



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	<ul style="list-style-type: none">• New data added to full data set Additional data added for one ednpoint.

Trial information

Trial identification

Sponsor protocol code	M15-562
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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
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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	Spain: 6
Country: Number of subjects enrolled	United States: 202
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
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
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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
Other, not specified	62	58	58
Withdrew consent	6	8	10
Adverse event, non-fatal	7	8	7
Lost to follow-up	1	-	2

Baseline characteristics

Reporting groups

Reporting group title	Placebo
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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
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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
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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
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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
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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
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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
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Subject analysis set type	Per protocol
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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
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Subject analysis set type	Per protocol
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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
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Subject analysis set type	Per protocol
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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
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Subject analysis set type	Per protocol
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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
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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
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End point timeframe:

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
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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
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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
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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)
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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 (Ctough)

End point title	Serum Concentration of ABBV-8E12 Prior to Infusion of a Day of Dosing (Ctough)
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End point description:

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

End point type	Secondary
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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

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
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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
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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)
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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
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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
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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)
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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)
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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
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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
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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)
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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
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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)
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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
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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
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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
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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)
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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
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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	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
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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
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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)
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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
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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
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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
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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
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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
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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 TESA 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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.0
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Reporting groups

Reporting group title	Placebo
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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
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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
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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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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

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%)
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
Investigations			
WEIGHT DECREASED			
subjects affected / exposed	11 / 126 (8.73%)	10 / 126 (7.94%)	13 / 125 (10.40%)
occurrences (all)	12	12	15
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
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
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
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
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
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	<p>Amendment 1</p> <ul style="list-style-type: none">• Updated body weight parameters to infusion times• Revised reference to 2 DMCs to 1 DMC who will review all clinical trial data of ABBV-8E12• Revised Exclusion Criterion 1 to adjust subject weight parameters for the safety of subjects who do not meet the minimum body weight requirement• Updated the formatting to the Cranial Nerves relative to the assessment of supranuclear gaze palsy and slowing of vertical saccades• Removed T2 weighted-gradient-echo EPI sequence, rsfMRI to minimize burden on subject and imaging sites• 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• Adjusted Table 5, Legend, Diagnostic Tools and Scale Order and Duration of Administration• Added an audiotaping component to the SEADL and UPDRS Part II• Updated volume of blood drawn for Biomarker samples from 10 ml to 11 ml• Added PK and ADA windows for Cohorts 1 and 2 (Section 5.3.1.2, Collection and Handling of Biomarker and Pharmacogenetic Research Samples).• Addition of volume for the 0.9% Sodium Chloride Injection/Solution for Infusion• 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	<p>Amendment 2</p> <ul style="list-style-type: none">• Updated Inclusion Criterion 1 to add a LAR to the subject informed consent and re-consenting process• Updated Inclusion Criterion 6 to change the minimum study partner contact from 3 to 10 hours per week• Modified vital sign parameters to include orthostatic measurements• Added post-lumbar puncture observation recommendation• 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• The addition of an exploratory endpoint scale, NNIPPS-PPS• The removal of the actigraphy assessments as an exploratory endpoint• 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	<p>Amendment 3</p> <ul style="list-style-type: none"> • 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 • Updated Introduction, Differences Statement, and Selection of Doses in the Study sections to reflect current status of the SAD study • 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. • Updated Selection of Study Population section to provide additional definition on screen failures and note that under certain circumstances, re-screening may occur • Updated Study Procedures and Vital Signs sections to remove requirement of obtaining body temperature by oral modality • Updated Section Study Procedures, Central ECG Reading, Cohort 2, Day 1, to remove the post dose ECG collection • Update Study Procedures, Clinical Laboratory Tests section to remove IgG as a required CSF Basic Lab • 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 • Updated Measurement Methods section, to clarify analysis of Serum and CSF Samples • Updated Efficacy Variables section to further include secondary and exploratory variables and include additional variables. • Updated Pharmacokinetic Variables section to clarify the analysis of ABBV-8E12 concentration in CSF • Updated Interim Analyses, to clarify futility interim analyses. • Updated Determination of Sample size, to reflect new sample size • Updated Preparation/Reconstitution of Dosage Form, Blinding, and Drug Accountability, to provide additional guidance on Investigational Product (IP) blinding and accountability.
19 October 2018	<p>Amendment 4</p> <ul style="list-style-type: none"> • 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. • 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	<p>Amendment 5</p> <ul style="list-style-type: none"> • 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 • 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