



Clinical trial results:

A Placebo-Controlled, Double-Blind, Parallel-Group, 24 Month Study With an Open-Label Extension Phase to Evaluate the Efficacy and Safety of Elenbecestat (E2609) in Subjects With Early Alzheimer's Disease Summary

EudraCT number	2016-003928-23
Trial protocol	GB ES CZ AT BG GR FR
Global end of trial date	15 January 2020

Results information

Result version number	v1 (current)
This version publication date	19 December 2023
First version publication date	30 January 2021

Trial information

Trial identification

Sponsor protocol code	E2609-G000-301
-----------------------	----------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02956486
WHO universal trial number (UTN)	-
Other trial identifiers	IND Number: 109308

Notes:

Sponsors

Sponsor organisation name	Eisai Ltd.
Sponsor organisation address	Mosquito Way, Hatfield, Hertfordshire, United Kingdom, AL10 9SN
Public contact	Eisai Medical Information, Eisai Ltd., +1 888-274-2378, esi_medinfo@eisai.com
Scientific contact	Eisai Medical Information, Eisai Ltd., +1 888-274-2378, esi_medinfo@eisai.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 January 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	15 January 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine whether elenbecestat (E2609) is superior to placebo on the change from baseline in the Clinical Dementia Rating - Sum Of Boxes (CDR-SB) at 24 months in subjects with Early Alzheimer's Disease (EAD)

Protection of trial subjects:

This study was conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following: - Principles of the World Medical Association Declaration of Helsinki (World Medical Association, 2008). - International Council on Harmonisation (ICH) E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. - Title 21 of the United States (US) Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and Institutional Review Board (IRB) regulations and applicable sections of US 21 CFR Part 312. - European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union (EU) country. All suspected unexpected serious adverse reactions were reported, as required, to the Competent Authorities of all involved EU member states. - Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP Subject Information and Informed Consent.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 October 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	Poland: 71
Country: Number of subjects enrolled	Spain: 101
Country: Number of subjects enrolled	United Kingdom: 154
Country: Number of subjects enrolled	Austria: 7
Country: Number of subjects enrolled	Bulgaria: 19
Country: Number of subjects enrolled	Czech Republic: 65
Country: Number of subjects enrolled	France: 54
Country: Number of subjects enrolled	Germany: 51
Country: Number of subjects enrolled	Greece: 15
Country: Number of subjects enrolled	China: 64
Country: Number of subjects enrolled	Croatia: 9

Country: Number of subjects enrolled	Hungary: 9
Country: Number of subjects enrolled	Russian Federation: 3
Country: Number of subjects enrolled	Slovakia: 38
Country: Number of subjects enrolled	Japan: 303
Country: Number of subjects enrolled	Canada: 49
Country: Number of subjects enrolled	United States: 823
Country: Number of subjects enrolled	Singapore: 11
Country: Number of subjects enrolled	Korea, Republic of: 84
Country: Number of subjects enrolled	Taiwan: 8
Country: Number of subjects enrolled	Argentina: 74
Country: Number of subjects enrolled	Chile: 17
Country: Number of subjects enrolled	Mexico: 4
Country: Number of subjects enrolled	Australia: 49
Country: Number of subjects enrolled	Denmark: 17
Country: Number of subjects enrolled	Finland: 4
Country: Number of subjects enrolled	Italy: 55
Country: Number of subjects enrolled	Portugal: 19
Country: Number of subjects enrolled	South Africa: 27
Worldwide total number of subjects	2204
EEA total number of subjects	688

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)	341
From 65 to 84 years	1841
85 years and over	22

Subject disposition

Recruitment

Recruitment details:

Subjects took part at 426 investigative sites in China,Bulgaria,Croatia,Czech Republic,Greece,Hungary,Poland,Russia,Slovakia,Japan,Canada,Singapore,South Korea,Taiwan,Argentina,Chile,Mexico,Australia,Austria,Denmark,Finland,France,Germany,Italy,Portugal, South Africa,Spain,United Kingdom and United States from 20 October 2016 to 15 January 2020.

Pre-assignment

Screening details:

This study included 2 parts: Core Phase and Extension Phase. A total of 9758 subjects were screened, of which 7546 subjects were screen failures and 2212 subjects were randomized in the study. The data for the studies E2609-G000-301 (NCT02956486, MissionAD1) and E2609-G000-302 (NCT03036280, MissionAD2) was pooled.

Period 1

Period 1 title	Core Phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Core Phase: Placebo

Arm description:

Subjects received one elenbecestat matching-placebo tablet, orally, once daily in the morning with or without food up to 24 months. Subjects were followed up for 3 months after last dose of elenbecestat matched placebo in core phase.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received one elenbecestat matching-placebo tablet, orally, once daily in the morning with or without food up to 24 months. Subjects were followed up for 3 months after last dose of elenbecestat matched placebo in core phase.

Arm title	Core Phase: Elenbecestat 50 mg
------------------	--------------------------------

Arm description:

Subjects received one elenbecestat 50 milligram (mg) tablet, orally, once daily in the morning with or without food up to 24 months. Subjects were followed up for 3 months after last dose of elenbecestat in core phase.

Arm type	Experimental
Investigational medicinal product name	Elenbecestat
Investigational medicinal product code	
Other name	E2609
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received one elenbecestat 50 mg tablet, orally, once daily in the morning with or without food up to 24 months. Subjects were followed up for 3 months after last dose of elenbecestat in core phase.

Number of subjects in period 1	Core Phase: Placebo	Core Phase: Elenbecestat 50 mg
Started	1105	1099
Full Analysis Set (FAS)	1084	1062
Completed	29	32
Not completed	1076	1067
Consent withdrawn by subject	99	102
Adverse Event	51	88
Not specified	26	18
Study terminated by sponsor	888	848
Lost to follow-up	8	6
Inadequate therapeutic effect	4	5

Period 2

Period 2 title	Extension Phase
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Extension Phase: Elenbecestat 50 mg
------------------	-------------------------------------

Arm description:

Eligible subjects who completed the core phase entered the extension phase and received one elenbecestat 50 mg tablet, orally, once daily in the morning with or without food until commercial availability of elenbecestat, or a lack of positive benefit-risk assessment was determined, whichever occurred first. Subjects were followed up for 1 month after the last dose of elenbecestat in the extension phase.

Arm type	Experimental
Investigational medicinal product name	Elenbecestat
Investigational medicinal product code	
Other name	E2609
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Eligible subjects who completed the core phase entered the extension phase and received one elenbecestat 50 mg tablet, orally, once daily in the morning with or without food until commercial availability of elenbecestat, or a lack of positive benefit-risk assessment was determined, whichever occurred first (up to a maximum of 5 months). Subjects were followed up for 1 month after last dose of elenbecestat in extension phase.

Number of subjects in period 2 ^[1]	Extension Phase: Elenbecestat 50 mg
Started	18
Completed	0
Not completed	18
Adverse Event	2
Study terminated by sponsor	16

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Only eligible subjects who completed core and consented for extension phase, entered extension phase.

Baseline characteristics

Reporting groups

Reporting group title	Core Phase: Placebo
-----------------------	---------------------

Reporting group description:

Subjects received one elenbecestat matching-placebo tablet, orally, once daily in the morning with or without food up to 24 months. Subjects were followed up for 3 months after last dose of elenbecestat matched placebo in core phase.

Reporting group title	Core Phase: Elenbecestat 50 mg
-----------------------	--------------------------------

Reporting group description:

Subjects received one elenbecestat 50 milligram (mg) tablet, orally, once daily in the morning with or without food up to 24 months. Subjects were followed up for 3 months after last dose of elenbecestat in core phase.

Reporting group values	Core Phase: Placebo	Core Phase: Elenbecestat 50 mg	Total
Number of subjects	1105	1099	2204
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	72.1 ± 7.09	71.9 ± 7.18	-
Gender categorical Units: Subjects			
Female	592	534	1126
Male	513	565	1078
Ethnicity Units: Subjects			
Hispanic or Latino	162	158	320
Not Hispanic or Latino	943	941	1884
Race Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	233	247	480
Native Hawaiian or Other Pacific Islander	0	2	2
Black or African American	12	22	34
White	851	817	1668
Unknown or Not Reported	8	11	19

End points

End points reporting groups

Reporting group title	Core Phase: Placebo
Reporting group description: Subjects received one elenbecestat matching-placebo tablet, orally, once daily in the morning with or without food up to 24 months. Subjects were followed up for 3 months after last dose of elenbecestat matched placebo in core phase.	
Reporting group title	Core Phase: Elenbecestat 50 mg
Reporting group description: Subjects received one elenbecestat 50 milligram (mg) tablet, orally, once daily in the morning with or without food up to 24 months. Subjects were followed up for 3 months after last dose of elenbecestat in core phase.	
Reporting group title	Extension Phase: Elenbecestat 50 mg
Reporting group description: Eligible subjects who completed the core phase entered the extension phase and received one elenbecestat 50 mg tablet, orally, once daily in the morning with or without food until commercial availability of elenbecestat, or a lack of positive benefit-risk assessment was determined, whichever occurred first. Subjects were followed up for 1 month after the last dose of elenbecestat in the extension phase.	

Primary: Core Phase: Change From Baseline up to Month 24 in the Clinical Dementia Rating-sum of Boxes (CDR-SB) Score

End point title	Core Phase: Change From Baseline up to Month 24 in the Clinical Dementia Rating-sum of Boxes (CDR-SB) Score
End point description: Clinical dementia rating(CDR)scale is a clinical global rating scale that requires interviewing both subject and informant who knows and has contact with subject.CDR scale:clinician directed assessment of both cognition and function, and is intended to capture state and therefore disease stage of subject.CDR scale:6 domains of subject function (memory, orientation, judgement and problem solving, community affairs, home and hobbies and personal care) on a 5-point scale in which no impairment=0, questionable impairment=0.5, mild impairment=1, moderate impairment=2 and severe impairment=3.CDR-SB:sum of individual domain scores and ranges from 0 to 18.Higher score indicates more impairment.FAS: group of randomized subjects who received at least 1 dose of drug in core phase and had baseline and at least 1 post-dose primary efficacy measurement.Subjects analyzed:all subjects included in mixed effects model for repeated measures (MMRM) who were evaluable this specific outcome measure.	
End point type	Primary
End point timeframe: Baseline (Day 1: before first dose in the core phase) up to Month 24 of the core phase	

End point values	Core Phase: Placebo	Core Phase: Elenbecestat 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1078	1053		
Units: score on a scale				
least squares mean (standard error)	2.17 (± 0.142)	1.99 (± 0.146)		

Statistical analyses

Statistical analysis title	Core Phase: Placebo,Core Phase: Elenbecestat 50 mg
Statistical analysis description: Analysis was based on the MMRM and factors for treatment group, visit, treatment group by visit interaction, clinical disease staging (mild cognitive impairment [MCI]/Prodromal, mild alzheimer'sdisease [AD]), concurrent AD medication use, region, apolipoprotein E (ApoE4) status (positive, negative) as fixed effects, and the baseline value and the baseline value by visit interaction as covariate.	
Comparison groups	Core Phase: Placebo v Core Phase: Elenbecestat 50 mg
Number of subjects included in analysis	2131
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.385
Method	MMRM
Parameter estimate	Least Square (LS) Mean Difference
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.57
upper limit	0.22

Primary: Extension Phase: Number of Subjects Reporting One or More Treatment-emergent Adverse Events (TEAEs)

End point title	Extension Phase: Number of Subjects Reporting One or More Treatment-emergent Adverse Events (TEAEs) ^[1]
-----------------	--

End point description:

A TEAE is defined as an adverse event that emerged during treatment or within 28 days following the last dose of study drug, having been absent at pretreatment (Baseline) or reemerged during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or worsened in severity during treatment relative to the pretreatment state, when the adverse event was continuous. Number of subjects with TEAEs (serious and non-serious adverse events) were reported based on their safety assessments of laboratory tests, suicidal ideation and suicidal behavior, drug abuse potential, physical examination, neurological examination, regular measurement of vital signs, magnetic resonance imaging and electrocardiogram parameter values. All safety subjects was the group of subjects who enrolled into the extension phase and received at least 1 dose of study drug in the extension phase.

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

End point timeframe:

From first dose of study drug up to approximately 6 months (including 1 month follow up) for the extension phase

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Extension Phase: Elenbecestat 50 mg			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: subjects	6			

Statistical analyses

No statistical analyses for this end point

Secondary: Core Phase: Change From Baseline up to Month 24 in Alzheimer's Disease Composite Score (ADCOMS)

End point title	Core Phase: Change From Baseline up to Month 24 in Alzheimer's Disease Composite Score (ADCOMS)
-----------------	---

End point description:

ADCOMS is a weighted linear combination of 12 items from three existing clinical scales: the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog), the Mini Mental State Examination (MMSE), and the CDR. Four items are from the ADAS-cog (A4 [Delayed Word Recall], A7 [Orientation], A8 [Word Recognition], A11 [Word Finding]); 2 items are from the MMSE (M1 [Orientation Time], M7 [Drawing]); 6 items are from the CDR (C1 [Personal Care], C2 [Community Affairs], C3 [Home and Hobbies], C4 [Judgment and Problem Solving], C5 [Memory], C6 [Orientation]). Composite score is derived from the variables from the 12 items, and ranges from 0 to 1.97, where higher score indicates worse performance. The FAS was the group of randomized subjects who received at least 1 dose of study drug in the core phase and had baseline and at least 1 post-dose primary efficacy measurement. Here "subjects analyzed" signifies all subjects included in MMRM who were evaluable for this specific outcome measure.

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

End point timeframe:

Baseline (Day 1: before first dose in the core phase) up to Month 24 of the core phase

End point values	Core Phase: Placebo	Core Phase: Elenbecestat 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1018	981		
Units: score on a scale				
least squares mean (standard error)	0.24 (\pm 0.014)	0.23 (\pm 0.015)		

Statistical analyses

Statistical analysis title	Core Phase: Placebo, Core Phase: Elenbecestat 50 mg
----------------------------	---

Statistical analysis description:

Analysis was based on the MMRM and factors for treatment group, visit, treatment group by visit interaction, clinical disease staging (MCI/Prodromal, mild AD), concurrent AD medication use, region, ApoE4 status (positive, negative) as fixed effects, and the baseline value and the baseline value by visit interaction as covariate.

Comparison groups	Core Phase: Placebo v Core Phase: Elenbecestat 50 mg
-------------------	--

Number of subjects included in analysis	1999
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.345
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.02

Secondary: Core Phase: Change From Baseline up to Month 24 in Amyloid Positron Emission Tomography (PET) Standardized Uptake Value Ratio (SUVR)

End point title	Core Phase: Change From Baseline up to Month 24 in Amyloid Positron Emission Tomography (PET) Standardized Uptake Value Ratio (SUVR)
-----------------	--

End point description:

Amyloid PET scan assesses cerebral amyloid load using 3 tracers (florbetapir, florbetaben and flutemetamol) which is standardized into centiloids for evaluation of AD. Centiloid values on centiloid scale is based on mean composite SUVR in cingulate, frontal, parietal and temporal cortexes using whole cerebellum as reference region. SUVR is ratio of tracer uptake in each of cingulate, frontal, parietal and temporal cortexes relative to cerebellum. The centiloid scale anchor points are 0 and 100, where 0 represents a high-certainty amyloid negative scan and 100 represents the amount of global amyloid deposition found in a typical AD scans. The pharmacodynamic (PD) analysis set was the group of subjects in the core phase who had sufficient PD data to derive at least 1 PD parameter. Here "subjects analyzed" signifies all subjects included in MMRM who were evaluable for this specific outcome measure.

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

End point timeframe:

Baseline (Day 1: before first dose in the core phase) up to Month 24 of the core phase

End point values	Core Phase: Placebo	Core Phase: Elenbecestat 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	268	248		
Units: score on a scale				
least squares mean (standard error)	7.81 (± 2.500)	-5.02 (± 2.046)		

Statistical analyses

Statistical analysis title	Core Phase: Placebo, Core Phase: Elenbecestat 50 mg
----------------------------	---

Statistical analysis description:

Analysis was based on the MMRM and factors for treatment group, visit, treatment group by visit interaction, clinical disease staging (MCI/Prodromal, mild AD), concurrent AD medication use, region, ApoE4 status (positive, negative) as fixed effects, and the baseline value and the baseline value by visit interaction as covariate.

Comparison groups	Core Phase: Elenbecestat 50 mg v Core Phase: Placebo
Number of subjects included in analysis	516
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-12.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.79
upper limit	-6.88

Secondary: Core Phase: Change From Baseline up to Month 24 in the CDR-SB Score for Subjects Enriched by Baseline Amyloid PET SUVR Between 1.2 and 1.6

End point title	Core Phase: Change From Baseline up to Month 24 in the CDR-SB Score for Subjects Enriched by Baseline Amyloid PET SUVR Between 1.2 and 1.6
-----------------	--

End point description:

CDR scale: clinician directed assessment of both cognition and function, and is intended to capture state and disease stage of subject. CDR scale: 6 domains of subject function (memory, orientation, judgement and problem solving, community affairs, home and hobbies and personal care) on a 5-point scale in which no impairment=0, questionable impairment=0.5, mild impairment=1, moderate impairment=2 and severe impairment=3. CDR-SB: sum of individual domain scores and ranges from 0 to 18. Higher score indicates more impairment. Amyloid PET scans allow in vivo assessment of cerebral amyloid load. SUVR indicates ratio of tracer uptake in frontal cortex relative to cerebellum or ratio of tracer uptake in whole brain relative to cerebellum.FAS:group of randomized subjects who received at least 1 dose of drug in core phase and had baseline and at least 1 post-dose primary efficacy measurement.Subjects analyzed:all subjects included in MMRM who were evaluable for this specific outcome measure.

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

End point timeframe:

Baseline (Day 1: before first dose in the core phase) up to Month 24 of the core phase

End point values	Core Phase: Placebo	Core Phase: Elenbecestat 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	664	617		
Units: score on a scale				
least squares mean (standard error)	1.97 (± 0.157)	1.74 (± 0.169)		

Statistical analyses

Statistical analysis title	Core Phase: Placebo,Core Phase: Elenbecestat 50 mg
----------------------------	--

Statistical analysis description:

Analysis was based on the MMRM and factors for treatment group, visit, treatment group by visit

interaction, clinical disease staging (MCI/Prodromal, mild AD), concurrent AD medication use, region, ApoE4 status (positive, negative) as fixed effects, and the baseline value and the baseline value by visit interaction as covariate.

Comparison groups	Core Phase: Placebo v Core Phase: Elenbecestat 50 mg
Number of subjects included in analysis	1281
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.316
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.67
upper limit	0.22

Secondary: Core Phase: Change From Baseline up to Month 24 in the ADCOMS for Subjects Enriched by Baseline Amyloid PET SUVR Between 1.2 and 1.6

End point title	Core Phase: Change From Baseline up to Month 24 in the ADCOMS for Subjects Enriched by Baseline Amyloid PET SUVR Between 1.2 and 1.6
-----------------	--

End point description:

ADCOMS:weighted linear combination of 12 items from 3 existing clinical scales:ADAS-cog,MMSE,and CDR.Four items are from the ADAS-cog(A4[Delayed Word Recall],A7[Orientation],A8[Word Recognition],A11[Word Finding]);2 items are from the MMSE(M1[Orientation Time],M7[Drawing]);6 items are from the CDR(C1[Personal Care],C2[Community Affairs],C3[Home and Hobbies],C4[Judgment and Problem Solving],C5[Memory],C6[Orientation]).Composite score:derived from variables from 12 items,and ranges from 0 to 1.97,where higher score indicates worse performance.Amyloid PET scans allow in vivo assessment of cerebral amyloid load.SUVR indicates ratio of tracer uptake in frontal cortex relative to cerebellum or ratio of tracer uptake in whole brain relative to cerebellum.FAS:randomized subjects who received at least 1 dose of drug in core phase and had baseline and at least 1 postdose primary efficacy measurement.Subjects analyzed:all subjects in MMRM who were evaluable for this specific outcome measure.

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

End point timeframe:

Baseline (Day 1: before first dose in the core phase) up to Month 24 of the core phase

End point values	Core Phase: Placebo	Core Phase: Elenbecestat 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	627	571		
Units: score on a scale				
least squares mean (standard error)	0.23 (± 0.017)	0.20 (± 0.018)		

Statistical analyses

Statistical analysis title	Core Phase: Placebo,Core Phase: Elenbecestat 50 mg
Statistical analysis description:	
Analysis was based on the MMRM and factors for treatment group, visit, treatment group by visit interaction, clinical disease staging (MCI/Prodromal, mild AD), concurrent AD medication use, region, ApoE4 status (positive, negative) as fixed effects, and the baseline value and the baseline value by visit interaction as covariate.	
Comparison groups	Core Phase: Placebo v Core Phase: Elenbecestat 50 mg
Number of subjects included in analysis	1198
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.254
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.02

Secondary: Core Phase: Change Per Year (Mean Slope) in CDR-SB Score up to Month 24

End point title	Core Phase: Change Per Year (Mean Slope) in CDR-SB Score up to Month 24
-----------------	---

End point description:

CDR scale:clinical global rating scale that requires interviewing both the subject and an informant who knows and has contact with subject.CDR scale is a clinician directed assessment of both cognition and function,and is intended to capture state and disease stage of subject. CDR scale:6 domains of subject function(memory,orientation,judgement and problem solving,community affairs,home and hobbies and personal care)on a 5-point scale in which no impairment=0,questionable impairment=0.5,mild impairment=1,moderate impairment=2 and severe impairment=3.CDR-SB:sum of individual domain scores and ranges from 0 to 18.Higher score indicates more impairment.In this outcome measure,change per year(mean slope)in CDR-SB score was calculated up to month 24,where higher change indicated more impairment and lower change indicated less impairment.FAS:group of randomized subjects who received at least 1 dose of drug in core phase and had baseline and at least 1 post-dose primary efficacy measurement.

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

End point timeframe:

Up to Month 24 of the core phase

End point values	Core Phase: Placebo	Core Phase: Elenbecestat 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1084	1062		
Units: change in score per year				
least squares mean (confidence interval 95%)	0.934 (0.838 to 1.030)	0.926 (0.828 to 1.024)		

Statistical analyses

Statistical analysis title	Core Phase: Placebo,Core Phase: Elenbecestat 50 mg
Statistical analysis description: Based on the linear mixed effects model, which included assessment time and treatment group by assessment time interaction as covariate with random intercept and slope.	
Comparison groups	Core Phase: Placebo v Core Phase: Elenbecestat 50 mg
Number of subjects included in analysis	2146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9088
Method	Linear mixed effects model
Parameter estimate	Difference of Mean Slope
Point estimate	-0.008
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.145
upper limit	0.129

Secondary: Core Phase: Time to Worsening of CDR Score up to Month 24

End point title	Core Phase: Time to Worsening of CDR Score up to Month 24
End point description: CDR scale:requires interviewing both the subject and an informant who knows and has contact with the subject.CDR scale:clinician directed assessment of both cognition and function,and is intended to capture state and disease stage of subject. CDR scale assesses 6 domains of subject function(memory,orientation,judgement and problem solving,community affairs,home and hobbies and personal care)on a 5-point scale in which no impairment=0,questionable impairment=0.5,mild impairment=1,moderate impairment=2 and severe impairment=3.The global CDR score is computed via an algorithm and ranges from 0 to 3.Higher score indicates more impairment.In this outcome measure,time(in months)to worsening of CDR score(that is, an increase from baseline by at least 0.5 points on the global CDR scale on 2 consecutive scheduled visits)up to month 24 was calculated.FAS:randomized subjects who received at least 1 dose of drug in core phase and had baseline and at least 1 post dose primary efficacy measurement.	
End point type	Secondary
End point timeframe: Up to Month 24 of the core phase	

End point values	Core Phase: Placebo	Core Phase: Elenbecestat 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1084	1062		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (24.07 to 99999)		

Statistical analyses

Statistical analysis title	Core Phase: Placebo,Core Phase: Elenbecestat 50 mg
Statistical analysis description:	
Based on a Cox regression model which included treatment group, clinical disease staging (MCI/Prodromal, mild AD), concurrent AD medication use, region, APOE4 status (positive, negative) as covariate.	
Comparison groups	Core Phase: Placebo v Core Phase: Elenbecestat 50 mg
Number of subjects included in analysis	2146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6155
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.16

Secondary: Core Phase: Time to Conversion to Dementia for Subjects Who Were Not Clinically Staged as Having Dementia at the Core Phase Baseline up to Month 24

End point title	Core Phase: Time to Conversion to Dementia for Subjects Who Were Not Clinically Staged as Having Dementia at the Core Phase Baseline up to Month 24
End point description:	
Time (in months) to conversion to dementia for subjects who were not clinically staged as having dementia at the core phase baseline (that is time from randomization to conversion to dementia in clinical diagnosis). The FAS was the group of randomized subjects who received at least 1 dose of study drug in the core phase and had baseline and at least 1 post-dose primary efficacy measurement. Here "subjects analyzed" signifies subjects who were evaluable for this outcome measure.	
End point type	Secondary
End point timeframe:	
Baseline (Day 1: before first dose in the core phase) up to Month 24 of the core phase	

End point values	Core Phase: Placebo	Core Phase: Elenbecestat 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	902	901		
Units: months				
median (confidence interval 95%)	23.05 (21.14 to 24.66)	21.40 (20.45 to 24.43)		

Statistical analyses

Statistical analysis title	Core Phase: Placebo,Core Phase: Elenbecestat 50 mg
Statistical analysis description:	
Based on a Cox regression model which included treatment group, concurrent AD medication use, region, APOE4 status (positive, negative) as covariate.	
Comparison groups	Core Phase: Placebo v Core Phase: Elenbecestat 50 mg
Number of subjects included in analysis	1803
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1281
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.96
upper limit	1.35

Secondary: Core Phase: Change From Baseline up to Month 24 in the Alzheimer's Disease Assessment Scale-cognition14 (ADAS-Cog14) Score

End point title	Core Phase: Change From Baseline up to Month 24 in the Alzheimer's Disease Assessment Scale-cognition14 (ADAS-Cog14) Score
End point description:	
<p>ADAS-cog14 is a psychometric instrument that evaluates 14-items (Immediate Word-recall [0-10], Commands [0-5], Constructional Praxis [0-5], Delayed Word-recall [0-10], Naming Objects/Fingers [0-5], Ideational Praxis [0-5], Orientation[0-8], Word Recognition [0-12], Remembering Test Instructions [0-5], Comprehension[0-5], Word Finding Difficulty [0-5], Spoken Language Ability [0-5], Executive Function [0-5], and Number Cancellation [0-5] test). It is considered to be more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects. The total score ranges from 0 to 90. Higher score indicates more impairment. The FAS was the group of randomized subjects who received at least 1 dose of study drug in the core phase and had baseline and at least 1 post-dose primary efficacy measurement. Here "subjects analyzed" signifies all subjects included in MMRM who were evaluable for this specific outcome measure.</p>	
End point type	Secondary
End point timeframe:	
Baseline (Day 1: before first dose in the core phase) up to Month 24 of the core phase	

End point values	Core Phase: Placebo	Core Phase: Elenbecestat 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1010	972		
Units: score on a scale				
least squares mean (standard error)	5.38 (\pm 0.490)	4.95 (\pm 0.520)		

Statistical analyses

Statistical analysis title	Core Phase: Placebo,Core Phase: Elenbecestat 50 mg
Statistical analysis description:	
Analysis was based on the MMRM and factors for treatment group, visit, treatment group by visit interaction, clinical disease staging (MCI/Prodromal, mild AD), concurrent AD medication use, region, ApoE4 status (positive, negative) as fixed effects, and the baseline value and the baseline value by visit interaction as covariate.	
Comparison groups	Core Phase: Placebo v Core Phase: Elenbecestat 50 mg
Number of subjects included in analysis	1982
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.525
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.75
upper limit	0.9

Secondary: Core Phase: Change From Baseline up to Month 24 in the MMSE Score

End point title	Core Phase: Change From Baseline up to Month 24 in the MMSE Score
End point description:	
MMSE:for screening purposes,staging of disease severity and measured in AD to follow disease progression and treatment effects.MMSE:composed of 30 questions grouped into domains(Orientation to Time[0-5], Orientation to Place[0-5],Registration[0-3],Attention and Calculation[0-5],Recall[0-3],Naming[0-2],Repetition[0-1],Comprehension[0-3],Reading[0-1],Writing[0-1],Drawing[0-1]).For each of MMSE domains,six items are computed(Orientation to Time[0-5],Orientation to Place[0-5],Registration[0-3],Attention and Calculation[0-5],Recall[0-3],Language:Naming,Repetition,Comprehension,Reading,Writing,and Drawing[0-9]).MMSE Total Score(ranges 0 to 30)=sum of six domains.If any domain score is missing then total score is missing.Higher score indicates better function.FAS:Subjects who received at least 1 dose of drug in core phase and had baseline and at least 1 postdose primary efficacy measurement.Subjects analyzed:signifies all subjects in MMRM who were evaluable for this specific outcome measure.	
End point type	Secondary

End point timeframe:

Baseline (Day 1: before first dose in the core phase) up to Month 24 of the core phase

End point values	Core Phase: Placebo	Core Phase: Elenbecestat 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1056	1017		
Units: score on a scale				
least squares mean (standard error)	-2.87 (\pm 0.234)	-2.87 (\pm 0.241)		

Statistical analyses

Statistical analysis title	Core Phase: Placebo,Core Phase: Elenbecestat 50 mg
----------------------------	--

Statistical analysis description:

Analysis was based on the MMRM and factors for treatment group, visit, treatment group by visit interaction, clinical disease staging (MCI/Prodromal, mild AD), concurrent AD medication use, region, ApoE4 status (positive, negative) as fixed effects, and the baseline value and the baseline value by visit interaction as covariate.

Comparison groups	Core Phase: Elenbecestat 50 mg v Core Phase: Placebo
Number of subjects included in analysis	2073
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.977
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.64
upper limit	0.62

Secondary: Core Phase: Change From Baseline up to Month 24 in the Functional Assessment Questionnaire (FAQ) Score

End point title	Core Phase: Change From Baseline up to Month 24 in the Functional Assessment Questionnaire (FAQ) Score
-----------------	--

End point description:

FAQ scores 10 items & measures activities of daily living (paying bills/balancing checkbook, assembling tax records, shopping alone for clothes or groceries, playing game of skill such as bridge or chess/working on a hobby, heating water & turning off stove, preparing balanced meal, keeping track of current events, paying attention & understanding television program, remembering appointments, driving or traveling out of neighborhood). Each item is rated as 0=Normal, 1=Has difficulty but does by self, 2=Requires assistance, 3=Dependent, or 8=Not Applicable. The Total score is the sum of all 10 items & ranges from 0 to 30. Higher score indicates more impairment. If any activity is missed, then the total score is missed. FAS: group of randomized subjects who received at least 1 dose of study drug in the core phase and had baseline and at least 1 post-dose primary efficacy measurement. Subjects analyzed: all subjects included in MMRM who were evaluable for this specific outcome measure.

End point type	Secondary
End point timeframe:	
Baseline (Day 1: before first dose in the core phase) up to Month 24 of the core phase	

End point values	Core Phase: Placebo	Core Phase: Elenbecestat 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1038	1001		
Units: score on a scale				
least squares mean (standard error)	5.20 (\pm 0.448)	5.32 (\pm 0.459)		

Statistical analyses

Statistical analysis title	Core Phase: Placebo,Core Phase: Elenbecestat 50 mg
Statistical analysis description:	
Analysis was based on the MMRM and factors for treatment group, visit, treatment group by visit interaction, clinical disease staging (MCI/Prodromal, mild AD), concurrent AD medication use, region, ApoE4 status (positive, negative) as fixed effects, and the baseline value and the baseline value by visit interaction as covariate.	
Comparison groups	Core Phase: Placebo v Core Phase: Elenbecestat 50 mg
Number of subjects included in analysis	2039
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.854
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.09
upper limit	1.32

Secondary: Core Phase: Change From Baseline up to Month 24 in the ADAS-cog14 Word List (Immediate Recall and Delayed Recall) Score

End point title	Core Phase: Change From Baseline up to Month 24 in the ADAS-cog14 Word List (Immediate Recall and Delayed Recall) Score
-----------------	---

End point description:

The ADAS-cog14 Word List is a summation of two items: "Immediate Word-recall" and "Delayed Word-recall". Immediate Word-recall test: Subjects are asked to recall words and the number of "No" responses for each trial (total 3 trials) are summed. Subscore: sum of scores from 3 trials, divided by 3. Score ranges from 0 to 10. Delayed Word-recall: Subjects used to recall words after a delay and the number of "No" responses are summed. Score ranges from 0 to 10. The Total Score ranges from 0 to 20. Higher score indicates more impairment. The FAS was the group of randomized subjects who received at least 1 dose of study drug in the core phase and had baseline and at least 1 post-dose primary efficacy measurement. Here "subjects analyzed" signifies all subjects included in MMRM who

were evaluable for this specific outcome measure.

End point type	Secondary
End point timeframe:	
Baseline (Day 1: before first dose in the core phase) up to Month 24 of the core phase	

End point values	Core Phase: Placebo	Core Phase: Elenbecestat 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1050	1005		
Units: score on a scale				
least squares mean (standard error)	1.63 (± 0.195)	1.36 (± 0.207)		

Statistical analyses

Statistical analysis title	Core Phase: Placebo,Core Phase: Elenbecestat 50 mg
----------------------------	--

Statistical analysis description:

Analysis was based on the MMRM and factors for treatment group, visit, treatment group by visit interaction, clinical disease staging (MCI/Prodromal, mild AD), concurrent AD medication use, region, ApoE4 status (positive, negative) as fixed effects, and the baseline value and the baseline value by visit interaction as covariate.

Comparison groups	Core Phase: Placebo v Core Phase: Elenbecestat 50 mg
Number of subjects included in analysis	2055
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.314
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.79
upper limit	0.26

Secondary: Core Phase: Change From Baseline up to Month 24 in the Alzheimer's Disease Assessment Scale-cognition11 (ADAS-Cog11) Score

End point title	Core Phase: Change From Baseline up to Month 24 in the Alzheimer's Disease Assessment Scale-cognition11 (ADAS-Cog11) Score
-----------------	--

End point description:

ADAS-cog11 is a psychometric instrument that evaluates 11-items (Immediate Word-recall [0 to 10], Commands [0-5], Constructional Praxis [0-5], Naming Objects/Fingers [0-5], Ideational Praxis [0-5], Orientation[0-8], Word Recognition [0-12], Remembering Test Instructions [0-5], Comprehension[0-5], Word Finding Difficulty [0-5], Spoken Language Ability [0-5] test) and is considered more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects. The Total score ranges from 0 to 70. Higher score indicates more impairment. The FAS was the group of randomized subjects who received at least 1 dose of study drug in the core phase and had baseline and at least 1 post-dose

primary efficacy measurement. Here “subjects analyzed” signifies all subjects included in MMRM who were evaluable for this specific outcome measure.

End point type	Secondary
End point timeframe:	
Baseline (Day 1: before first dose in the core phase) up to Month 24 of the core phase	

End point values	Core Phase: Placebo	Core Phase: Elenbecestat 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1010	972		
Units: score on a scale				
least squares mean (standard error)	4.11 (± 0.370)	4.18 (± 0.391)		

Statistical analyses

Statistical analysis title	Core Phase: Placebo,Core Phase: Elenbecestat 50 mg
Statistical analysis description:	
Analysis was based on the MMRM and factors for treatment group, visit, treatment group by visit interaction, clinical disease staging (MCI/Prodromal, mild AD), concurrent AD medication use, region, ApoE4 status (positive, negative) as fixed effects, and the baseline value and the baseline value by visit interaction as covariate.	
Comparison groups	Core Phase: Placebo v Core Phase: Elenbecestat 50 mg
Number of subjects included in analysis	1982
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.895
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.93
upper limit	1.07

Secondary: Core Phase: Change From Last Dose in the CDR-SB Score

End point title	Core Phase: Change From Last Dose in the CDR-SB Score
End point description:	

CDR scale: a clinical global rating scale that requires interviewing both the subject and an informant who knows and has contact with the subject. The CDR scale is a clinician directed assessment of both cognition and function, and is intended to capture the state and therefore the disease stage of the subject. The CDR scale assesses 6 domains of subject function (memory, orientation, judgement and problem solving, community affairs, home and hobbies and personal care) on a 5-point scale in which no impairment=0, questionable impairment=0.5, mild impairment=1, moderate impairment=2 and severe impairment=3. The CDR-SB is a sum of the individual domain scores and ranges from 0 to 18.

Higher scores indicates more impairment. FAS: group of randomized subjects who received at least 1 dose of study drug in the core phase and had baseline and at least 1 post-dose primary efficacy measurement. Here "subjects analyzed" signifies subjects who were evaluable for this outcome measure.

End point type	Secondary
End point timeframe:	
From last dose in the core phase (up to Month 24) up to 3 months follow up (up to Month 27)	

End point values	Core Phase: Placebo	Core Phase: Elenbecestat 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	759	734		
Units: score on a scale				
least squares mean (standard error)	0.40 (\pm 0.045)	0.44 (\pm 0.046)		

Statistical analyses

Statistical analysis title	Core Phase: Placebo,Core Phase: Elenbecestat 50 mg
-----------------------------------	--

Statistical analysis description:

Analysis was based on the MMRM and factors for treatment group, visit, treatment group by visit interaction, clinical disease staging (MCI/Prodromal, mild AD), concurrent AD medication use, region, ApoE4 status (positive, negative) as fixed effects, and the baseline value as covariate.

Comparison groups	Core Phase: Placebo v Core Phase: Elenbecestat 50 mg
Number of subjects included in analysis	1493
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.542
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.09
upper limit	0.17

Secondary: Core Phase: Change From Last Dose in the ADCOMS

End point title	Core Phase: Change From Last Dose in the ADCOMS
-----------------	---

End point description:

ADCOMS is a weighted linear combination of 12 items from three existing clinical scales: the ADAS-cog, the MMSE, and the CDR. Four items are from the ADAS-cog (A4 [Delayed Word Recall], A7 [Orientation], A8 [Word Recognition], A11 [Word Finding]); 2 items are from the MMSE (M1 [Orientation Time], M7 [Drawing]); 6 items are from the CDR (C1 [Personal Care], C2 [Community Affairs], C3 [Home and Hobbies], C4 [Judgment and Problem Solving], C5 [Memory], C6 [Orientation]). Composite score is derived from the variables from the 12 items, and ranges from 0 to 1.97, where higher score indicates worse performance. The FAS was the group of randomized subjects who received at least 1 dose of study drug in the core phase and had baseline and at least 1 post-dose primary efficacy

measurement. Here "subjects analyzed" signifies subjects who were evaluable for this outcome measure.

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

End point timeframe:

From last dose in the core phase (up to Month 24) up to 3 months follow-up (up to Month 27)

End point values	Core Phase: Placebo	Core Phase: Elenbecestat 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	666	646		
Units: score on a scale				
least squares mean (standard error)	0.06 (± 0.005)	0.06 (± 0.005)		

Statistical analyses

Statistical analysis title	Core Phase: Placebo,Core Phase: Elenbecestat 50 mg
----------------------------	--

Statistical analysis description:

Analysis was based on the MMRM and factors for treatment group, visit, treatment group by visit interaction, clinical disease staging (MCI/Prodromal, mild AD), concurrent AD medication use, region, ApoE4 status (positive, negative) as fixed effects, and the baseline value as covariate.

Comparison groups	Core Phase: Placebo v Core Phase: Elenbecestat 50 mg
Number of subjects included in analysis	1312
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.38
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.01

Secondary: Core Phase: Change From Last Dose in the ADAS-cog11 Score

End point title	Core Phase: Change From Last Dose in the ADAS-cog11 Score
-----------------	---

End point description:

ADAS-cog11 is a psychometric instrument that evaluates 11-items (Immediate Word-recall [0 to 10], Commands [0-5], Constructional Praxis [0-5], Naming Objects/Fingers [0-5], Ideational Praxis [0-5], Orientation[0-8], Word Recognition [0-12], Remembering Test Instructions [0-5], Comprehension[0-5], Word Finding Difficulty [0-5], Spoken Language Ability [0-5] test) and is considered more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects. The Total score ranges from 0 to 70. Higher score indicates more impairment. The FAS was the group of randomized subjects who received at least 1 dose of study drug in the core phase and had baseline and at least 1 post-dose primary efficacy measurement. Here "subjects analyzed" signifies subjects who were evaluable for this outcome measure.

End point type	Secondary
End point timeframe:	
From last dose in the core phase (up to Month 24) up to 3 months follow-up (up to Month 27)	

End point values	Core Phase: Placebo	Core Phase: Elenbecestat 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	679	647		
Units: score on a scale				
least squares mean (standard error)	0.95 (± 0.150)	0.56 (± 0.153)		

Statistical analyses

Statistical analysis title	Core Phase: Placebo,Core Phase: Elenbecestat 50 mg
Statistical analysis description:	
Analysis was based on the MMRM and factors for treatment group, visit, treatment group by visit interaction, clinical disease staging (MCI/Prodromal, mild AD), concurrent AD medication use, region, ApoE4 status (positive, negative) as fixed effects, and the baseline value as covariate.	
Comparison groups	Core Phase: Placebo v Core Phase: Elenbecestat 50 mg
Number of subjects included in analysis	1326
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.063
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.82
upper limit	0.02

Secondary: Core Phase: Change From Last Dose in the ADAS-cog14 Score

End point title	Core Phase: Change From Last Dose in the ADAS-cog14 Score
End point description:	
ADAS-cog14 is a psychometric instrument that evaluates 14-items (Immediate Word-recall [0 to 10], Commands [0-5], Constructional Praxis [0-5], Delayed Word-recall [0-10], Naming Objects/Fingers [0-5], Ideational Praxis [0-5], Orientation[0-8], Word Recognition [0-12], Remembering Test Instructions [0-5], Comprehension[0-5], Word Finding Difficulty [0-5], Spoken Language Ability [0-5], Executive Function [0-5], and Number Cancellation [0-5] test). It is considered to be more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects. The Total Score ranges from 0 to 90. Higher score indicates more impairment. The FAS was the group of randomized subjects who received at least 1 dose of study drug in the core phase and had baseline and at least 1 post-dose primary efficacy measurement. Here "subjects analyzed" signifies subjects who were evaluable for this outcome measure.	
End point type	Secondary

End point timeframe:

From last dose in the core phase (up to Month 24) up to 3 months follow-up (up to Month 27)

End point values	Core Phase: Placebo	Core Phase: Elenbecestat 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	679	647		
Units: score on a scale				
least squares mean (standard error)	0.96 (\pm 0.196)	0.40 (\pm 0.201)		

Statistical analyses

Statistical analysis title	Core Phase: Placebo,Core Phase: Elenbecestat 50 mg
Statistical analysis description:	
Analysis was based on the MMRM and factors for treatment group, visit, treatment group by visit interaction, clinical disease staging (MCI/Prodromal, mild AD), concurrent AD medication use, region, ApoE4 status (positive, negative) as fixed effects, and the baseline value as covariate.	
Comparison groups	Core Phase: Elenbecestat 50 mg v Core Phase: Placebo
Number of subjects included in analysis	1326
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.045 ^[2]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.11
upper limit	-0.01

Notes:

[2] - Based on a MMRM, which included baseline as a covariate with treatment groups as fixed effects.

Secondary: Core Phase: Change From Last Dose in the MMSE Score

End point title	Core Phase: Change From Last Dose in the MMSE Score
End point description:	
MMSE:instrument used for screening purposes,staging of disease severity and measured longitudinally in AD to follow disease progression/treatment effects.MMSE:composed of 30 questions grouped into domains(Orientation to Time[0-5],Orientation to Place[0-5],Registration[0-3],Attention and Calculation[0-5],Recall[0-3],Naming[0-2],Repetition[0-1],Comprehension[0-3],Reading[0-1],Writing[0-1],Drawing[0-1]).For each MMSE domains,six items are computed(Orientation to Time[0-5],Orientation to Place[0-5],Registration[0-3],Attention and Calculation[0-5],Recall[0-3],Language:Naming,Repetition,Comprehension,Reading,Writing,and Drawing[0-9]).MMSE Total Score(ranges from 0 to 30)=sum of six domains.If any domain score is missing then total score is missing.Higher score indicates better function.FAS:Subjects who received at least 1 dose of drug and had baseline and at least 1 post-dose primary efficacy measurement."Subjects analyzed"signifies subjects evaluable for this outcome measure.	
End point type	Secondary

End point timeframe:

From last dose in the core phase (up to Month 24) up to 3 months follow-up (up to Month 27)

End point values	Core Phase: Placebo	Core Phase: Elenbecestat 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	734	719		
Units: score on a scale				
least squares mean (standard error)	-0.22 (\pm 0.101)	-0.26 (\pm 0.102)		

Statistical analyses

Statistical analysis title	Core Phase: Placebo,Core Phase: Elenbecestat 50 mg
----------------------------	--

Statistical analysis description:

Analysis was based on the MMRM and factors for treatment group, visit, treatment group by visit interaction, clinical disease staging (MCI/Prodromal, mild AD), concurrent AD medication use, region, ApoE4 status (positive, negative) as fixed effects, and the baseline value as covariate.

Comparison groups	Core Phase: Placebo v Core Phase: Elenbecestat 50 mg
Number of subjects included in analysis	1453
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.799
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.32
upper limit	0.24

Secondary: Core Phase: Change From Last Dose in the ADAS-cog14 Word List (Immediate Recall and Delayed Recall) Score

End point title	Core Phase: Change From Last Dose in the ADAS-cog14 Word List (Immediate Recall and Delayed Recall) Score
-----------------	---

End point description:

The ADAS-cog14 Word List is a summation of two items: "Immediate Word-recall" and "Delayed Word-recall". Immediate Word-recall test: Subjects are asked to recall words and the number of "No" responses for each trial (total 3 trials) are summed. Subscore: sum of scores from 3 trials, divided by 3. Score ranges from 0 to 10. Delayed Word-recall: Subjects used to recall words after a delay and the number of "No" responses are summed. Score ranges from 0 to 10. The Total Score ranges from 0 to 20. Higher score indicates more impairment. The FAS was the group of randomized subjects who received at least 1 dose of study drug in the core phase and had baseline and at least 1 post-dose primary efficacy measurement. Here "subjects analyzed" signifies subjects who were evaluable for this outcome measure.

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

End point timeframe:

From last dose in the core phase (up to Month 24) up to 3 months follow-up (up to Month 27)

End point values	Core Phase: Placebo	Core Phase: Elenbecestat 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	707	685		
Units: score on a scale				
least squares mean (standard error)	0.54 (\pm 0.088)	0.22 (\pm 0.090)		

Statistical analyses

Statistical analysis title	Core Phase: Placebo,Core Phase: Elenbecestat 50 mg
Statistical analysis description:	
Analysis was based on the MMRM and factors for treatment group, visit, treatment group by visit interaction, clinical disease staging (MCI/Prodromal, mild AD), concurrent AD medication use, region, ApoE4 status (positive, negative) as fixed effects, and the baseline value as covariate.	
Comparison groups	Core Phase: Placebo v Core Phase: Elenbecestat 50 mg
Number of subjects included in analysis	1392
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.56
upper limit	-0.07

Secondary: Extension Phase: Change From Core Phase Baseline up to Month 12 of the Extension Phase in CDR-SB Score

End point title	Extension Phase: Change From Core Phase Baseline up to Month 12 of the Extension Phase in CDR-SB Score
End point description:	
The CDR scale is a clinical global rating scale that requires interviewing both the subject and an informant who knows and has contact with the subject. The CDR scale is a clinician directed assessment of both cognition and function, and is intended to capture the state and therefore the disease stage of the subject. The CDR scale assesses 6 domains of subject function (memory, orientation, judgement and problem solving, community affairs, home and hobbies and personal care) on a 5-point scale in which no impairment=0, questionable impairment=0.5, mild impairment=1, moderate impairment=2 and severe impairment=3. The CDR-SB is a sum of the individual domain scores and ranges from 0 to 18. Higher score indicates more impairment. Data could not be reported as the study was terminated prior to reaching the specified time point for assessment in the extension phase. Statistical analysis plan was modified to indicate that the extension phase analysis was not done.	
End point type	Secondary

End point timeframe:

Baseline (Day 1: before first dose in the core phase) up to Month 12 of the extension phase

End point values	Extension Phase: Elenbecestat 50 mg			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[3]			
Units: score on a scale				
least squares mean (standard error)	()			

Notes:

[3] - No subjects were analysed for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Extension Phase: Change From Core Phase Baseline up to Month 12 of the Extension Phase in ADCOMS

End point title	Extension Phase: Change From Core Phase Baseline up to Month 12 of the Extension Phase in ADCOMS
-----------------	--

End point description:

ADCOMS is a weighted linear combination of 12 items from three existing clinical scales: the ADAS-cog, the MMSE, and the CDR. Four items are from the ADAS-cog (A4 [Delayed Word Recall], A7 [Orientation], A8 [Word Recognition], A11 [Word Finding]); 2 items are from the MMSE (M1 [Orientation Time], M7 [Drawing]); 6 items are from the CDR (C1 [Personal Care], C2 [Community Affairs], C3 [Home and Hobbies], C4 [Judgment and Problem Solving], C5 [Memory], C6 [Orientation]). Composite score is derived from the variables from the 12 items, and ranges from 0 to 1.97, where higher score indicates worse performance. Data could not be reported as the study was terminated prior to reaching the specified time point for assessment in the extension phase. Statistical analysis plan was modified to indicate that the extension phase analysis was not done.

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

End point timeframe:

Baseline (Day 1: before first dose in the core phase) up to Month 12 of the extension phase

End point values	Extension Phase: Elenbecestat 50 mg			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[4]			
Units: score on a scale				
least squares mean (standard error)	()			

Notes:

[4] - No subjects were analysed for this outcome measure.

Statistical analyses

Secondary: Extension Phase: Change From Core Phase Baseline up to Month 12 of the Extension Phase in MMSE Score

End point title	Extension Phase: Change From Core Phase Baseline up to Month 12 of the Extension Phase in MMSE Score
End point description:	
MMSE: cognitive instrument used for screening purposes, staging of disease severity and is often measured longitudinally in AD clinical studies to follow disease progression and treatment effects. MMSE: 30 questions grouped into domains (Orientation to Time [0-5], Orientation to Place [0-5], Registration [0-3], Attention and Calculation [0-5], Recall [0-3], Naming [0-2], Repetition [0-1], Comprehension [0-3], Reading [0-1], Writing [0-1], Drawing [0-1]). For each of MMSE domains, six items are computed (Orientation to Time [0-5], Orientation to Place [0-5], Registration [0-3], Attention and Calculation [0-5], Recall [0-3], Language: Naming, Repetition, Comprehension, Reading, Writing, and Drawing [0-9]). MMSE Total Score: sum of six domains and ranges from 0 to 30. If any domain score is missing then total score is missing. Higher score indicates better function. Data: not reported as study terminated prior to reaching specified time point. Statistical analysis plan: modified to indicate that	
End point type	Secondary
End point timeframe:	
Baseline (Day 1: before first dose in the core phase) up to Month 12 of the extension phase	

End point values	Extension Phase: Elenbecestat 50 mg			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[5]			
Units: score on a scale				
least squares mean (standard error)	()			

Notes:

[5] - No subjects were analysed for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Extension Phase: Change From Core Phase Baseline up to Month 12 of the Extension Phase in FAQ Score

End point title	Extension Phase: Change From Core Phase Baseline up to Month 12 of the Extension Phase in FAQ Score
End point description:	
FAQ scores 10 items & measures activities of daily living (paying bills/balancing checkbook, assembling tax records, shopping alone for clothes or groceries, playing game of skill such as bridge or chess/working on a hobby, heating water & turning off stove, preparing balanced meal, keeping track of current events, paying attention & understanding television program, remembering appointments, driving or traveling out of neighborhood). Each item is rated as follows: 0=Normal, 1=Has difficulty but does by self, 2=Requires assistance, 3=Dependent, or 8=Not Applicable. The total score is the sum of all 10 items & ranges from 0 to 30. Higher score indicates more impairment. If any activity is missed, then the total score is missed. Data could not be reported as the study was terminated prior to reaching the specified time point for assessment in the extension phase. Statistical analysis plan was modified to indicate that the extension phase analysis was not done.	
End point type	Secondary
End point timeframe:	
Baseline (Day 1: before first dose in the core phase) up to Month 12 of the extension phase	

End point values	Extension Phase: Elenbecestat 50 mg			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[6]			
Units: score on a scale				
least squares mean (standard error)	()			

Notes:

[6] - No subjects were analysed for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Extension Phase: Change From Core Phase Baseline up to Month 12 of the Extension Phase in ADAS-cog14 Score

End point title	Extension Phase: Change From Core Phase Baseline up to Month 12 of the Extension Phase in ADAS-cog14 Score
-----------------	--

End point description:

ADAS-cog14 is a psychometric instrument that evaluates 14-items (Immediate Word-recall [0 to 10], Commands [0-5], Constructional Praxis [0-5], Delayed Word-recall [0-10], Naming Objects/Fingers [0-5], Ideational Praxis [0-5], Orientation[0-8], Word Recognition [0-12], Remembering Test Instructions [0-5], Comprehension[0-5], Word Finding Difficulty [0-5], Spoken Language Ability [0-5], Executive Function [0-5], and Number Cancellation [0-5] test). It is considered to be more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects. The total score ranges from 0 to 90. Higher score indicates more impairment. Data could not be reported as the study was terminated prior to reaching the specified time point for assessment in the extension phase. Statistical analysis plan was modified to indicate that the extension phase analysis was not done.

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

End point timeframe:

Baseline (Day 1: before first dose in the core phase) up to Month 12 of the extension phase

End point values	Extension Phase: Elenbecestat 50 mg			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[7]			
Units: score on a scale				
least squares mean (standard error)	()			

Notes:

[7] - No subjects were analysed for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Extension Phase: Change From Core Phase Baseline up to Month 12 of the Extension Phase in ADAS-cog14 Word List (Immediate Recall and Delayed Recall) Score

End point title	Extension Phase: Change From Core Phase Baseline up to Month 12 of the Extension Phase in ADAS-cog14 Word List (Immediate Recall and Delayed Recall) Score
-----------------	--

End point description:

The ADAS-cog14 Word List is a summation of two items: "Immediate Word-recall" and "Delayed Word-recall". Immediate Word-recall test: Subjects are asked to recall words and the number of "No" responses for each trial (total 3 trials) are summed. Subscore: sum of scores from 3 trials, divided by 3. Score ranges from 0 to 10. Delayed Word-recall: Subjects used to recall words after a delay and the number of "No" responses are summed. Score ranges from 0 to 10. The Total Score ranges from 0 to 20. Higher score indicates more impairment. Data could not be reported as the study was terminated prior to reaching the specified time point for assessment in the extension phase. Statistical analysis plan was modified to indicate that the extension phase analysis was not done.

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

End point timeframe:

Baseline (Day 1: before first dose in the core phase) up to Month 12 of the extension phase

End point values	Extension Phase: Elenbecestat 50 mg			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[8]			
Units: score on a scale				
least squares mean (standard error)	()			

Notes:

[8] - No subjects were analysed for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Extension Phase: Time to Conversion to Dementia for Subjects Who Were Not Clinically Staged as Having Dementia at the Core Phase Baseline up to Month 12 of the Extension Phase

End point title	Extension Phase: Time to Conversion to Dementia for Subjects Who Were Not Clinically Staged as Having Dementia at the Core Phase Baseline up to Month 12 of the Extension Phase
-----------------	---

End point description:

Time (in months) to conversion to dementia for subjects who were not clinically staged as having dementia at the core phase baseline (that is time from randomization to conversion to dementia in clinical diagnosis). Data could not be reported as the study was terminated prior to reaching the specified time point for assessment in the extension phase. Statistical analysis plan was modified to indicate that the extension phase analysis was not done.

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

End point timeframe:

Baseline (Day 1: before first dose in the core phase) up to Month 12 of the extension phase

End point values	Extension Phase: Elenbecestat 50 mg			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[9]			
Units: months				
median (confidence interval 95%)	(to)			

Notes:

[9] - No subjects were analysed for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to approximately 27 months (including 3 months follow up) for the Core Phase and up to approximately 6 months (including 1 month follow up) for the Extension Phase

Adverse event reporting additional description:

Core Phase: adverse events were reported for SAS (group of subjects who received at least 1 dose of drug and had at least 1 post-dose safety assessment). Extension Phase: adverse events were reported for All Safety Subjects analysis set: group of subjects who enrolled into extension phase and received at least 1 dose of drug in extension phase.

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

Dictionary used

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

Dictionary version	22.0
--------------------	------

Reporting groups

Reporting group title	Core Phase: Placebo
-----------------------	---------------------

Reporting group description:

Subjects received one elenbecestat matching-placebo tablet, orally, once daily in the morning with or without food up to 24 months. Subjects were followed up for 3 months after last dose of elenbecestat matched placebo in core phase.

Reporting group title	Core Phase: Elenbecestat 50 mg
-----------------------	--------------------------------

Reporting group description:

Subjects received one elenbecestat 50 mg tablet, orally, once daily in the morning with or without food up to 24 months. Subjects were followed up for 3 months after last dose of elenbecestat in core phase.

Reporting group title	Extension Phase: Elenbecestat 50 mg
-----------------------	-------------------------------------

Reporting group description:

Eligible subjects who completed the core phase entered the extension phase and received one elenbecestat 50 mg tablet, orally, once daily in the morning with or without food until commercial availability of elenbecestat, or a lack of positive benefit-risk assessment was determined, whichever occurred first. Subjects were followed up for 1 month after last dose of elenbecestat in extension phase.

Serious adverse events	Core Phase: Placebo	Core Phase: Elenbecestat 50 mg	Extension Phase: Elenbecestat 50 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	117 / 1105 (10.59%)	134 / 1099 (12.19%)	0 / 18 (0.00%)
number of deaths (all causes)	6	3	0
number of deaths resulting from adverse events	3	2	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung adenocarcinoma			
subjects affected / exposed	0 / 1105 (0.00%)	2 / 1099 (0.18%)	0 / 18 (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
Breast cancer			

subjects affected / exposed	3 / 1105 (0.27%)	1 / 1099 (0.09%)	0 / 18 (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
Benign gastric neoplasm			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Bladder adenocarcinoma stage unspecified			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Endometrial cancer			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Gastric adenoma			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Lymphoma			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Metastatic malignant melanoma			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Rectal adenocarcinoma			

subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Salivary gland cancer			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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			
subjects affected / exposed	2 / 1105 (0.18%)	0 / 1099 (0.00%)	0 / 18 (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
Lung neoplasm			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Mucinous adenocarcinoma of appendix			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Pancreatic carcinoma			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Squamous cell carcinoma of pharynx			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Vulval neoplasm			

subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Waldenstrom's macroglobulinaemia			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 1105 (0.09%)	1 / 1099 (0.09%)	0 / 18 (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
Aortic aneurysm			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Deep vein thrombosis			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Haematoma			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Hypertensive urgency			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Orthostatic hypotension			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery stenosis			

subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Blood pressure inadequately controlled			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Thrombosis			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	1 / 1105 (0.09%)	2 / 1099 (0.18%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 1105 (0.09%)	2 / 1099 (0.18%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Malaise			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Oedema peripheral			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Pain			

subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chills			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	0 / 1105 (0.00%)	2 / 1099 (0.18%)	0 / 18 (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
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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 polyp			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Cystocele			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 1105 (0.18%)	2 / 1099 (0.18%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			

subjects affected / exposed	1 / 1105 (0.09%)	1 / 1099 (0.09%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 1105 (0.09%)	1 / 1099 (0.09%)	0 / 18 (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
Acute respiratory failure			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Dyspnoea exertional			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Pneumothorax			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Pulmonary hypertension			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Respiratory disorder			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Asthma			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Epistaxis			

subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Lung disorder			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Nasal polyps			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Pneumothorax spontaneous			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	2 / 1105 (0.18%)	2 / 1099 (0.18%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aggression			
subjects affected / exposed	0 / 1105 (0.00%)	2 / 1099 (0.18%)	0 / 18 (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
Delirium			
subjects affected / exposed	0 / 1105 (0.00%)	2 / 1099 (0.18%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delusion			
subjects affected / exposed	1 / 1105 (0.09%)	1 / 1099 (0.09%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Agitation			

subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Completed suicide			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Confusional state			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disorientation			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic behaviour			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hallucination, visual			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Psychotic disorder			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood potassium decreased			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
C-reactive protein increased			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heart rate irregular			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Hepatic enzyme increased			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver function test increased			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Pancreatic enzymes increased			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cell count increased			

subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	4 / 1105 (0.36%)	7 / 1099 (0.64%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 7	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	1 / 1105 (0.09%)	3 / 1099 (0.27%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 1105 (0.00%)	3 / 1099 (0.27%)	0 / 18 (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
Head injury			
subjects affected / exposed	0 / 1105 (0.00%)	2 / 1099 (0.18%)	0 / 18 (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
Rib fracture			
subjects affected / exposed	2 / 1105 (0.18%)	1 / 1099 (0.09%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	1 / 1105 (0.09%)	1 / 1099 (0.09%)	0 / 18 (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
Spinal compression fracture			

subjects affected / exposed	1 / 1105 (0.09%)	1 / 1099 (0.09%)	0 / 18 (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
Brain contusion			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Facial bones fracture			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Foot fracture			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Humerus fracture			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Jaw fracture			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Post procedural complication			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Sternal fracture			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Subcutaneous haematoma			

subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Thoracic vertebral fracture			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Tibia fracture			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Accidental overdose			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Coronary vascular graft stenosis			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Hand fracture			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Radius fracture			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Road traffic accident			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Subdural haematoma			

subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Upper limb fracture			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Wrist fracture			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Congenital, familial and genetic disorders			
Type V hyperlipidaemia			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	3 / 1105 (0.27%)	2 / 1099 (0.18%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	1 / 1105 (0.09%)	2 / 1099 (0.18%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 1105 (0.00%)	2 / 1099 (0.18%)	0 / 18 (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
Tachycardia			
subjects affected / exposed	0 / 1105 (0.00%)	2 / 1099 (0.18%)	0 / 18 (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

Acute myocardial infarction			
subjects affected / exposed	3 / 1105 (0.27%)	1 / 1099 (0.09%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus node dysfunction			
subjects affected / exposed	2 / 1105 (0.18%)	1 / 1099 (0.09%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	1 / 1105 (0.09%)	1 / 1099 (0.09%)	0 / 18 (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 arrest			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Coronary artery stenosis			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Pericarditis			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Myocardial infarction			
subjects affected / exposed	3 / 1105 (0.27%)	0 / 1099 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Cardiomyopathy			

subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Coronary artery disease			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Mitral valve incompetence			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Paroxysmal atrioventricular block			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Sinus arrest			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 1105 (0.09%)	4 / 1099 (0.36%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	1 / 1105 (0.09%)	2 / 1099 (0.18%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	1 / 1105 (0.09%)	2 / 1099 (0.18%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			

subjects affected / exposed	1 / 1105 (0.09%)	2 / 1099 (0.18%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	0 / 1105 (0.00%)	2 / 1099 (0.18%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Normal pressure hydrocephalus			
subjects affected / exposed	0 / 1105 (0.00%)	2 / 1099 (0.18%)	0 / 18 (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
Presyncope			
subjects affected / exposed	2 / 1105 (0.18%)	1 / 1099 (0.09%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 1105 (0.09%)	1 / 1099 (0.09%)	0 / 18 (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
Unresponsive to stimuli			
subjects affected / exposed	1 / 1105 (0.09%)	1 / 1099 (0.09%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Altered state of consciousness			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain injury			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Cerebral ventricle dilatation			

subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Facial paralysis			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Myoclonus			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Paraesthesia			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Parkinsonism			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Petit mal epilepsy			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Cerebral infarction			

subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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 ischaemia			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Dementia Alzheimer's type			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Epilepsy			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Haemorrhagic stroke			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Hypoaesthesia			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Ischaemic stroke			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Lacunar stroke			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Lumbar radiculopathy			

subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Partial seizures			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Transient ischaemic attack			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Lymphadenopathy			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Lymphopenia			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	1 / 1105 (0.09%)	3 / 1099 (0.27%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Idiopathic orbital inflammation			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Retinal artery occlusion			

subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Diplopia			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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 disorders			
Abdominal pain			
subjects affected / exposed	3 / 1105 (0.27%)	1 / 1099 (0.09%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	2 / 1105 (0.18%)	1 / 1099 (0.09%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticular perforation			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Gastritis			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Nausea			

subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Oesophageal spasm			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Small intestinal obstruction			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Umbilical hernia			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Ascites			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Colitis			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Pancreatitis acute			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Vomiting			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Hepatobiliary disorders			
Hepatitis acute			

subjects affected / exposed	1 / 1105 (0.09%)	1 / 1099 (0.09%)	0 / 18 (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
Autoimmune hepatitis			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Cholecystitis			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Cholecystitis acute			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Hepatic mass			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Drug eruption			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity vasculitis			

subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxic skin eruption			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Actinic keratosis			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 1105 (0.00%)	2 / 1099 (0.18%)	0 / 18 (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
Ureterolithiasis			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Chronic kidney disease			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Nephrolithiasis			

subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Urethral meatus stenosis			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Endocrine disorders			
Thyroid mass			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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			
Muscular weakness			
subjects affected / exposed	0 / 1105 (0.00%)	2 / 1099 (0.18%)	0 / 18 (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
Osteoarthritis			
subjects affected / exposed	6 / 1105 (0.54%)	1 / 1099 (0.09%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Muscle twitching			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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

Haemarthrosis			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Intervertebral disc degeneration			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Lumbar spinal stenosis			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Neck pain			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Spinal stenosis			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 1105 (0.27%)	5 / 1099 (0.45%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 3	2 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	2 / 1105 (0.18%)	5 / 1099 (0.45%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	2 / 1105 (0.18%)	3 / 1099 (0.27%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			

subjects affected / exposed	1 / 1105 (0.09%)	2 / 1099 (0.18%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 1105 (0.00%)	2 / 1099 (0.18%)	0 / 18 (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
Diverticulitis			
subjects affected / exposed	0 / 1105 (0.00%)	2 / 1099 (0.18%)	0 / 18 (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
Subcutaneous abscess			
subjects affected / exposed	0 / 1105 (0.00%)	2 / 1099 (0.18%)	0 / 18 (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
Sepsis			
subjects affected / exposed	1 / 1105 (0.09%)	1 / 1099 (0.09%)	0 / 18 (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
Abscess limb			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Alpha haemolytic streptococcal infection			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Appendicitis			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Atypical pneumonia			

subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Bronchitis viral			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Colonic abscess			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Gastroenteritis viral			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Lower respiratory tract infection viral			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Pneumonia bacterial			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Gastroenteritis			
subjects affected / exposed	2 / 1105 (0.18%)	0 / 1099 (0.00%)	0 / 18 (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
Appendicitis perforated			

subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Campylobacter gastroenteritis			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Enteritis infectious			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Erysipelas			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Febrile infection			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Infected skin ulcer			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Ophthalmic herpes zoster			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Osteomyelitis			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Postoperative wound infection			

subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Pyelonephritis			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Urosepsis			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	1 / 1105 (0.09%)	2 / 1099 (0.18%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	2 / 1105 (0.18%)	1 / 1099 (0.09%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 1105 (0.00%)	1 / 1099 (0.09%)	0 / 18 (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
Hyponatraemia			
subjects affected / exposed	2 / 1105 (0.18%)	0 / 1099 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acidosis			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Diabetes mellitus			

subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Hypokalaemia			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 1105 (0.09%)	0 / 1099 (0.00%)	0 / 18 (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

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Core Phase: Placebo	Core Phase: Elenbecestat 50 mg	Extension Phase: Elenbecestat 50 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	292 / 1105 (26.43%)	391 / 1099 (35.58%)	6 / 18 (33.33%)
Investigations			
Blood sodium decreased			
subjects affected / exposed	0 / 1105 (0.00%)	0 / 1099 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	55 / 1105 (4.98%)	66 / 1099 (6.01%)	0 / 18 (0.00%)
occurrences (all)	79	101	0
Fall			
subjects affected / exposed	60 / 1105 (5.43%)	61 / 1099 (5.55%)	0 / 18 (0.00%)
occurrences (all)	71	79	0
Vascular disorders			

Varicose vein subjects affected / exposed occurrences (all)	0 / 1105 (0.00%) 0	0 / 1099 (0.00%) 0	1 / 18 (5.56%) 1
Nervous system disorders			
Cerebral microhaemorrhage subjects affected / exposed occurrences (all)	0 / 1105 (0.00%) 0	0 / 1099 (0.00%) 0	1 / 18 (5.56%) 1
Cognitive disorder subjects affected / exposed occurrences (all)	0 / 1105 (0.00%) 0	0 / 1099 (0.00%) 0	2 / 18 (11.11%) 2
Dizziness subjects affected / exposed occurrences (all)	45 / 1105 (4.07%) 49	57 / 1099 (5.19%) 61	0 / 18 (0.00%) 0
Somnolence subjects affected / exposed occurrences (all)	0 / 1105 (0.00%) 0	0 / 1099 (0.00%) 0	1 / 18 (5.56%) 1
Blood and lymphatic system disorders			
Lymphopenia subjects affected / exposed occurrences (all)	18 / 1105 (1.63%) 18	70 / 1099 (6.37%) 89	0 / 18 (0.00%) 0
General disorders and administration site conditions			
Gait disturbance subjects affected / exposed occurrences (all)	0 / 1105 (0.00%) 0	0 / 1099 (0.00%) 0	1 / 18 (5.56%) 1
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	0 / 1105 (0.00%) 0	0 / 1099 (0.00%) 0	1 / 18 (5.56%) 1
Rash subjects affected / exposed occurrences (all)	22 / 1105 (1.99%) 26	60 / 1099 (5.46%) 78	0 / 18 (0.00%) 0
Psychiatric disorders			
Abnormal dreams subjects affected / exposed occurrences (all)	36 / 1105 (3.26%) 42	57 / 1099 (5.19%) 66	0 / 18 (0.00%) 0
Nightmare			

subjects affected / exposed occurrences (all)	0 / 1105 (0.00%) 0	0 / 1099 (0.00%) 0	1 / 18 (5.56%) 1
Renal and urinary disorders Urine flow decreased subjects affected / exposed occurrences (all)	0 / 1105 (0.00%) 0	0 / 1099 (0.00%) 0	1 / 18 (5.56%) 1
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	0 / 1105 (0.00%) 0	0 / 1099 (0.00%) 0	1 / 18 (5.56%) 1
Osteoarthritis subjects affected / exposed occurrences (all)	0 / 1105 (0.00%) 0	0 / 1099 (0.00%) 0	1 / 18 (5.56%) 1
Pain in extremity subjects affected / exposed occurrences (all)	0 / 1105 (0.00%) 0	0 / 1099 (0.00%) 0	1 / 18 (5.56%) 1
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	67 / 1105 (6.06%) 80	71 / 1099 (6.46%) 86	0 / 18 (0.00%) 0
Upper respiratory tract infection subjects affected / exposed occurrences (all)	50 / 1105 (4.52%) 56	58 / 1099 (5.28%) 63	0 / 18 (0.00%) 0
Viral infection subjects affected / exposed occurrences (all)	0 / 1105 (0.00%) 0	0 / 1099 (0.00%) 0	1 / 18 (5.56%) 1
Metabolism and nutrition disorders Hyponatraemia subjects affected / exposed occurrences (all)	0 / 1105 (0.00%) 0	0 / 1099 (0.00%) 0	1 / 18 (5.56%) 1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 November 2016	<p>Amendment 01 to study E2609-G000-301 (2016-003928-23):</p> <ul style="list-style-type: none">-Added that randomization was stratified according to region, disease status, and use of concomitant medications. Randomization was no longer to be stratified by apolipoprotein E (ApoE) genotype.-Added the requirement for central reading of ECG recordings for consistency.-Added a secondary objective to determine whether elenbecestat was superior to placebo on the ADAS-cog14 Word List (immediate recall and delayed recall) at 24 months in subjects with EAD.-Added a secondary objective to determine whether elenbecestat was superior to placebo on the change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up).-Additional instructions were provided regarding temporary suspension of study drug following lymphocytopenia and subsequent rechallenge.-Administration of the Modified Hachinski Scale was moved to Tier 1 instead of Tier 2 to identify those subjects with vascular dementia and exclude them earlier in the screening process.-Addition of sleep/dream questionnaire for subjects reporting AEs of abnormal dreams, nightmares or sleep terrors.-Added requirement to measure absolute lymphocyte count (ALC) every 4 weeks for subjects who had a Grade 2 or greater lymphocytopenia during the follow-up period.-Clinical chemistry and hematology test were made mandatory at the second Follow-up Visit.-Added clarification regarding testing of blood samples for immunological assessments.- Malignant neoplasms within 5 years of Screening were excluded from the study (changed from 3 years).- Clarified that subjects who were illiterate were excluded from participation in the study.- Additional blood samples for PD evaluation were added at follow up.

06 February 2017	<p>Amendment 02 to study E2609-G000-301 (2016-003928-23) and amendment 01 to study E2609-G000-302 (2016-004128-42):</p> <ul style="list-style-type: none"> -Added China to the list of regions to participate in the study and changed the number of levels of stratification by region from 6 to 7 (added by Amendment 02 to Study 301 only: China was already included in Study 302). -Added an exclusion for moderate to severe hepatic impairment and provided specific criteria. -Prothrombin time and International Normalized Ratio (INR) (derived from prothrombin time) were added as a required part of Screening. -Added that subjects who developed moderate to severe hepatic impairment during the study were to discontinue study drug. -Removed exclusion of subjects undergoing lumbar puncture (LP) procedure with a medical condition with bleeding risk that is not under adequate control and provided additional guidance for subjects receiving concomitant anticoagulation/antiplatelet therapy. These subjects were to have prothrombin time and INR prior to CSF LP; if they were assessed by the investigator to be at risk for bleeding, they were to be excluded from CSF collection. -Added clarification to the exclusion criteria to specify that ALC was derived from the complete blood count with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they were present) and calculated by the white blood cell count × percentage of lymphocytes. -Added that subjects who were assessed by both amyloid PET and CSF were required to wait for a minimum of 48 hours between the 2 procedures and deleted that CSF must be collected before PET assessment. -Completion of the Sleep/Dream Questionnaire when triggered by AEs related to abnormal dreams, nightmares, or sleep terror was added for all study visits.
04 April 2017	<p>Amendment 03 to study E2609-G000-301 (2016-003928-23) and amendment 02 to study E2609-G000-302 (2016-004128-42):</p> <ul style="list-style-type: none"> -Added that start of open-label Extension Phase would require a protocol amendment with prior approval from applicable Health Authorities. -Added that the end of the study for the double-blind Randomization Phase would be the date of the last study visit (Visit 15) for the last subject in the double-blind Randomization Phase. -Extended the requirement of compliance with local standard of care for concomitant use of AChEI or memantine for symptomatic treatment of AD to include initiation or changing dose of AChEI or memantine during the study. -Revised the description of blood/CSF collection and assay for PD and exploratory biomarkers. -Specified that PBMCs were to be stored for testing as required. -Added that subjects who develop seizures were to be discontinued from study drug. -Defined severe infection as follows: sepsis; deep tissue (invasive) infection; any infection requiring intravenous (IV) antibiotics; any infection requiring hospitalization (if outpatient at onset); any infection leading to need for oxygen, pressors or fluids to support blood pressure (BP), or intubation; any infection that requires major surgical intervention; pseudomembranous colitis due to <i>C. difficile</i>; typhlitis; osteomyelitis; and meningitis. -Added guidance to action to be taken with drug administration for subjects who developed severe infections. -Revised study drug interruption and discontinuation criteria for skin rash and herpes infections. Added instructions for drug consultation with medical monitor and potential rechallenge. -Corrected description for calculating immediate memory score on ADAS-cog14. -Added measurement of prothrombin time, INR (derived from prothrombin time), and activated partial thromboplastin time to each study visit.

28 June 2017	<p>Amendment 04 to study E2609-G000-301 (2016-003928-23) and amendment 03 to study E2609-G000-302 (2016-004128-42):</p> <ul style="list-style-type: none"> -Specified the duration of the Prerandomization Phase and that randomization was to occur no more than 10 days after completion of all screening Added that for any given subject, every effort was to be made to ensure that the diagnosing clinician (responsible for the initial diagnosis and for disease staging) and the CDR rater remained unchanged throughout the study. -Removed PD blood specimen collection from the Screening Period and stipulated that Baseline blood draws for PD assessment were to be performed predose at Visit 2 (Randomization Phase) rather than during Screening. -Specified that safety assessments of immune status were to be performed throughout the study. -Specified that the MMSE and CDR requirements are to be met at Screening. -Listed CSF Aβ(1-42) and tau:Aβ (1-42) ratio as examples of AD biomarkers for brain amyloid pathology. -Added that PET scans performed at the ED Visit should only be performed if 6 months has elapsed since the prior PET scan. -Specified that historical PET scans must have been positive for amyloid in order to be considered for eligibility purposes. -Added that subjects must have the capacity to provide informed consent (as determined in accordance with applicable professional standards and local laws/regulations) to enroll in the study. -Added that the study partner must be literate. -Specified that findings of "diffuse" white matter disease "as defined by a score of 3 on the age-related white matter changes score" on centrally read brain MRI scan at Screening were exclusionary. Clarified that evidence of multiple lacunar infarcts was exclusionary, regardless of region, whereas evidence of stroke was exclusionary when it involved a major vascular territory. -Provided guidance for possible inclusion of subjects successfully treated for hepatitis C.
19 July 2018	<p>Amendment 05 to study E2609-G000-301 (2016-003928-23) and Amendment 04 to study E2609-G000-302 (2016-004128-42):</p> <ul style="list-style-type: none"> -An optional tau PET longitudinal substudy was added for study eligible subjects from select geographical sites in the US (based on the proximity to the tau PET ligand manufacturing sites) that have had an amyloid positive study specific PET scan and consented to participate in the optional amyloid PET longitudinal substudy.

21 January 2019	<p>Amendment 06 to study E2609-G000-301 (2016-003928-23) and Amendment 05 to study E2609-G000-302 (2016-004128-42):</p> <ul style="list-style-type: none"> -Added details for the open-label Extension Phase. -Added the plan for pooling of Studies 301 and 302 analysis, with decreased subjects and sites in each study. -Key secondary objectives were defined among the multiple secondary objectives, indicating those of most importance that were tested in a hierarchical manner. -Added Alzheimer's Disease Composite Score (ADCOMS) as a secondary objective for the Core Studies. -Added of CDR-SB and ADCOMS enriched by baseline amyloid PET standardized uptake value ratio (SUVR) as a secondary objective for the Core Studies. -Added a biomarker objective and endpoints for the Core Studies. -Revised the country list to reflect that South Africa was a participating country. -Added that if subjects had non MRI compatible devices fitted during treatment, then a computed tomography scan could be utilized to assess safety, if deemed appropriate by the investigator. -Added that CSF was to be used to assess PD, PK, and exploratory biomarkers. -Added that CSF and PET assessments were to be conducted before any other visit assessments and while the study was still study drug -Added that new AEs were to be collected for 4 weeks post last dose and followed-up for 12 weeks, or until resolution, whichever came first. AEs relating to study procedures were to be collected until the end of study participation. -Allowed for historical CSF samples, if collected, processed, and stored under appropriate conditions and approved by the sponsor, to be analyzed to determine CSF amyloid positivity. -Added that levels of Vitamin B12 may be confirmed with reflex testing to include methylmalonic acid analysis, if available in region. -Revised exclusion criterion to specify that if the QTcF machine read was greater than 440 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs were to be performed.
23 May 2019	<p>Amendment 07 to study E2609-G000-301 (2016-003928-23) and Amendment 06 to study E2609-G000-302 (2016-004128-42):</p> <ul style="list-style-type: none"> -To comply with applicable professional standards and local laws/regulations, added that subjects in Japan who lost the capacity to provide informed consent during the Core Studies were eligible for inclusion in the Extension Phase if the investigators obtain subject assent and consent of the legal representative.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Study terminated early due to unfavorable risk-benefit ratio including no evidence of potential efficacy and adverse event profile with drug was worse than placebo. Small sample size at 24 month timepoint of core phase limits interpretability of data.

Notes: