in the double-blind treatment period and will be 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. | |

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: 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. | |
| End point type | Primary |
| End point timeframe: Baseline to Week 49 for Cohort 1, 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 (\pm 0.533) | 24.09 (\pm 0.589) | | |
| Week 49 | 3.96 (\pm 0.658) | 6.85 (\pm 0.643) | | |
| Week 61 | 5.71 (\pm 0.907) | 8.47 (\pm 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 Cohort 1, 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 (\pm 0.764) | 59.74 (\pm 0.842) | | |
| Week 49 | -7.63 (\pm 1.002) | -6.80 (\pm 0.974) | | |
| Week 61 | -9.29 (\pm 1.343) | -7.57 (\pm 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 Cohort 1, 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) | | |
| Week 49 | 1.80 (± 0.217) | 1.54 (± 0.214) | | |
| Week 61 | 2.45 (± 0.367) | 2.28 (± 0.393) | | |

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 | = 0.3501 |
| 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 |

| | |
|---|---|
| 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 |

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 Cohort 1, 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) | | |
| Week 49 | -2.86 (± 0.330) | -3.12 (± 0.325) | | |
| Week 61 | -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: | |
| Up to CCOD of July 20, 2021 (approximately 2.5 years) | |

| 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) | 83.7 | 81.1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentration of R07105705 at Specified Timepoints

| | |
|--|--|
| End point title | Serum Concentration of R07105705 at Specified Timepoints |
| End point description: | |
| Data collection is ongoing and the results will be disclosed within 1 year from Study Completion | |
| 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 | |

| End point values | Semorinemab | Placebo | | |
|--------------------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[1] | 0 ^[2] | | |
| Units: ug/mL | | | | |
| arithmetic mean (standard deviation) | () | () | | |

Notes:

[1] - Data collection is ongoing and the results will be disclosed within 1 year from Study Completion

[2] - Data collection is ongoing and the results will be disclosed within 1 year from Study Completion

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: | Data collection is ongoing and the results will be disclosed within 1 year from Study Completion |
| 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 | 0 ^[3] | 0 ^[4] | | |
| Units: ug/mL | | | | |
| arithmetic mean (standard deviation) | () | () | | |

Notes:

[3] - Data collection is ongoing and the results will be disclosed within 1 year from Study Completion

[4] - Data collection is ongoing and the results will be disclosed within 1 year from Study Completion

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. Data collection is ongoing and the results will be disclosed within 1 year from Study Completion |
| 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 | 0 ^[5] | 0 ^[6] | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | | | | |

Notes:

[5] - Data collection is ongoing and the results will be disclosed within 1 year from Study Completion

[6] - Data collection is ongoing and the results will be disclosed within 1 year from Study Completion

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: | Data collection is ongoing and the results will be disclosed within 1 year from Study Completion |
| 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 | 0 ^[7] | 0 ^[8] | | |
| Units: Participants | | | | |
| number (not applicable) | | | | |

Notes:

[7] - Data collection is ongoing and the results will be disclosed within 1 year from Study Completion

[8] - Data collection is ongoing and the results will be disclosed within 1 year from Study Completion

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.

Data collection is ongoing and the results will be disclosed within 1 year from Study Completion

| | |
|--|-----------|
| 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 | 0 ^[9] | 0 ^[10] | | |
| Units: Units on a Scale | | | | |
| least squares mean (standard error) | () | () | | |

Notes:

[9] - Data collection is ongoing and the results will be disclosed within 1 year from Study Completion

[10] - Data collection is ongoing and the results will be disclosed within 1 year from Study Completion

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.

Data collection is ongoing and the results will be disclosed within 1 year from Study Completion

| | |
|--|-----------|
| 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 | 0 ^[11] | 0 ^[12] | | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | () | () | | |

Notes:

[11] - Data collection is ongoing and the results will be disclosed within 1 year from Study Completion

[12] - Data collection is ongoing and the results will be disclosed within 1 year from Study Completion

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.

Data collection is ongoing and the results will be disclosed within 1 year from Study Completion

| | |
|----------------|-----------|
| 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 | 0 ^[13] | 0 ^[14] | | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | () | () | | |

Notes:

[13] - Data collection is ongoing and the results will be disclosed within 1 year from Study Completion

[14] - Data collection is ongoing and the results will be disclosed within 1 year from Study Completion

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.

Data collection is ongoing and the results will be disclosed within 1 year from Study Completion

| | |
|----------------|-----------|
| 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 | 0 ^[15] | 0 ^[16] | | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | () | () | | |

Notes:

[15] - Data collection is ongoing and the results will be disclosed within 1 year from Study Completion

[16] - Data collection is ongoing and the results will be disclosed within 1 year from Study Completion

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.

Data collection is ongoing and the results will be disclosed within 1 year from Study Completion

| | |
|----------------|-----------|
| 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 | 0 ^[17] | 0 ^[18] | | |
| Units: ug/ml | | | | |
| arithmetic mean (standard deviation) | () | () | | |

Notes:

[17] - Data collection is ongoing and the results will be disclosed within 1 year from Study Completion

[18] - Data collection is ongoing and the results will be disclosed within 1 year from Study Completion

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.

Data collection is ongoing and the results will be disclosed within 1 year from Study Completion

| | |
|----------------|-----------|
| 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 | 0 ^[19] | 0 ^[20] | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | | | | |

Notes:

[19] - Data collection is ongoing and the results will be disclosed within 1 year from Study Completion

[20] - Data collection is ongoing and the results will be disclosed within 1 year from Study Completion

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to CCOD of July 20, 2021 (approximately 2.5 years)

Adverse event reporting additional description:

The adverse events presented refer to those that occurred in the double-blind period only.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 24.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | Semorinemab |
|-----------------------|-------------|

Reporting group description:

Semorinemab will be administered intravenously in the double-blind treatment period and will be 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.

| Serious adverse events | Semorinemab | Placebo | |
|---|-------------------|-------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 22 / 135 (16.30%) | 22 / 132 (16.67%) | |
| number of deaths (all causes) | 1 | 2 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Transitional cell carcinoma recurrent | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 132 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 132 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Invasive ductal breast carcinoma | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 132 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|-----------------|-----------------|--|
| Adenocarcinoma metastatic subjects affected / exposed | 1 / 135 (0.74%) | 0 / 132 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal neoplasm subjects affected / exposed | 0 / 135 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ovarian cancer subjects affected / exposed | 1 / 135 (0.74%) | 0 / 132 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders Peripheral artery thrombosis subjects affected / exposed | 1 / 135 (0.74%) | 0 / 132 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic aneurysm subjects affected / exposed | 0 / 135 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions Non-cardiac chest pain subjects affected / exposed | 0 / 135 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death subjects affected / exposed | 1 / 135 (0.74%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Respiratory, thoracic and mediastinal disorders Pulmonary embolism | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Agitation | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 3 / 132 (2.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| SARS-CoV-2 test positive | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 132 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 2 / 132 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 132 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Patella fracture | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 132 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Head injury | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint dislocation | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 132 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Craniocerebral injury | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 132 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Bradycardia | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 132 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 132 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stress cardiomyopathy | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 132 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper motor neurone lesion | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 132 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Seizure | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 132 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysarthria | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 132 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Leukocytosis | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 132 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Inguinal hernia strangulated | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 132 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 2 / 132 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hernial eventration | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 132 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 132 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydronephrosis | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| COVID-19 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 2 / 132 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 132 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 2 / 132 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cystitis | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 132 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 132 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Diabetic metabolic decompensation | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 132 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 1 / 132 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Semorinemab | Placebo | |
|---|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 77 / 135 (57.04%) | 71 / 132 (53.79%) | |
| Injury, poisoning and procedural complications | | | |
| Infusion related reaction | | | |
| subjects affected / exposed | 14 / 135 (10.37%) | 5 / 132 (3.79%) | |
| occurrences (all) | 30 | 9 | |
| Fall | | | |
| subjects affected / exposed | 14 / 135 (10.37%) | 19 / 132 (14.39%) | |
| occurrences (all) | 19 | 28 | |
| Vascular disorders | | | |

| | | | |
|---|---|--|--|
| Hypertension subjects affected / exposed occurrences (all) | 8 / 135 (5.93%) 10 | 5 / 132 (3.79%) 5 | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) | 8 / 135 (5.93%) 8 11 / 135 (8.15%) 14 | 9 / 132 (6.82%) 11 9 / 132 (6.82%) 10 | |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) | 7 / 135 (5.19%) 7 | 5 / 132 (3.79%) 6 | |
| Psychiatric disorders Agitation subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all) Depression subjects affected / exposed occurrences (all) Anxiety subjects affected / exposed occurrences (all) | 8 / 135 (5.93%) 8 7 / 135 (5.19%) 7 10 / 135 (7.41%) 10 9 / 135 (6.67%) 11 | 5 / 132 (3.79%) 5 2 / 132 (1.52%) 2 6 / 132 (4.55%) 6 12 / 132 (9.09%) 12 | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 7 / 135 (5.19%) 7 | 4 / 132 (3.03%) 4 | |
| Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all) Nasopharyngitis | 10 / 135 (7.41%) 14 | 16 / 132 (12.12%) 19 | |

| | | | |
|-----------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 9 / 135 (6.67%) | 3 / 132 (2.27%) | |
| occurrences (all) | 10 | 3 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 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