# EU Clinical Trials Register

## Clinical trial results:
## A Randomized, Double-Blind, Placebo-Controlled Multiple Dose Study to Assess Efficacy, Safety, Tolerability, and Pharmacokinetics of ABBV-8E12 in Progressive Supranuclear Palsy

### Summary

| | |
|---|---|
| EudraCT number | 2016-001635-12 |
| Trial protocol | DE FR IT ES |
| Global end of trial date | 20 November 2019 |

### Results information

| | |
|---|---|
| Result version number | v2 (current) |
| This version publication date | 03 March 2021 |
| First version publication date | 03 December 2020 |
| Version creation reason | • New data added to full data set<br>Additional data added for one ednpoint. |

### Trial information

#### Trial identification

| | |
|---|---|
| Sponsor protocol code | M15-562 |

#### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02985879 |
| WHO universal trial number (UTN) | - |

Notes:

#### Sponsors

| | |
|---|---|
| Sponsor organisation name | AbbVie |
| Sponsor organisation address | AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6-4UB |
| Public contact | Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@abbvie.com |
| Scientific contact | Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@abbvie.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 | 20 November 2019 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 20 November 2019 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

This was a Phase 2, randomized, double-blind, placebo-controlled, multiple dose, multicenter study with a screening period of ≤ 8 wks, a 52-wk treatment (Tx) period, and 20-week follow-up after the last study drug dose (for those who prematurely discontinued from Tx, declined to participate in or did not qualify for a long term extension [LTE] study). Extended Tx was available for those who completed the 52-wk Tx and entered the long-term extension Study M15-563. There were 3 cohorts: Cohort 1, Cohort J1, and Cohort 2. Cohort 1 had augmented safety and pharmacokinetic (PK) assessments in the first 30 subjects enrolled into the study from countries other than Japan. Cohort J1 had augmented safety and PK assessments in the first 9 subjects enrolled into the study from Japan. Cohort 2 was all others enrolled in the study.This study was prematurely discontinued because the program for progressive supranuclear palsy was discontinued due to lack of efficacy of study drug.

Protection of trial subjects:

Subject must have been able to understand the nature of the study and given the opportunity to have any questions answered. The subject voluntarily signed the Independent Ethics Committee (IEC)/Independent Review Board (IRB) approved Informed Consent, prior to the conduct of any study procedures (including any changes occurring in the subject's current therapeutic regimen). In the absence of subject's ability to provide the informed consent, the informed consent was signed by a person who had the legal right to act on behalf of the subject following national laws. In Germany, where the subject's legally authorized representative (LAR) is not permitted to sign the IEC/IRB approved Informed Consent form on behalf of the subject, evaluation by an independent psychiatrist was to be sought if the investigator who was evaluating the subject for inclusion in the study doubted the subject's cognitive ability to independently provide informed consent.

| | |
|---|---|
| Background therapy: - | |
| Evidence for comparator: - | |
| Actual start date of recruitment | 12 December 2016 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Australia: 17 |
| Country: Number of subjects enrolled | Canada: 32 |
| Country: Number of subjects enrolled | France: 12 |
| Country: Number of subjects enrolled | Germany: 18 |
| Country: Number of subjects enrolled | Italy: 57 |
| Country: Number of subjects enrolled | Japan: 33 |
| Country: Number of subjects enrolled | Spain: 6 |
| Country: Number of subjects enrolled | United States: 202 |

| Worldwide total number of subjects | 377 |
|---|---|
| EEA total number of subjects | 93 |

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) | 99 |
| From 65 to 84 years | 276 |
| 85 years and over | 2 |

# Subject disposition

## Recruitment

Recruitment details: -

## Pre-assignment

Screening details:

Safety dataset: all randomized participants who received at least one dose of study drug

## Period 1

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

### Arms

| Are arms mutually exclusive? | Yes |
|---|---|
| **Arm title** | Placebo |

Arm description:

0.9% Sodium Chloride Injection/Solution for Infusion; intravenous infusions at Day 1, Day 15, and Day 29, then every 28 days for 52 weeks

| Arm type | Placebo |
|---|---|
| Investigational medicinal product name | 0.9% Sodium Chloride Injection/Solution for Infusion |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Participants with 44-49 kg body weight (BW) had an intravenous infusion rate of 3.5 mL/min or 210 mL/hr; those with 50-58 kg BW, 4.0 mL/min or 240 mL/hr; and those with a BW >59 kg, 4.7 mL/min or 282 mL/hr.

| **Arm title** | ABBV-8E12 2000 mg |
|---|---|

Arm description:

Intravenous infusions at Day 1, Day 15, and Day 29, then every 28 days for 52 weeks; 300 mg/15 mL (participants in countries other than Japan or Spain); 1000 mg/10 mL (for participants in Japan or Spain)

| Arm type | Experimental |
|---|---|
| Investigational medicinal product name | ABBV-8E12 |
| Investigational medicinal product code | |
| Other name | Tilavonemab |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Participants with 44-49 kg body weight (BW) had an intravenous infusion rate of 3.5 mL/min or 210 mL/hr; those with 50-58 kg BW, 4.0 mL/min or 240 mL/hr; and those with a BW >59 kg, 4.7 mL/min or 282 mL/hr. For participants in Cohort 2, ABBV-8E12 doses may have been decreased after the evaluation by the Data Monitoring Committee of available safety, tolerability and pharmacokinetic data.

| **Arm title** | ABBV-8E12 4000 mg |
|---|---|

Arm description:

Intravenous infusions at Day 1, Day 15, and Day 29, then every 28 days for 52 weeks; 300 mg/15 mL (participants in countries other than Japan or Spain); 1000 mg/10 mL (for participants in Japan or Spain)

| Arm type | Experimental |
|---|---|
| Investigational medicinal product name | ABBV-8E12 |
| Investigational medicinal product code | |
| Other name | Tilavonemab |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Participants with 44-49 kg body weight (BW) had an intravenous infusion rate of 3.5 mL/min or 210 mL/hr; those with 50-58 kg BW, 4.0 mL/min or 240 mL/hr; and those with a BW >59 kg, 4.7 mL/min or 282 mL/hr. For participants in Cohort 2, ABBV-8E12 doses may have been decreased after the evaluation by the Data Monitoring Committee of available safety, tolerability and pharmacokinetic data.

| **Number of subjects in period 1** | Placebo | ABBV-8E12 2000 mg | ABBV-8E12 4000 mg |
|---|---|---|---|
| Started | 126 | 126 | 125 |
| Completed | 50 | 52 | 48 |
| Not completed | 76 | 74 | 77 |
|    Adverse event, non-fatal | 7 | 8 | 7 |
|    Other, not specified | 62 | 58 | 58 |
|    Withdrew consent | 6 | 8 | 10 |
|    Lost to follow-up | 1 | - | 2 |

## Baseline characteristics

### Reporting groups

| Reporting group title | Placebo |
|---|---|

Reporting group description:

0.9% Sodium Chloride Injection/Solution for Infusion; intravenous infusions at Day 1, Day 15, and Day 29, then every 28 days for 52 weeks

| Reporting group title | ABBV-8E12 2000 mg |
|---|---|

Reporting group description:

Intravenous infusions at Day 1, Day 15, and Day 29, then every 28 days for 52 weeks; 300 mg/15 mL (participants in countries other than Japan or Spain); 1000 mg/10 mL (for participants in Japan or Spain)

| Reporting group title | ABBV-8E12 4000 mg |
|---|---|

Reporting group description:

Intravenous infusions at Day 1, Day 15, and Day 29, then every 28 days for 52 weeks; 300 mg/15 mL (participants in countries other than Japan or Spain); 1000 mg/10 mL (for participants in Japan or Spain)

| Reporting group values | Placebo | ABBV-8E12 2000 mg | ABBV-8E12 4000 mg |
|---|---|---|---|
| Number of subjects | 126 | 126 | 125 |
| Age categorical | | | |
| Units: Subjects | | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 68.1 | 68.3 | 70.0 |
| standard deviation | ± 6.22 | ± 7.25 | ± 6.85 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 53 | 49 | 56 |
| Male | 73 | 77 | 69 |

| Reporting group values | Total | | |
|---|---|---|---|
| Number of subjects | 377 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 158 | | |
| Male | 219 | | |

# End points

## End points reporting groups

| Reporting group title | Placebo |
|---|---|

Reporting group description:

0.9% Sodium Chloride Injection/Solution for Infusion; intravenous infusions at Day 1, Day 15, and Day 29, then every 28 days for 52 weeks

| Reporting group title | ABBV-8E12 2000 mg |
|---|---|

Reporting group description:

Intravenous infusions at Day 1, Day 15, and Day 29, then every 28 days for 52 weeks; 300 mg/15 mL (participants in countries other than Japan or Spain); 1000 mg/10 mL (for participants in Japan or Spain)

| Reporting group title | ABBV-8E12 4000 mg |
|---|---|

Reporting group description:

Intravenous infusions at Day 1, Day 15, and Day 29, then every 28 days for 52 weeks; 300 mg/15 mL (participants in countries other than Japan or Spain); 1000 mg/10 mL (for participants in Japan or Spain)

| Subject analysis set title | Cohort 1, ABBV-8E12 2000 mg |
|---|---|
| Subject analysis set type | Per protocol |

Subject analysis set description:

First 30 participants enrolled into the global study from countries other than Japan who received augmented safety and PK assessments and ABBV-8E12 at a dose of 2000 mg

| Subject analysis set title | Cohort 1, ABBV-8E12 4000 mg |
|---|---|
| Subject analysis set type | Per protocol |

Subject analysis set description:

First 30 participants enrolled into the global study from countries other than Japan who received augmented safety and PK assessments and ABBV-8E12 at a dose of 4000 mg

| Subject analysis set title | Cohort J1, ABBV-8E12 2000 mg |
|---|---|
| Subject analysis set type | Per protocol |

Subject analysis set description:

First 9 participants enrolled into the study from Japan who received augmented safety and PK assessments and ABBV-8E12 at a dose of 2000 mg

| Subject analysis set title | Cohort J1, ABBV-8E12 4000 mg |
|---|---|
| Subject analysis set type | Per protocol |

Subject analysis set description:

First 9 participants enrolled into the study from Japan who received augmented safety and PK assessments and ABBV-8E12 at a dose of 4000 mg

## Primary: Change From Baseline to Week 52 in Progressive Supranuclear Palsy Rating Scale (PSPRS) Total Score

| End point title | Change From Baseline to Week 52 in Progressive Supranuclear Palsy Rating Scale (PSPRS) Total Score |
|---|---|

End point description:

The PSPRS consists of 28 items grouped in six domains: daily activities (by history); behavior; bulbar; ocular motor; limb motor; and gait/midline. Items are scored on a 0 to 4 scale, except for six items that are scored on a 0 to 2 scale, with the total score ranging from 0 to 100. Higher scores indicate more severe disability or movement abnormality. Positive changes in score indicate worsening from baseline.

| End point type | Primary |
|---|---|

End point timeframe:

Baseline, Week 52

| End point values | Placebo | ABBV-8E12 2000 mg | ABBV-8E12 4000 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 59[1] | 56[2] | 59[3] | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | 10.5 (± 0.94) | 10.5 (± 0.96) | 11.4 (± 0.94) | |

Notes:

[1] - ITT set:randomized subjects who rcvd ≥1 dose of study drug with available data at baseline and Wk 52

[2] - ITT set:randomized subjects who rcvd ≥1 dose of study drug with available data at baseline and Wk 52

[3] - ITT set:randomized subjects who rcvd ≥1 dose of study drug with available data at baseline and Wk 52

## Statistical analyses

| Statistical analysis title | ABBV-8E12 2000 mg vs Placebo |
|---|---|

Statistical analysis description:

The primary efficacy analysis utilized a likelihood-based, mixed-effects model, repeated measures (MMRM) analysis of the change from baseline for each postbaseline value and compared each ABBV-8E12 dose group with the placebo group. The model, which used all observed data, included fixed, categorical effects for treatment, site, visit, baseline score-by-visit interaction and treatment-by-visit interaction, with continuous fixed covariates for the corresponding baseline score.

| Comparison groups | Placebo v ABBV-8E12 2000 mg |
|---|---|
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.998 |
| Method | Mixed-effects model, repeated measures |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | -2.63 |
|     upper limit | 2.63 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.34 |

| Statistical analysis title | ABBV-8E12 4000 mg vs Placebo |
|---|---|

Statistical analysis description:

The primary efficacy analysis utilized a likelihood-based, mixed-effects model, repeated measures (MMRM) analysis of the change from baseline for each postbaseline value and compared each ABBV-8E12 dose group with the placebo group. The model, which used all observed data, included fixed, categorical effects for treatment, site, visit, baseline score-by-visit interaction and treatment-by-visit interaction, with continuous fixed covariates for the corresponding baseline score.

| Comparison groups | Placebo v ABBV-8E12 4000 mg |
|---|---|
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.464 |
| Method | Mixed-effects model repeated measures |
| Parameter estimate | LS Mean Difference |
| Point estimate | 1 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | -1.63 |
|     upper limit | 3.58 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.32 |

## Primary: Number of Participants With Adverse Events

| End point title | Number of Participants With Adverse Events[4] |
|---|---|

End point description:

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. The investigator assessed the relationship of each event to the use of study drug as either reasonable possibility or no reasonable possibility. A serious adverse event (SAE) is an event that results in death, is life-threatening, requires or prolongs hospitalization, results in a congenital anomaly, persistent or significant disability/incapacity or is an important medical event that, based on medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above. Treatment-emergent events (TEAEs) are defined as any event that began or worsened in severity from first dose of study drug until 20 weeks after the last dose. For more details on AEs please see the Adverse Event section.

| End point type | Primary |
|---|---|

End point timeframe:

From the first dose of study drug until 20 weeks following discontinuation of study drug administration have elapsed (approximately 5 half-lives), up to 80 weeks

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis not applicable for this endpoint.

| End point values | Placebo | ABBV-8E12 2000 mg | ABBV-8E12 4000 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 126[5] | 126[6] | 125[7] | |
| Units: participants | 108 | 111 | 111 | |

Notes:

[5] - Safety Dataset: all randomized subjects who received at least one dose of study drug

[6] - Safety Dataset: all randomized subjects who received at least one dose of study drug

[7] - Safety Dataset: all randomized subjects who received at least one dose of study drug

## Statistical analyses

No statistical analyses for this end point

**Secondary: Mean Change From Baseline to Week 52 in Midbrain Atrophy As Measured by Volumetric Magnetic Resonance Imaging (MRI)**

| End point title | Mean Change From Baseline to Week 52 in Midbrain Atrophy As Measured by Volumetric Magnetic Resonance Imaging (MRI) |
|---|---|

End point description:

Magnetic resonance imaging (MRI) of several different brain regions was performed and volumetric analysis was conducted to quantify midbrain atrophy. Negative changes in values indicate a reduction in volume.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline, Week 52

| **End point values** | Placebo | ABBV-8E12 2000 mg | ABBV-8E12 4000 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 53[8] | 55[9] | 54[10] | |
| Units: mm^3 | | | | |
| least squares mean (standard error) | -122.0 (± 9.64) | -129.1 (± 9.69) | -128.3 (± 9.69) | |

Notes:

[8] - ITT set:randomized subjects who rcvd ≥1 dose of study drug with available data at baseline and Wk 52

[9] - ITT set:randomized subjects who rcvd ≥1 dose of study drug with available data at baseline and Wk 52

[10] - ITT set:randomized subjects who rcvd ≥1 dose of study drug with available data at baseline and Wk 52

**Statistical analyses**

| **Statistical analysis title** | ABBV-8E12 2000 mg vs Placebo |
|---|---|

Statistical analysis description:

The analysis utilized a likelihood-based, mixed-effects model, repeated measures (MMRM) analysis of the change from baseline for each postbaseline value and compared each ABBV-8E12 dose group with the placebo group. The model, which used all observed data, included fixed, categorical effects for treatment, site, visit, baseline score-by-visit interaction and treatment-by-visit interaction, with continuous fixed covariates for the corresponding baseline score.

| Comparison groups | Placebo v ABBV-8E12 2000 mg |
|---|---|
| Number of subjects included in analysis | 108 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.597 |
| Method | Mixed-effects model repeated measures |
| Parameter estimate | LS Mean Difference |
| Point estimate | -7.2 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | -33.86 |
|     upper limit | 19.53 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 13.54 |

| Statistical analysis title | ABBV-8E12 4000 mg vs Placebo |
|---|---|

Statistical analysis description:

The analysis utilized a likelihood-based, mixed-effects model, repeated measures (MMRM) analysis of the change from baseline for each postbaseline value and compared each ABBV-8E12 dose group with the placebo group. The model, which used all observed data, included fixed, categorical effects for treatment, site, visit, baseline score-by-visit interaction and treatment-by-visit interaction, with continuous fixed covariates for the corresponding baseline score.

| Comparison groups | ABBV-8E12 4000 mg v Placebo |
|---|---|
| Number of subjects included in analysis | 107 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.642 |
| Method | Mixed-effects model repeated measures |
| Parameter estimate | LS Mean Difference |
| Point estimate | -6.3 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | -33.04 |
|     upper limit | 20.42 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 13.56 |

## Secondary: Clinical Global Impression of Change (CGI-C) Score at Week 52

| End point title | Clinical Global Impression of Change (CGI-C) Score at Week 52 |
|---|---|

End point description:

The Clinical Global Impression of Change (CGI-C) score is a clinician's rating scale for assessing Global Improvement of Change. The CGI-C rates improvement by 7 categories: very much improved (1), much improved (2), minimally improved (3), no change (4), minimally worse (5), much worse (6), very much worse (7). The CGI-C score ranges from 1 to 7, with lower scores indicating improvement.

| End point type | Secondary |
|---|---|

End point timeframe:

Week 52

| End point values | Placebo | ABBV-8E12 2000 mg | ABBV-8E12 4000 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 50[11] | 48[12] | 51[13] | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | 5.1 (± 0.11) | 5.1 (± 0.11) | 5.0 (± 0.11) | |

Notes:

[11] - ITT set:randomized subjects who rcvd ≥1 dose of study drug with available data at Wk 52

[12] - ITT set:randomized subjects who rcvd ≥1 dose of study drug with available data at Wk 52

[13] - ITT set:randomized subjects who rcvd ≥1 dose of study drug with available data at Wk 52

## Statistical analyses

| Statistical analysis title | ABBV-8E12 2000 mg vs Placebo |
|---|---|

Statistical analysis description:

The analysis utilized a likelihood-based, mixed-effects model, repeated measures (MMRM) analysis of the change from baseline for each postbaseline value and compared each ABBV-8E12 dose group with the placebo group. The model, which used all observed data, included fixed, categorical effects for treatment, site, visit, baseline score-by-visit interaction and treatment-by-visit interaction, with continuous fixed covariates for the corresponding baseline score.

| Comparison groups | Placebo v ABBV-8E12 2000 mg |
|---|---|
| Number of subjects included in analysis | 98 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.756 |
| Method | Mixed-effects model repeated measures |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | -0.36 |
|     upper limit | 0.26 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.16 |

| Statistical analysis title | ABBV-8E12 4000 mg vs Placebo |
|---|---|

Statistical analysis description:

The analysis utilized a likelihood-based, mixed-effects model, repeated measures (MMRM) analysis of the change from baseline for each postbaseline value and compared each ABBV-8E12 dose group with the placebo group. The model, which used all observed data, included fixed, categorical effects for treatment, site, visit, baseline score-by-visit interaction and treatment-by-visit interaction, with continuous fixed covariates for the corresponding baseline score.

| Comparison groups | Placebo v ABBV-8E12 4000 mg |
|---|---|
| Number of subjects included in analysis | 101 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.409 |
| Method | Mixed-effects model repeated measures |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.1 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.44 |
| upper limit | 0.18 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.16 |

## Secondary: Time to Maximum Observed Serum Concentration (Tmax) for ABBV-8E12

| End point title | Time to Maximum Observed Serum Concentration (Tmax) for ABBV-8E12 |
|---|---|

End point description:

The time to maximum plasma concentration (Tmax; measured in hours) is the time it takes for a drug to achieve Cmax, the maximum plasma concentration. Tmax was measured after the first and the fifth doses in Cohort 1 and Cohort J1.

| End point type | Secondary |
|---|---|

End point timeframe:

First Dosing Interval, 2 weeks, Day 1-14; Fifth Dosing Interval, 4 weeks, Day 85-113

| **End point values** | Cohort 1, ABBV-8E12 2000 mg | Cohort 1, ABBV-8E12 4000 mg | Cohort J1, ABBV-8E12 2000 mg | Cohort J1, ABBV-8E12 4000 mg |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 11[14] | 9[15] | 3[16] | 3[17] |
| Units: hours | | | | |
| median (full range (min-max)) | | | | |
| 1st Dosing Interval, 2 wks, d 1-14; n=11,9,3,3 | 4.0 (3.2 to 6.1) | 4.1 (3.2 to 5.6) | 5.0 (4.0 to 5.2) | 4.8 (4.3 to 4.9) |
| 5th Dosing Interval, 4 wks, d 85-113; n= 9,7,2,2 | 3.6 (2.9 to 5.5) | 4.0 (3.3 to 46.2) | 5.0 (4.4 to 5.7) | 3.4 (3.2 to 3.5) |

Notes:

[14] - Participants in Cohort 1 with available data

[15] - Participants in Cohort 1 with available data

[16] - Participants in Cohort J1 with available data

[17] - Participants in Cohort J1 with available data

### Statistical analyses

No statistical analyses for this end point

## Secondary: Area Under the Concentration Time Curve (AUC) for ABBV-8E12

| End point title | Area Under the Concentration Time Curve (AUC) for ABBV-8E12 |
|---|---|

End point description:

The area under the plasma concentration-time curve (AUC; measured in μg•day/mL) is a method of measurement to determine the total exposure of a drug in blood plasma. The AUC24 of ABBV-8E12 was estimated using noncompartmental methods after the first and the fifth doses in Cohort 1 and Cohort J1.

| End point type | Secondary |
|---|---|

End point timeframe:

First Dosing Interval, 2 weeks, Day 1-14; Fifth Dosing Interval, 4 weeks, Day 85-113

| **End point values** | Cohort 1, ABBV-8E12 2000 mg | Cohort 1, ABBV-8E12 4000 mg | Cohort J1, ABBV-8E12 2000 mg | Cohort J1, ABBV-8E12 4000 mg |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 11[18] | 9[19] | 3[20] | 3[21] |
| Units: µg•day/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| 1st Dosing Interval, 2 wks, d 1-14; n=11,9,3,3 | 5070 (± 25) | 10400 (± 21) | 5950 (± 12) | 10400 (± 11) |
| 5th Dosing Interval, 4 wks, d 85-113; n= 10,8,3,3 | 13900 (± 28) | 31600 (± 36) | 15200 (± 21) | 23900 (± 15) |

Notes:

[18] - Participants in Cohort 1 with available data

[19] - Participants in Cohort 1 with available data

[20] - Participants in Cohort J1 with available data

[21] - Participants in Cohort J1 with available data

## Statistical analyses

No statistical analyses for this end point

## Secondary: Serum Concentration of ABBV-8E12 Prior to Infusion of a Day of Dosing (Ctrough)

| End point title | Serum Concentration of ABBV-8E12 Prior to Infusion of a Day of Dosing (Ctrough) |
|---|---|

End point description:

The concentration of ABBV-8E12 immediately prior to infusion of the fifth dose (Ctrough; measured in µg/mL) was estimated using non-compartmental methods in Cohort 1 and Cohort J1.

| End point type | Secondary |
|---|---|

End point timeframe:

First day of the Fifth Dosing Interval, Day 85

| **End point values** | Cohort 1, ABBV-8E12 2000 mg | Cohort 1, ABBV-8E12 4000 mg | Cohort J1, ABBV-8E12 2000 mg | Cohort J1, ABBV-8E12 4000 mg |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 10[22] | 8[23] | 3[24] | 3[25] |
| Units: µg/mL | | | | |
| geometric mean (geometric coefficient of variation) | 353 (± 27) | 657 (± 45) | 345 (± 32) | 595 (± 16) |

Notes:

[22] - Participants in Cohort 1 with available data

[23] - Participants in Cohort 1 with available data

[24] - Participants in Cohort J1 with available data

[25] - Participants in Cohort J1 with available data

## Statistical analyses

No statistical analyses for this end point

## Secondary: Maximum Observed Serum Concentration (Cmax) for ABBV-8E12

| End point title | Maximum Observed Serum Concentration (Cmax) for ABBV-8E12 |
|---|---|

End point description:

The maximum observed serum concentration after the first and the fifth doses in Cohort 1 and Cohort J1 was determined.

| End point type | Secondary |
|---|---|

End point timeframe:

First Dosing Interval, 2 weeks, Day 1-14; Fifth Dosing Interval, 4 weeks, Day 85-113

| **End point values** | Cohort 1, ABBV-8E12 2000 mg | Cohort 1, ABBV-8E12 4000 mg | Cohort J1, ABBV-8E12 2000 mg | Cohort J1, ABBV-8E12 4000 mg |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 11[26] | 9[27] | 3[28] | 3[29] |
| Units: µg/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| 1st Dosing Interval, 2 wks, d 1-14; n=11,9,3,3 | 714 (± 32) | 1450 (± 20) | 853 (± 6) | 1580 (± 13) |
| 5th Dosing Interval, 4 wks, d 85-113; n= 9,7,2,2 | 1070 (± 56) | 2350 (± 23) | 1010 (± 21) | 1960 (± 15) |

Notes:

[26] - Participants in Cohort 1 with available data

[27] - Participants in Cohort 1 with available data

[28] - Participants in Cohort J1 with available data

[29] - Participants in Cohort J1 with available data

## Statistical analyses

No statistical analyses for this end point

## Secondary: Mean Change From Baseline to Week 52 in Unified Parkinson's Disease Rating Scale (UPDRS) Part II (Activities of Daily Living)

| End point title | Mean Change From Baseline to Week 52 in Unified Parkinson's Disease Rating Scale (UPDRS) Part II (Activities of Daily Living) |
|---|---|

End point description:

The Unified Parkinson's Disease Rating Scale (UPDRS) is an Investigator-used rating tool to follow the longitudinal course of Parkinson's disease. The Part II score is the sum of the answers to the 13 questions related to Activities of Daily Living, and ranges from 0-52. Higher scores are associated with more disability. Positive changes in score indicate worsening from baseline

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline, Week 52

| End point values | Placebo | ABBV-8E12 2000 mg | ABBV-8E12 4000 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 63[30] | 60[31] | 60[32] | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | 5.6 (± 0.62) | 5.8 (± 0.63) | 7.0 (± 0.63) | |

Notes:

[30] - ITT set:randomized subjects who rcvd ≥1 dose of study drug with available data at baseline and Wk 52

[31] - ITT set:randomized subjects who rcvd ≥1 dose of study drug with available data at baseline and Wk 52

[32] - ITT set:randomized subjects who rcvd ≥1 dose of study drug with available data at baseline and Wk 52

## Statistical analyses

| Statistical analysis title | ABBV-8E12 2000 mg vs Placebo |
|---|---|

Statistical analysis description:

The analysis utilized a likelihood-based, mixed-effects model, repeated measures (MMRM) analysis of the change from baseline for each postbaseline value and compared each ABBV-8E12 dose group with the placebo group. The model, which used all observed data, included fixed, categorical effects for treatment, site, visit, baseline score-by-visit interaction and treatment-by-visit interaction, with continuous fixed covariates for the corresponding baseline score.

| Comparison groups | Placebo v ABBV-8E12 2000 mg |
|---|---|
| Number of subjects included in analysis | 123 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.812 |
| Method | Mixed-effects model repeated measures |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.52 |
| upper limit | 1.93 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.88 |

| Statistical analysis title | ABBV-8E12 4000 mg vs Placebo |
|---|---|

Statistical analysis description:

The analysis utilized a likelihood-based, mixed-effects model, repeated measures (MMRM) analysis of the change from baseline for each postbaseline value and compared each ABBV-8E12 dose group with the placebo group. The model, which used all observed data, included fixed, categorical effects for treatment, site, visit, baseline score-by-visit interaction and treatment-by-visit interaction, with continuous fixed covariates for the corresponding baseline score.

| Comparison groups | Placebo v ABBV-8E12 4000 mg |
|---|---|
| Number of subjects included in analysis | 123 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.104 |
| Method | Mixed-effects model repeated measures |
| Parameter estimate | LS Mean Difference |
| Point estimate | 1.4 |
| Confidence interval | |
|    level | 95 % |
|    sides | 2-sided |
|    lower limit | -0.3 |
|    upper limit | 3.16 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.88 |

## Secondary: Mean Change From Baseline to Week 52 in Schwab and England Activities of Daily Living Scale (SEADL)

| End point title | Mean Change From Baseline to Week 52 in Schwab and England Activities of Daily Living Scale (SEADL) |
|---|---|

End point description:

The Schwab and England Activities of Daily Living (SEADL) consists of ten items intended to evaluate the daily life activities of a participant. The SEADL is composed of two sections: the first is a self-reported questionnaire in which participants grade their own daily life activities, such as dressing, using the toilet, resting, eating, and social activities (subjective assessment), and the second is an assessment of motor functions, such as postural balance, speaking, rigidity, and tremors, conducted by a clinician (objective assessment). It is a percentage scale divided into deciles, and the results are reported between 0% (bedridden) and 100% (healthy). Negative changes in values indicate a decline in health.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline, Week 52

| **End point values** | Placebo | ABBV-8E12 2000 mg | ABBV-8E12 4000 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 58[33] | 56[34] | 60[35] | |
| Units: percentage of independence | | | | |
| least squares mean (standard error) | -20.6 (± 1.79) | -18.0 (± 1.82) | -20.5 (± 1.77) | |

Notes:

[33] - ITT set:randomized subjects who rcvd ≥1 dose of study drug with available data at baseline and Wk 52

[34] - ITT set:randomized subjects who rcvd ≥1 dose of study drug with available data at baseline and Wk 52

[35] - ITT set:randomized subjects who rcvd ≥1 dose of study drug with available data at baseline and Wk 52

## Statistical analyses

| Statistical analysis title | ABBV-8E12 2000 mg vs Placebo |
|---|---|

Statistical analysis description:

The analysis utilized a likelihood-based, mixed-effects model, repeated measures (MMRM) analysis of the change from baseline for each postbaseline value and compared each ABBV-8E12 dose group with the placebo group. The model, which used all observed data, included fixed, categorical effects for treatment, site, visit, baseline score-by-visit interaction and treatment-by-visit interaction, with continuous fixed covariates for the corresponding baseline score.

| Comparison groups | Placebo v ABBV-8E12 2000 mg |
|---|---|
| Number of subjects included in analysis | 114 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.323 |
| Method | Mixed-effects model repeated measures |
| Parameter estimate | LS Mean Difference |
| Point estimate | 2.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.48 |
| upper limit | 7.51 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.53 |

| Statistical analysis title | ABBV-8E12 4000 mg vs Placebo |
|---|---|

Statistical analysis description:

The analysis utilized a likelihood-based, mixed-effects model, repeated measures (MMRM) analysis of the change from baseline for each postbaseline value and compared each ABBV-8E12 dose group with the placebo group. The model, which used all observed data, included fixed, categorical effects for treatment, site, visit, baseline score-by-visit interaction and treatment-by-visit interaction, with continuous fixed covariates for the corresponding baseline score.

| Comparison groups | Placebo v ABBV-8E12 4000 mg |
|---|---|
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.974 |
| Method | Mixed-effects model repeated measures |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.86 |
| upper limit | 5.02 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.51 |

**Secondary: Mean Change From Baseline to Week 52 in Clinical Global Impression of**

## Severity (CGI-S) Score

| End point title | Mean Change From Baseline to Week 52 in Clinical Global Impression of Severity (CGI-S) Score |
|---|---|

End point description:

The CGI-S is a clinician's rating of disease severity. The CGI-S rates severity of illness on a 7-point scale, using a range of responses from 1 (normal) through 7 (the most severely ill). This rating is based upon observed and reported symptoms, behavior, and function in the past 7 days. Positive changes in score indicate worsening from baseline.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline, Week 52

| **End point values** | Placebo | ABBV-8E12 2000 mg | ABBV-8E12 4000 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 50[36] | 48[37] | 51[38] | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | 0.6 (± 0.10) | 0.6 (± 0.10) | 0.6 (± 0.10) | |

Notes:

[36] - ITT set:randomized subjects who rcvd ≥1 dose of study drug with available data at baseline and Wk 52

[37] - ITT set:randomized subjects who rcvd ≥1 dose of study drug with available data at baseline and Wk 52

[38] - ITT set:randomized subjects who rcvd ≥1 dose of study drug with available data at baseline and Wk 52

## Statistical analyses

| **Statistical analysis title** | ABBV-8E12 2000 mg vs Placebo |
|---|---|

Statistical analysis description:

The analysis utilized a likelihood-based, mixed-effects model, repeated measures (MMRM) analysis of the change from baseline for each postbaseline value and compared each ABBV-8E12 dose group with the placebo group. The model, which used all observed data, included fixed, categorical effects for treatment, site, visit, baseline score-by-visit interaction and treatment-by-visit interaction, with continuous fixed covariates for the corresponding baseline score.

| Comparison groups | Placebo v ABBV-8E12 2000 mg |
|---|---|
| Number of subjects included in analysis | 98 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.761 |
| Method | Mixed-effects model repeated measures |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.31 |
| upper limit | 0.23 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.14 |

| **Statistical analysis title** | ABBV-8E12 4000 mg vs Placebo |
|---|---|

Statistical analysis description:

The analysis utilized a likelihood-based, mixed-effects model, repeated measures (MMRM) analysis of the change from baseline for each postbaseline value and compared each ABBV-8E12 dose group with the placebo group. The model, which used all observed data, included fixed, categorical effects for treatment, site, visit, baseline score-by-visit interaction and treatment-by-visit interaction, with continuous fixed covariates for the corresponding baseline score.

| Comparison groups | ABBV-8E12 4000 mg v Placebo |
|---|---|
| Number of subjects included in analysis | 101 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.678 |
| Method | Mixed-effects model repeated measures |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.32 |
| upper limit | 0.21 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.13 |

## Secondary: Mean Change From Baseline to Week 52 in Progressive Supranuclear Palsy Health Related Quality of Life Scale (PSPQoL) Total Score

| End point title | Mean Change From Baseline to Week 52 in Progressive Supranuclear Palsy Health Related Quality of Life Scale (PSPQoL) Total Score |
|---|---|

End point description:

The PSP-QoL is a validated patient-reported outcome measure, specifically designed to assess the quality of life of participants with PSP. There are 45 items and two subscales: physical and mental impact. Items are scored from 0 (no problem) to 4 (extreme problems). The total subscale sum scores are linearly converted into a 0 to 100 scale, and higher scores indicate a lower quality of life. Positive changes in score indicate a decline in quality of life.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline, Week 52

| End point values | Placebo | ABBV-8E12 2000 mg | ABBV-8E12 4000 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 62[39] | 59[40] | 60[41] | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | 9.2 (± 1.63) | 10.3 (± 1.65) | 10.0 (± 1.64) | |

Notes:

[39] - ITT set:randomized subjects who rcvd ≥1 dose of study drug with available data at baseline and Wk 52

[40] - ITT set:randomized subjects who rcvd ≥1 dose of study drug with available data at baseline and Wk 52

[41] - ITT set:randomized subjects who rcvd ≥1 dose of study drug with available data at baseline and Wk 52

## Statistical analyses

| Statistical analysis title | ABBV-8E12 2000 mg vs Placebo |
|---|---|

Statistical analysis description:

The analysis utilized a likelihood-based, mixed-effects model, repeated measures (MMRM) analysis of the change from baseline for each postbaseline value and compared each ABBV-8E12 dose group with the placebo group. The model, which used all observed data, included fixed, categorical effects for treatment, site, visit, baseline score-by-visit interaction and treatment-by-visit interaction, with continuous fixed covariates for the corresponding baseline score.

| Comparison groups | Placebo v ABBV-8E12 2000 mg |
|---|---|
| Number of subjects included in analysis | 121 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.653 |
| Method | Mixed-effects model repeated measures |
| Parameter estimate | LS Mean Difference |
| Point estimate | 1 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | -3.5 |
|     upper limit | 5.57 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.3 |

| Statistical analysis title | ABBV-8E12 4000 mg vs Placebo |
|---|---|

Statistical analysis description:

The primary efficacy analysis utilized a likelihood-based, mixed-effects model, repeated measures (MMRM) analysis of the change from baseline for each postbaseline value and compared each ABBV-8E12 dose group with the placebo group. The model, which used all observed data, included fixed, categorical effects for treatment, site, visit, baseline score-by-visit interaction and treatment-by-visit interaction, with continuous fixed covariates for the corresponding baseline score.

| Comparison groups | Placebo v ABBV-8E12 4000 mg |
|---|---|

| Number of subjects included in analysis | 122 |
|---|---|
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.748 |
| Method | Mixed-effects model repeated measures |
| Parameter estimate | LS Mean Difference |
| Point estimate | 1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.5 |
| upper limit | 5.57 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.3 |

## Secondary: Mean Change From Baseline to Week 52 in Progressive Supranuclear Palsy Staging System Score (PSP-SS) Score

| End point title | Mean Change From Baseline to Week 52 in Progressive Supranuclear Palsy Staging System Score (PSP-SS) Score |
|---|---|

End point description:

The Progressive Supranuclear Palsy Rating Scale (PSPRS) consists of 28 items grouped in six domains: daily activities (by history); behavior; bulbar; ocular motor; limb motor; and gait/midline. Items are scored on a 0 to 4 scale, except for four items that are scored on a 0 to 2 scale, with the total score ranging from 0 to 100. Higher scores indicate more severe disability or movement abnormality. The PSP-SS score is a composite of the dysphagia and gait items from the PSPRS. Positive changes in score indicate worsening from baseline.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline, Week 52

| **End point values** | Placebo | ABBV-8E12 2000 mg | ABBV-8E12 4000 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 59[42] | 57[43] | 59[44] | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | 0.8 (± 0.24) | 0.9 (± 0.24) | 1.0 (± 0.24) | |

Notes:

[42] - ITT set:randomized subjects who rcvd ≥1 dose of study drug with available data at baseline and Wk 52

[43] - ITT set:randomized subjects who rcvd ≥1 dose of study drug with available data at baseline and Wk 52

[44] - ITT set:randomized subjects who rcvd ≥1 dose of study drug with available data at baseline and Wk 52

## Statistical analyses

| **Statistical analysis title** | ABBV-8E12 2000 mg vs Placebo |
|---|---|

Statistical analysis description:

The analysis utilized a likelihood-based, mixed-effects model, repeated measures (MMRM) analysis of

the change from baseline for each postbaseline value and compared each ABBV-8E12 dose group with the placebo group. The model, which used all observed data, included fixed, categorical effects for treatment, site, visit, baseline score-by-visit interaction and treatment-by-visit interaction, with continuous fixed covariates for the corresponding baseline score.

| Comparison groups | Placebo v ABBV-8E12 2000 mg |
|---|---|
| Number of subjects included in analysis | 116 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.828 |
| Method | Mixed-effects model repeated measures |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.6 |
| upper limit | 0.74 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.34 |

| **Statistical analysis title** | ABBV-8E12 4000 mg vs Placebo |
|---|---|

Statistical analysis description:

The primary efficacy analysis utilized a likelihood-based, mixed-effects model, repeated measures (MMRM) analysis of the change from baseline for each postbaseline value and compared each ABBV-8E12 dose group with the placebo group. The model, which used all observed data, included fixed, categorical effects for treatment, site, visit, baseline score-by- visit interaction and treatment-by-visit interaction, with continuous fixed covariates for the corresponding baseline score.

| Comparison groups | Placebo v ABBV-8E12 4000 mg |
|---|---|
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.543 |
| Method | Mixed-effects model repeated measures |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.46 |
| upper limit | 0.87 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.34 |

**Secondary: Mean Change From Baseline to Week 52 in Third Ventricle Atrophy As Measured by Volumetric Magnetic Resonance Imaging (MRI)**

| End point title | Mean Change From Baseline to Week 52 in Third Ventricle Atrophy As Measured by Volumetric Magnetic Resonance Imaging (MRI) |
|---|---|

End point description:

Magnetic resonance imaging (MRI) of several different brain regions was performed and volumetric analysis was conducted to quantify third ventricle atrophy. Positive changes in values indicate an increase in volume.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline, Week 52

| **End point values** | Placebo | ABBV-8E12 2000 mg | ABBV-8E12 4000 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 54[45] | 58[46] | 53[47] | |
| Units: mm^3 | | | | |
| least squares mean (standard error) | 157.9 (± 18.27) | 152.4 (± 18.04) | 125.0 (± 18.57) | |

Notes:

[45] - ITT set:randomized subjects who rcvd ≥1 dose of study drug with available data at baseline and Wk 52

[46] - ITT set:randomized subjects who rcvd ≥1 dose of study drug with available data at baseline and Wk 52

[47] - ITT set:randomized subjects who rcvd ≥1 dose of study drug with available data at baseline and Wk 52

## Statistical analyses

| **Statistical analysis title** | ABBV-8E12 2000 mg vs Placebo |
|---|---|

Statistical analysis description:

The analysis utilized a likelihood-based, mixed-effects model, repeated measures (MMRM) analysis of the change from baseline for each postbaseline value and compared each ABBV-8E12 dose group with the placebo group. The model, which used all observed data, included fixed, categorical effects for treatment, site, visit, baseline score-by-visit interaction and treatment-by-visit interaction, with continuous fixed covariates for the corresponding baseline score.

| Comparison groups | ABBV-8E12 2000 mg v Placebo |
|---|---|
| Number of subjects included in analysis | 112 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.829 |
| Method | Mixed-effects model repeated measures |
| Parameter estimate | LS Mean Difference |
| Point estimate | -5.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -55.66 |
| upper limit | 44.63 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 25.44 |

| Statistical analysis title | ABBV-8E12 4000 mg vs Placebo |
|---|---|

Statistical analysis description:

The analysis utilized a likelihood-based, mixed-effects model, repeated measures (MMRM) analysis of the change from baseline for each postbaseline value and compared each ABBV-8E12 dose group with the placebo group. The model, which used all observed data, included fixed, categorical effects for treatment, site, visit, baseline score-by-visit interaction and treatment-by-visit interaction, with continuous fixed covariates for the corresponding baseline score.

| Comparison groups | Placebo v ABBV-8E12 4000 mg |
|---|---|
| Number of subjects included in analysis | 107 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.206 |
| Method | Mixed-effects model repeated measures |
| Parameter estimate | LS Mean Difference |
| Point estimate | -32.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -83.94 |
| upper limit | 18.23 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 25.92 |

## Secondary: Mean Change From Baseline to Week 52 in Superior Cerebellar Peduncle Atrophy As Measured by Volumetric Magnetic Resonance Imaging (MRI)

| End point title | Mean Change From Baseline to Week 52 in Superior Cerebellar Peduncle Atrophy As Measured by Volumetric Magnetic Resonance Imaging (MRI) |
|---|---|

End point description:

Magnetic resonance imaging (MRI) of several different brain regions was performed and volumetric analysis was conducted to quantify Superior cerebellar peduncle atrophy. Negative changes in values indicate a reduction in volume.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline, Week 52

| End point values | Placebo | ABBV-8E12 2000 mg | ABBV-8E12 4000 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 51[48] | 55[49] | 54[50] | |
| Units: mm^3 | | | | |
| least squares mean (standard error) | -8.3 (± 2.78) | -4.3 (± 2.74) | -3.7 (± 2.74) | |

Notes:

[48] - ITT set:randomized subjects who rcvd ≥1 dose of study drug with available data at baseline and Wk 52

[49] - ITT set:randomized subjects who rcvd ≥1 dose of study drug with available data at baseline and

Wk 52

[50] - ITT set:randomized subjects who rcvd ≥1 dose of study drug with available data at baseline and Wk 52

## Statistical analyses

| Statistical analysis title | ABBV-8E12 2000 mg vs Placebo |
|---|---|

Statistical analysis description:

The analysis utilized a likelihood-based, mixed-effects model, repeated measures (MMRM) analysis of the change from baseline for each postbaseline value and compared each ABBV-8E12 dose group with the placebo group. The model, which used all observed data, included fixed, categorical effects for treatment, site, visit, baseline score-by-visit interaction and treatment-by-visit interaction, with continuous fixed covariates for the corresponding baseline score.

| Comparison groups | Placebo v ABBV-8E12 2000 mg |
|---|---|
| Number of subjects included in analysis | 106 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.304 |
| Method | Mixed-effects model repeated measures |
| Parameter estimate | LS Mean Difference |
| Point estimate | 4 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | -3.65 |
|     upper limit | 11.65 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.88 |

| Statistical analysis title | ABBV-8E12 4000 mg vs Placebo |
|---|---|

Statistical analysis description:

The analysis utilized a likelihood-based, mixed-effects model, repeated measures (MMRM) analysis of the change from baseline for each postbaseline value and compared each ABBV-8E12 dose group with the placebo group. The model, which used all observed data, included fixed, categorical effects for treatment, site, visit, baseline score-by-visit interaction and treatment-by-visit interaction, with continuous fixed covariates for the corresponding baseline score.

| Comparison groups | Placebo v ABBV-8E12 4000 mg |
|---|---|
| Number of subjects included in analysis | 105 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.243 |
| Method | Mixed-effects model repeated measures |
| Parameter estimate | LS Mean Difference |
| Point estimate | 4.5 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.11 |
| upper limit | 12.19 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.88 |

## Secondary: Mean Change From Baseline to Week 52 in Brainstem Atrophy As Measured by Volumetric Magnetic Resonance Imaging (MRI)

| End point title | Mean Change From Baseline to Week 52 in Brainstem Atrophy As Measured by Volumetric Magnetic Resonance Imaging (MRI) |
|---|---|

End point description:

Magnetic resonance imaging (MRI) of several different brain regions was performed and volumetric analysis was conducted to quantify brainstem atrophy. Negative changes in values indicate a reduction in volume.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline, Week 52

| **End point values** | Placebo | ABBV-8E12 2000 mg | ABBV-8E12 4000 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 48[51] | 49[52] | 43[53] | |
| Units: mm^3 | | | | |
| least squares mean (standard error) | -374.5 (± 38.42) | -400.9 (± 38.60) | -341.3 (± 40.61) | |

Notes:

[51] - ITT set:randomized subjects who rcvd ≥1 dose of study drug with available data at baseline and Wk 52

[52] - ITT set:randomized subjects who rcvd ≥1 dose of study drug with available data at baseline and Wk 52

[53] - ITT set:randomized subjects who rcvd ≥1 dose of study drug with available data at baseline and Wk 52

## Statistical analyses

| **Statistical analysis title** | ABBV-8E12 2000 mg vs Placebo |
|---|---|

Statistical analysis description:

The analysis utilized a likelihood-based, mixed-effects model, repeated measures (MMRM) analysis of the change from baseline for each postbaseline value and compared each ABBV-8E12 dose group with the placebo group. The model, which used all observed data, included fixed, categorical effects for treatment, site, visit, baseline score-by-visit interaction and treatment-by-visit interaction, with continuous fixed covariates for the corresponding baseline score.

| Comparison groups | Placebo v ABBV-8E12 2000 mg |
|---|---|

| | |
|---|---|
| Number of subjects included in analysis | 97 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.625 |
| Method | Mixed-effects model repeated measures |
| Parameter estimate | LS Mean Difference |
| Point estimate | -26.4 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | -132.76 |
|     upper limit | 79.94 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 53.86 |

| | |
|---|---|
| **Statistical analysis title** | ABBV-8E12 4000 mg vs Placebo |

Statistical analysis description:

The analysis utilized a likelihood-based, mixed-effects model, repeated measures (MMRM) analysis of the change from baseline for each postbaseline value and compared each ABBV-8E12 dose group with the placebo group. The model, which used all observed data, included fixed, categorical effects for treatment, site, visit, baseline score-by-visit interaction and treatment-by-visit interaction, with continuous fixed covariates for the corresponding baseline score.

| | |
|---|---|
| Comparison groups | ABBV-8E12 4000 mg v Placebo |
| Number of subjects included in analysis | 91 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.55 |
| Method | Mixed-effects model repeated measures |
| Parameter estimate | LS Mean Difference |
| Point estimate | 33.2 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | -76.34 |
|     upper limit | 142.71 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 55.47 |

## Secondary: Mean Change From Baseline to Week 52 in Whole Brain Atrophy As Measured by Volumetric Magnetic Resonance Imaging (MRI)

| | |
|---|---|
| End point title | Mean Change From Baseline to Week 52 in Whole Brain Atrophy As Measured by Volumetric Magnetic Resonance Imaging (MRI) |

End point description:

Magnetic resonance imaging (MRI) of several different brain regions was performed and volumetric analysis was conducted to quantify whole brain atrophy. Negative changes in values indicate a reduction in volume.

| End point type | Secondary |
|---|---|
| End point timeframe:<br><br>Baseline, Week 52 | |

| End point values | Placebo | ABBV-8E12<br>2000 mg | ABBV-8E12<br>4000 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 45[54] | 46[55] | 49[56] | |
| Units: mm^3 | | | | |
| least squares mean (standard error) | -22496.2 (± 1793.36) | -20757.1 (± 1783.00) | -18811.3 (± 1740.72) | |

Notes:

[54] - ITT set:randomized subjects who rcvd ≥1 dose of study drug with available data at baseline and Wk 52

[55] - ITT set:randomized subjects who rcvd ≥1 dose of study drug with available data at baseline and Wk 52

[56] - ITT set:randomized subjects who rcvd ≥1 dose of study drug with available data at baseline and Wk 52

## Statistical analyses

| Statistical analysis title | ABBV-8E12 2000 mg vs Placebo |
|---|---|

Statistical analysis description:

The analysis utilized a likelihood-based, mixed-effects model, repeated measures (MMRM) analysis of the change from baseline for each postbaseline value and compared each ABBV-8E12 dose group with the placebo group. The model, which used all observed data, included fixed, categorical effects for treatment, site, visit, baseline score-by-visit interaction and treatment-by-visit interaction, with continuous fixed covariates for the corresponding baseline score.

| Comparison groups | Placebo v ABBV-8E12 2000 mg |
|---|---|
| Number of subjects included in analysis | 91 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.488 |
| Method | Mixed-effects model repeated measures |
| Parameter estimate | LS Mean Difference |
| Point estimate | 1739.1 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | -3201.75 |
|     upper limit | 6680.02 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2502.95 |

| Statistical analysis title | ABBV-8E12 4000 mg vs Placebo |
|---|---|

Statistical analysis description:

The analysis utilized a likelihood-based, mixed-effects model, repeated measures (MMRM) analysis of the change from baseline for each postbaseline value and compared each ABBV-8E12 dose group with the placebo group. The model, which used all observed data, included fixed, categorical effects for

treatment, site, visit, baseline score-by-visit interaction and treatment-by-visit interaction, with continuous fixed covariates for the corresponding baseline score.

| Comparison groups | Placebo v ABBV-8E12 4000 mg |
|---|---|
| Number of subjects included in analysis | 94 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.14 |
| Method | Mixed-effects model repeated measures |
| Parameter estimate | LS Mean Difference |
| Point estimate | 3684.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1225.46 |
| upper limit | 8595.29 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2487.32 |

## Secondary: Mean Change From Baseline to Week 52 in Frontal Lobe Atrophy As Measured by Volumetric Magnetic Resonance Imaging (MRI)

| End point title | Mean Change From Baseline to Week 52 in Frontal Lobe Atrophy As Measured by Volumetric Magnetic Resonance Imaging (MRI) |
|---|---|

End point description:

Magnetic resonance imaging (MRI) of several different brain regions was performed and volumetric analysis was conducted to quantify frontal lobe atrophy. Positive changes in values indicate an increase in volume.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline, Week 52

| **End point values** | Placebo | ABBV-8E12 2000 mg | ABBV-8E12 4000 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 48[57] | 49[58] | 43[59] | |
| Units: mm^3 | | | | |
| least squares mean (standard error) | 1052.6 (± 425.55) | 1260.5 (± 423.96) | 1186.1 (± 445.18) | |

Notes:

[57] - ITT set:randomized subjects who rcvd ≥1 dose of study drug with available data at baseline and Wk 52

[58] - ITT set:randomized subjects who rcvd ≥1 dose of study drug with available data at baseline and Wk 52

[59] - ITT set:randomized subjects who rcvd ≥1 dose of study drug with available data at baseline and Wk 52

## Statistical analyses

| Statistical analysis title | ABBV-8E12 2000 mg vs Placebo |
|---|---|

Statistical analysis description:

The analysis utilized a likelihood-based, mixed-effects model, repeated measures (MMRM) analysis of the change from baseline for each postbaseline value and compared each ABBV-8E12 dose group with the placebo group. The model, which used all observed data, included fixed, categorical effects for treatment, site, visit, baseline score-by-visit interaction and treatment-by-visit interaction, with continuous fixed covariates for the corresponding baseline score.

| Comparison groups | Placebo v ABBV-8E12 2000 mg |
|---|---|
| Number of subjects included in analysis | 97 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.726 |
| Method | Mixed-effects model repeated measures |
| Parameter estimate | LS Mean Difference |
| Point estimate | 207.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -962.98 |
| upper limit | 1378.88 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 592.68 |

| Statistical analysis title | ABBV-8E12 4000 mg vs Placebo |
|---|---|

Statistical analysis description:

The analysis utilized a likelihood-based, mixed-effects model, repeated measures (MMRM) analysis of the change from baseline for each postbaseline value and compared each ABBV-8E12 dose group with the placebo group. The model, which used all observed data, included fixed, categorical effects for treatment, site, visit, baseline score-by-visit interaction and treatment-by-visit interaction, with continuous fixed covariates for the corresponding baseline score.

| Comparison groups | Placebo v ABBV-8E12 4000 mg |
|---|---|
| Number of subjects included in analysis | 91 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.828 |
| Method | Mixed-effects model repeated measures |
| Parameter estimate | LS Mean Difference |
| Point estimate | 133.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1075.26 |
| upper limit | 1342.4 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 611.91 |

**Secondary: Mean Time to Loss of Ability to Walk Independently as Measured by**

## Progressive Supranuclear Palsy Rating Scale (PSPRS) Item 26

| End point title | Mean Time to Loss of Ability to Walk Independently as Measured by Progressive Supranuclear Palsy Rating Scale (PSPRS) Item 26 |
|---|---|

End point description:

The PSPRS consists of 28 items grouped in six domains: daily activities (by history); behavior; bulbar; ocular motor; limb motor; and gait/midline. Items are scored on a 0 to 4 scale, except for six items that are scored on a 0 to 2 scale, with the total score ranging from 0 to 100. Higher scores indicate more severe disability or movement abnormality. Item 26 pertains to gait, scored as either 0 (normal); 1 (slightly wide-based or irregular or slight pulsion on turns); 2 (must walk slowly or occasionally use walls or helper to avoid falling, especially on turns); 3 (must use assistance all or almost all the time); or 4 (unable to walk, even with walker; may be able to transfer).

| End point type | Secondary |
|---|---|

End point timeframe:

From Baseline to Week 52

| End point values | Placebo | ABBV-8E12 2000 mg | ABBV-8E12 4000 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 126[60] | 126[61] | 125[62] | |
| Units: days | | | | |
| median (confidence interval 95%) | 169.0 (89.0 to 255.0) | 170.0 (87.0 to 253.0) | 203.0 (169.0 to 255.0) | |

Notes:

[60] - ITT dataset: all randomized subjects who received at least 1 dose of study drug with available data

[61] - ITT dataset: all randomized subjects who received at least 1 dose of study drug with available data

[62] - ITT dataset: all randomized subjects who received at least 1 dose of study drug with available data

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events and serious adverse events collected from 1st dose of study drug until 20 wks after discontinuation, up to 80 wks. Serious adverse events and protocol-related nonserious adverse events collected from informed consent.

Adverse event reporting additional description:

TEAEs and TESAEs are defined as any AE or TESAE with onset or worsening reported by a participant from the time that the first dose of study is administered until 20 weeks (approximately 5 half-lives) have elapsed following discontinuation of study drug. TEAEs were collected whether elicited or spontaneously reported by the participant.

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

### Dictionary used

| Dictionary name | MedDRA |
|---|---|
| Dictionary version | 22.0 |

### Reporting groups

| Reporting group title | Placebo |
|---|---|

Reporting group description:

0.9% Sodium Chloride Injection/Solution for Infusion; intravenous infusions at Day 1, Day 15, and Day 29, then every 28 days for 52 weeks

| Reporting group title | ABBV-8E12 2000mg |
|---|---|

Reporting group description:

Intravenous infusions at Day 1, Day 15, and Day 29, then every 28 days for 52 weeks; 300 mg/15 mL (participants in countries other than Japan or Spain); 1000 mg/10 mL (for participants in Japan or Spain)

| Reporting group title | ABBV-8E12 4000mg |
|---|---|

Reporting group description:

Intravenous infusions at Day 1, Day 15, and Day 29, then every 28 days for 52 weeks; 300 mg/15 mL (participants in countries other than Japan or Spain); 1000 mg/10 mL (for participants in Japan or Spain)

| Serious adverse events | Placebo | ABBV-8E12 2000mg | ABBV-8E12 4000mg |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 33 / 126 (26.19%) | 29 / 126 (23.02%) | 34 / 125 (27.20%) |
| number of deaths (all causes) | 8 | 9 | 9 |
| number of deaths resulting from adverse events | 8 | 9 | 9 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| BREAST CANCER | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 0 / 126 (0.00%) | 1 / 125 (0.80%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PROSTATE CANCER | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 126 (0.00%) | 1 / 126 (0.79%) | 0 / 125 (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 |
| **PROSTATE CANCER METASTATIC** | | | |
| subjects affected / exposed | 1 / 126 (0.79%) | 0 / 126 (0.00%) | 0 / 125 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Vascular disorders** | | | |
| **DEEP VEIN THROMBOSIS** | | | |
| subjects affected / exposed | 1 / 126 (0.79%) | 0 / 126 (0.00%) | 0 / 125 (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 |
| **HAEMORRHAGE** | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 1 / 126 (0.79%) | 0 / 125 (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 |
| **HYPERTENSION** | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 0 / 126 (0.00%) | 1 / 125 (0.80%) |
| 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 / 126 (0.79%) | 2 / 126 (1.59%) | 1 / 125 (0.80%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| **DISEASE PROGRESSION** | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 0 / 126 (0.00%) | 1 / 125 (0.80%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| **GAIT DISTURBANCE** | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 0 / 126 (0.00%) | 1 / 125 (0.80%) |
| 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 PHYSICAL HEALTH DETERIORATION | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 0 / 126 (0.00%) | 1 / 125 (0.80%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PYREXIA | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 0 / 126 (0.00%) | 2 / 125 (1.60%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| DRUG HYPERSENSITIVITY | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 0 / 126 (0.00%) | 1 / 125 (0.80%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| ACUTE RESPIRATORY DISTRESS SYNDROME | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 1 / 126 (0.79%) | 0 / 125 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| ASPIRATION | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 1 / 126 (0.79%) | 0 / 125 (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 |
| CHOKING | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 0 / 126 (0.00%) | 1 / 125 (0.80%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| COUGH | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 1 / 126 (0.79%) | 0 / 125 (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 |
| DYSPNOEA | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 126 (0.00%) | 0 / 126 (0.00%) | 1 / 125 (0.80%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **HYPOXIA** | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 0 / 126 (0.00%) | 1 / 125 (0.80%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **INTERSTITIAL LUNG DISEASE** | | | |
| subjects affected / exposed | 1 / 126 (0.79%) | 0 / 126 (0.00%) | 0 / 125 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **PNEUMONIA ASPIRATION** | | | |
| subjects affected / exposed | 2 / 126 (1.59%) | 3 / 126 (2.38%) | 1 / 125 (0.80%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| **PNEUMOTHORAX** | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 0 / 126 (0.00%) | 1 / 125 (0.80%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **PULMONARY EMBOLISM** | | | |
| subjects affected / exposed | 1 / 126 (0.79%) | 1 / 126 (0.79%) | 0 / 125 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **RESPIRATORY ARREST** | | | |
| subjects affected / exposed | 1 / 126 (0.79%) | 0 / 126 (0.00%) | 0 / 125 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| **RESPIRATORY DISTRESS** | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 0 / 126 (0.00%) | 1 / 125 (0.80%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| **RESPIRATORY FAILURE** | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 126 (0.00%) | 1 / 126 (0.79%) | 1 / 125 (0.80%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| **Psychiatric disorders** | | | |
| COMPLETED SUICIDE | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 1 / 126 (0.79%) | 0 / 125 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| DELIRIUM | | | |
| subjects affected / exposed | 1 / 126 (0.79%) | 0 / 126 (0.00%) | 0 / 125 (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 |
| MENTAL STATUS CHANGES | | | |
| subjects affected / exposed | 1 / 126 (0.79%) | 0 / 126 (0.00%) | 0 / 125 (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 |
| PSYCHOTIC DISORDER | | | |
| subjects affected / exposed | 1 / 126 (0.79%) | 0 / 126 (0.00%) | 0 / 125 (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 |
| SUICIDAL IDEATION | | | |
| subjects affected / exposed | 1 / 126 (0.79%) | 0 / 126 (0.00%) | 0 / 125 (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 |
| SUICIDE ATTEMPT | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 1 / 126 (0.79%) | 0 / 125 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Investigations** | | | |
| RESIDUAL URINE VOLUME | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 1 / 126 (0.79%) | 0 / 125 (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 | | | |
|---|---|---|---|
| **BRAIN CONTUSION** | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 1 / 126 (0.79%) | 0 / 125 (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 |
| **CERVICAL VERTEBRAL FRACTURE** | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 2 / 126 (1.59%) | 1 / 125 (0.80%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **CLAVICLE FRACTURE** | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 0 / 126 (0.00%) | 1 / 125 (0.80%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **CONCUSSION** | | | |
| subjects affected / exposed | 1 / 126 (0.79%) | 1 / 126 (0.79%) | 0 / 125 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **CONTUSION** | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 0 / 126 (0.00%) | 1 / 125 (0.80%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **FACIAL BONES FRACTURE** | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 1 / 126 (0.79%) | 0 / 125 (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 |
| **FALL** | | | |
| subjects affected / exposed | 6 / 126 (4.76%) | 5 / 126 (3.97%) | 6 / 125 (4.80%) |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 7 | 0 / 7 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **FEMORAL NECK FRACTURE** | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 1 / 126 (0.79%) | 0 / 125 (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 |
| **FEMUR FRACTURE** | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 126 (1.59%) | 1 / 126 (0.79%) | 2 / 125 (1.60%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **FIBULA FRACTURE** | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 0 / 126 (0.00%) | 1 / 125 (0.80%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **FOREIGN BODY ASPIRATION** | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 0 / 126 (0.00%) | 1 / 125 (0.80%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **GUN SHOT WOUND** | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 1 / 126 (0.79%) | 0 / 125 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| **HEAD INJURY** | | | |
| subjects affected / exposed | 2 / 126 (1.59%) | 0 / 126 (0.00%) | 0 / 125 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **HIP FRACTURE** | | | |
| subjects affected / exposed | 3 / 126 (2.38%) | 1 / 126 (0.79%) | 0 / 125 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **HUMERUS FRACTURE** | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 1 / 126 (0.79%) | 1 / 125 (0.80%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **JOINT DISLOCATION** | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 1 / 126 (0.79%) | 0 / 125 (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 |
| **PERIPROSTHETIC FRACTURE** | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 126 (0.00%) | 1 / 126 (0.79%) | 0 / 125 (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 |
| RADIUS FRACTURE | | | |
| subjects affected / exposed | 1 / 126 (0.79%) | 0 / 126 (0.00%) | 0 / 125 (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 |
| RIB FRACTURE | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 2 / 126 (1.59%) | 3 / 125 (2.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SKIN LACERATION | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 2 / 126 (1.59%) | 0 / 125 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SKULL FRACTURE | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 0 / 126 (0.00%) | 1 / 125 (0.80%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SPINAL FRACTURE | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 0 / 126 (0.00%) | 1 / 125 (0.80%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SUBDURAL HAEMATOMA | | | |
| subjects affected / exposed | 3 / 126 (2.38%) | 0 / 126 (0.00%) | 2 / 125 (1.60%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| ULNA FRACTURE | | | |
| subjects affected / exposed | 1 / 126 (0.79%) | 0 / 126 (0.00%) | 0 / 125 (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 |
| UPPER LIMB FRACTURE | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 126 (0.00%) | 1 / 126 (0.79%) | 0 / 125 (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 |

**WRIST FRACTURE**

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 126 (0.00%) | 1 / 126 (0.79%) | 1 / 125 (0.80%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Cardiac disorders

**ACUTE MYOCARDIAL INFARCTION**

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 126 (0.00%) | 1 / 126 (0.79%) | 0 / 125 (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 | 1 / 126 (0.79%) | 1 / 126 (0.79%) | 0 / 125 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

**CARDIAC FAILURE**

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 126 (0.00%) | 1 / 126 (0.79%) | 0 / 125 (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 CONGESTIVE**

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 126 (0.00%) | 1 / 126 (0.79%) | 0 / 125 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |

**CARDIO-RESPIRATORY ARREST**

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 126 (0.00%) | 0 / 126 (0.00%) | 1 / 125 (0.80%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |

**CARDIOPULMONARY FAILURE**

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 126 (0.79%) | 0 / 126 (0.00%) | 0 / 125 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |

Nervous system disorders

| | | | |
|---|---|---|---|
| **APHASIA** | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 0 / 126 (0.00%) | 1 / 125 (0.80%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **BRAIN MIDLINE SHIFT** | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 0 / 126 (0.00%) | 1 / 125 (0.80%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| **CARPAL TUNNEL SYNDROME** | | | |
| subjects affected / exposed | 1 / 126 (0.79%) | 0 / 126 (0.00%) | 0 / 125 (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 |
| **CEREBRAL HAEMORRHAGE** | | | |
| subjects affected / exposed | 1 / 126 (0.79%) | 0 / 126 (0.00%) | 0 / 125 (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 |
| **HEMIPARESIS** | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 0 / 126 (0.00%) | 1 / 125 (0.80%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **LOSS OF CONSCIOUSNESS** | | | |
| subjects affected / exposed | 1 / 126 (0.79%) | 0 / 126 (0.00%) | 3 / 125 (2.40%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **PROGRESSIVE SUPRANUCLEAR PALSY** | | | |
| subjects affected / exposed | 4 / 126 (3.17%) | 1 / 126 (0.79%) | 2 / 125 (1.60%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| **SEIZURE** | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 1 / 126 (0.79%) | 0 / 125 (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 |
| **SPINAL STROKE** | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 126 (0.00%) | 0 / 126 (0.00%) | 1 / 125 (0.80%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| **SUBDURAL HYGROMA** | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 0 / 126 (0.00%) | 1 / 125 (0.80%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **SYNCOPE** | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 2 / 126 (1.59%) | 0 / 125 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Blood and lymphatic system disorders** | | | |
| **LEUKOCYTOSIS** | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 0 / 126 (0.00%) | 1 / 125 (0.80%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| **Eye disorders** | | | |
| **CATARACT** | | | |
| subjects affected / exposed | 1 / 126 (0.79%) | 0 / 126 (0.00%) | 1 / 125 (0.80%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **EYE SWELLING** | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 0 / 126 (0.00%) | 1 / 125 (0.80%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **OCULAR HYPERAEMIA** | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 0 / 126 (0.00%) | 1 / 125 (0.80%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Gastrointestinal disorders** | | | |
| **COLITIS ISCHAEMIC** | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 0 / 126 (0.00%) | 1 / 125 (0.80%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| **DYSPHAGIA** | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 0 / 126 (0.00%) | 2 / 125 (1.60%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **ENTEROVESICAL FISTULA** | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 0 / 126 (0.00%) | 1 / 125 (0.80%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **GASTRIC PERFORATION** | | | |
| subjects affected / exposed | 1 / 126 (0.79%) | 0 / 126 (0.00%) | 0 / 125 (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 |
| **GASTROINTESTINAL HAEMORRHAGE** | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 2 / 126 (1.59%) | 1 / 125 (0.80%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| **GASTROINTESTINAL HYPERMOTILITY** | | | |
| subjects affected / exposed | 1 / 126 (0.79%) | 0 / 126 (0.00%) | 0 / 125 (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 |
| **INTESTINAL OBSTRUCTION** | | | |
| subjects affected / exposed | 1 / 126 (0.79%) | 1 / 126 (0.79%) | 0 / 125 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| **PANCREATITIS** | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 1 / 126 (0.79%) | 0 / 125 (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 |
| **VOMITING** | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 0 / 126 (0.00%) | 1 / 125 (0.80%) |
| 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 | | | |

| | | | |
|---|---|---|---|
| **BILE DUCT STONE** | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 1 / 126 (0.79%) | 0 / 125 (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 and urinary disorders** | | | |
| ACUTE KIDNEY INJURY | | | |
| subjects affected / exposed | 1 / 126 (0.79%) | 0 / 126 (0.00%) | 0 / 125 (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 |
| BLADDER OBSTRUCTION | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 1 / 126 (0.79%) | 0 / 125 (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 |
| DYSURIA | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 0 / 126 (0.00%) | 1 / 125 (0.80%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| MICTURITION DISORDER | | | |
| subjects affected / exposed | 1 / 126 (0.79%) | 0 / 126 (0.00%) | 0 / 125 (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 |
| NOCTURIA | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 1 / 126 (0.79%) | 0 / 125 (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 |
| URETEROLITHIASIS | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 1 / 126 (0.79%) | 0 / 125 (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 |
| URINARY RETENTION | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 1 / 126 (0.79%) | 0 / 125 (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 |
| **Musculoskeletal and connective tissue** | | | |

| disorders | | | |
|---|---|---|---|
| **MUSCLE RIGIDITY** | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 0 / 126 (0.00%) | 1 / 125 (0.80%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **MUSCULOSKELETAL CHEST PAIN** | | | |
| subjects affected / exposed | 1 / 126 (0.79%) | 0 / 126 (0.00%) | 0 / 125 (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 |
| **OSTEOARTHRITIS** | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 0 / 126 (0.00%) | 1 / 125 (0.80%) |
| 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** | | | |
| **CELLULITIS** | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 2 / 126 (1.59%) | 0 / 125 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **CHOLECYSTITIS INFECTIVE** | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 0 / 126 (0.00%) | 1 / 125 (0.80%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **CYSTITIS** | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 0 / 126 (0.00%) | 1 / 125 (0.80%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **INFLUENZA** | | | |
| subjects affected / exposed | 1 / 126 (0.79%) | 0 / 126 (0.00%) | 0 / 125 (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 |
| **NASOPHARYNGITIS** | | | |
| subjects affected / exposed | 1 / 126 (0.79%) | 0 / 126 (0.00%) | 0 / 125 (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 |

| | | | |
|---|---|---|---|
| ORCHITIS | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 0 / 126 (0.00%) | 1 / 125 (0.80%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PNEUMONIA | | | |
| subjects affected / exposed | 4 / 126 (3.17%) | 1 / 126 (0.79%) | 3 / 125 (2.40%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| PNEUMONIA MYCOPLASMAL | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 1 / 126 (0.79%) | 0 / 125 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| SEPSIS | | | |
| subjects affected / exposed | 1 / 126 (0.79%) | 1 / 126 (0.79%) | 0 / 125 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| URINARY TRACT INFECTION | | | |
| subjects affected / exposed | 3 / 126 (2.38%) | 0 / 126 (0.00%) | 1 / 125 (0.80%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| DEHYDRATION | | | |
| subjects affected / exposed | 1 / 126 (0.79%) | 0 / 126 (0.00%) | 0 / 125 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| HYPOGLYCAEMIA | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 1 / 126 (0.79%) | 1 / 125 (0.80%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| MALNUTRITION | | | |
| subjects affected / exposed | 1 / 126 (0.79%) | 0 / 126 (0.00%) | 0 / 125 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Placebo | ABBV-8E12 2000mg | ABBV-8E12 4000mg |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 83 / 126 (65.87%) | 75 / 126 (59.52%) | 80 / 125 (64.00%) |
| Investigations | | | |
| WEIGHT DECREASED | | | |
| subjects affected / exposed | 11 / 126 (8.73%) | 10 / 126 (7.94%) | 13 / 125 (10.40%) |
| occurrences (all) | 12 | 12 | 15 |
| Injury, poisoning and procedural complications | | | |
| CONTUSION | | | |
| subjects affected / exposed | 17 / 126 (13.49%) | 16 / 126 (12.70%) | 23 / 125 (18.40%) |
| occurrences (all) | 23 | 20 | 30 |
| FALL | | | |
| subjects affected / exposed | 43 / 126 (34.13%) | 37 / 126 (29.37%) | 48 / 125 (38.40%) |
| occurrences (all) | 96 | 70 | 85 |
| SKIN ABRASION | | | |
| subjects affected / exposed | 15 / 126 (11.90%) | 11 / 126 (8.73%) | 8 / 125 (6.40%) |
| occurrences (all) | 27 | 16 | 9 |
| SKIN LACERATION | | | |
| subjects affected / exposed | 19 / 126 (15.08%) | 17 / 126 (13.49%) | 21 / 125 (16.80%) |
| occurrences (all) | 29 | 19 | 26 |
| Nervous system disorders | | | |
| DIZZINESS | | | |
| subjects affected / exposed | 2 / 126 (1.59%) | 8 / 126 (6.35%) | 4 / 125 (3.20%) |
| occurrences (all) | 2 | 9 | 4 |
| HEADACHE | | | |
| subjects affected / exposed | 8 / 126 (6.35%) | 9 / 126 (7.14%) | 4 / 125 (3.20%) |
| occurrences (all) | 13 | 11 | 4 |
| General disorders and administration site conditions | | | |
| FATIGUE | | | |
| subjects affected / exposed | 2 / 126 (1.59%) | 9 / 126 (7.14%) | 4 / 125 (3.20%) |
| occurrences (all) | 9 | 19 | 4 |
| Gastrointestinal disorders | | | |
| CONSTIPATION | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 7 / 126 (5.56%) | 9 / 126 (7.14%) | 6 / 125 (4.80%) |
| occurrences (all) | 7 | 12 | 6 |
| **DIARRHOEA** | | | |
| subjects affected / exposed | 6 / 126 (4.76%) | 10 / 126 (7.94%) | 8 / 125 (6.40%) |
| occurrences (all) | 6 | 10 | 10 |
| **Respiratory, thoracic and mediastinal disorders** | | | |
| **COUGH** | | | |
| subjects affected / exposed | 9 / 126 (7.14%) | 5 / 126 (3.97%) | 5 / 125 (4.00%) |
| occurrences (all) | 10 | 6 | 5 |
| **Skin and subcutaneous tissue disorders** | | | |
| **RASH** | | | |
| subjects affected / exposed | 8 / 126 (6.35%) | 4 / 126 (3.17%) | 3 / 125 (2.40%) |
| occurrences (all) | 8 | 4 | 3 |
| **Psychiatric disorders** | | | |
| **ANXIETY** | | | |
| subjects affected / exposed | 7 / 126 (5.56%) | 2 / 126 (1.59%) | 0 / 125 (0.00%) |
| occurrences (all) | 8 | 2 | 0 |
| **DEPRESSION** | | | |
| subjects affected / exposed | 8 / 126 (6.35%) | 10 / 126 (7.94%) | 3 / 125 (2.40%) |
| occurrences (all) | 8 | 12 | 3 |
| **INSOMNIA** | | | |
| subjects affected / exposed | 5 / 126 (3.97%) | 6 / 126 (4.76%) | 8 / 125 (6.40%) |
| occurrences (all) | 6 | 8 | 8 |
| **Musculoskeletal and connective tissue disorders** | | | |
| **MUSCULOSKELETAL PAIN** | | | |
| subjects affected / exposed | 8 / 126 (6.35%) | 3 / 126 (2.38%) | 8 / 125 (6.40%) |
| occurrences (all) | 8 | 3 | 8 |
| **Infections and infestations** | | | |
| **UPPER RESPIRATORY TRACT INFECTION** | | | |
| subjects affected / exposed | 8 / 126 (6.35%) | 5 / 126 (3.97%) | 6 / 125 (4.80%) |
| occurrences (all) | 9 | 5 | 9 |
| **URINARY TRACT INFECTION** | | | |
| subjects affected / exposed | 14 / 126 (11.11%) | 13 / 126 (10.32%) | 18 / 125 (14.40%) |
| occurrences (all) | 19 | 14 | 28 |

# More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol?  Yes

| Date | Amendment |
|---|---|
| 18 August 2016 | Amendment 1<br><br>• Updated body weight parameters to infusion times<br>• Revised reference to 2 DMCs to 1 DMC who will review all clinical trial data of ABBV-8E12<br>• Revised Exclusion Criterion 1 to adjust subject weight parameters for the safety of subjects who do not meet the minimum body weight requirement<br>• Updated the formatting to the Cranial Nerves relative to the assessment of supranuclear gaze palsy and slowing of vertical saccades<br>• Removed T2 weighted-gradient-echo EPI sequence, rsfMRI to minimize burden on subject and imaging sites<br>• Updated Table 5, Diagnostic Tools and Scale Order and Duration of Administration, to revise the administration time points of the PGI-C, and order for the CGI-S and CGI-C<br>• Adjusted Table 5, Legend, Diagnostic Tools and Scale Order and Duration of Administration<br>• Added an audiotaping component to the SEADL and UPDRS Part II<br>• Updated volume of blood drawn for Biomarker samples from 10 ml to 11 ml<br>• Added PK and ADA windows for Cohorts 1 and 2 (Section 5.3.1.2, Collection and Handling of Biomarker and Pharmacogenetic Research Samples).<br>• Addition of volume for the 0.9% Sodium Chloride Injection/Solution for Infusion<br>• Revised reference to the Product Complaint eCRF since Product Complaint reporting will be done through a Product Complaint Form (Section 6.2.2, Reporting) |
| 31 October 2016 | Amendment 2<br><br>• Updated Inclusion Criterion 1 to add a LAR to the subject informed consent and re-consenting process<br>• Updated Inclusion Criterion 6 to change the minimum study partner contact from 3 to 10 hours per week<br>• Modified vital sign parameters to include orthostatic measurements<br>• Added post-lumbar puncture observation recommendation<br>• Adjusted Table 5, Diagnostic Tools and Scale Order and Duration of Administration to include the NNIPPS-PPS; table was also modified to provide guidance on the order of scale administration at the Screening Visit, to include splitting the screening visit into 2 Screening Visits; and time points for selected scales were shifted to earlier visits<br>• The addition of an exploratory endpoint scale, NNIPPS-PPS<br>• The removal of the actigraphy assessments as an exploratory endpoint<br>• Shifted administration of the Letter Fluency assessment at Week 12/Day 85 and Week 36/Day 253 to Week 8/Day 57 and Week 32/Day 225. Also added the RBANS and Color Trails Test (Parts 1 and 2) at the additional time points |

| | |
|---|---|
| 26 January 2018 | **Amendment 3**<br><br>• Updated List of Abbreviations and Definition of Terms, to define Study Drug Infusion Visit and clarify that visit-specified procedures may be conducted over 2 consecutive days<br>• Updated Introduction, Differences Statement, and Selection of Doses in the Study sections to reflect current status of the SAD study<br>• Updated Overall Study Design and Plan: Description section to reflect anticipated number of participating sites due to an increase in the number of study subjects, and to update DMC members and review schedule in-line with the increased number of subjects.<br>• Updated Selection of Study Population section to provide additional definition on screen failures and note that under certain circumstances, re-screening may occur<br>• Updated Study Procedures and Vital Signs sections to remove requirement of obtaining body temperature by oral modality<br>• Updated Section Study Procedures, Central ECG Reading, Cohort 2, Day 1, to remove the post dose ECG collection<br>• Update Study Procedures, Clinical Laboratory Tests section to remove IgG as a required CSF Basic Lab<br>• Updated Study Procedures, Diagnostic Tools and Scale Order and Duration of Administration section, to correct the recommended scale order for the CGI-C, SEADL and UPDRS Part II scales and update the approximate administration duration for the CGIC-S and SEADL scales<br>• Updated Measurement Methods section, to clarify analysis of Serum and CSF Samples<br>• Updated Efficacy Variables section to further include secondary and exploratory variables and include additional variables.<br>• Updated Pharmacokinetic Variables section to clarify the analysis of ABBV-8E12 concentration in CSF<br>• Updated Interim Analyses, to clarify futility interim analyses.<br>• Updated Determination of Sample size, to reflect new sample size<br>• Updated Preparation/Reconstitution of Dosage Form, Blinding, and Drug Accountability, to provide additional guidance on Investigational Product (IP) blinding and accountability. |
| 19 October 2018 | **Amendment 4**<br><br>• Updated Study Procedures, and Study Activities sections to reflect the current diagnostic tools, scale order and duration and study activities in order to reflect the current diagnostic tools, scale order and duration and study activities for all countries.<br>• Updated the Treatment Administered section to define the study drug infusion rate during the study in order to reduce study drug infusion time in the 1000 mg/10 mL formulation. Other revisions were made throughout the protocol, including the synopsis, to merge country-specific languages. |
| 13 December 2018 | **Amendment 5**<br><br>• Updated Study Procedures and Study Activities sections to add Progressive Supranuclear Palsy (PSP) clinical features during the Screening Period in order to gather more specific data regarding PSP signs and symptoms prior to enrollment in the trial<br>• Updated Study Activities section to add telephone contacts at Weeks 12, 24, 36, and 52 for subjects who prematurely discontinue in order to learn about the condition of subjects since their premature discontinuation from the study |

Notes:

---

## Interruptions (globally)

Were there any global interruptions to the trial?  No

## Limitations and caveats

---

None reported