Clinical trial results:
A Randomized, Two-Period, Double-Blind Placebo-Controlled and Open-Label, Multicenter Extension Study to Determine the Long-Term Safety and Tolerability of JNJ-54861911 in Subjects in the Early Alzheimer's Disease Spectrum

Summary

EudraCT number	2014-004274-41
Trial protocol	BE SE DE ES FR NL
Global end of trial date	28 June 2018

Results information

Result version number	v1 (current)
This version publication date	11 July 2019
First version publication date	11 July 2019

Trial information

Trial identification

Sponsor protocol code	54861911ALZ2004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02406027
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Research & Development, LLC
Sponsor organisation address	920 Route 202 South, Raritan, United States, NJ 08869
Public contact	Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.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	28 June 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 June 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the long-term safety and tolerability of atabecestat in subjects in the early Alzheimer's disease (AD) spectrum who had completed a Phase 1b or Phase 2 clinical trial with atabecestat (for example, study 54861911ALZ2002), who were willing to continue their assigned treatment.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. Safety evaluations included monitoring of adverse events (AEs), clinical laboratory parameters (chemistry, hematology, urinalysis), vital signs, electrocardiograms (ECG), neurological, physical examination, amyloid related imaging abnormalities [ARIA]-edema or effusion [E] and ARIA-hemosiderin [H]); suicidality risk assessment (Columbia Suicide Severity Rating Scale [C-SSRS]); dermatologic and ophthalmologic examinations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 July 2015
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	Belgium: 13
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Spain: 37
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Netherlands: 8
Country: Number of subjects enrolled	Sweden: 12
Worldwide total number of subjects	90
EEA total number of subjects	90

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)	19
From 65 to 84 years	71
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted from 07 July 2015 to 28 June 2018. Subjects who completed their treatment period as described under parent protocol in study 54861911ALZ2002 (NCT02260674) or any ongoing/future Phase 1b or Phase 2 atabecestat clinical study were enrolled in this study.

Pre-assignment

Screening details:

A Total of 90 subjects were enrolled into period 1 (double-blind treatment phase). Of 90 subjects, 77 subjects completed period 1 and went on to receive active atabecestat treatment during period 2. All 77 subjects discontinued study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Double-blind Treatment Phase (Period 1): Placebo

Arm description:

Subjects received placebo matched to atabecestat orally, once daily from Day 1 up to Week 52 in the Double-blind treatment 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 placebo matched to atabecestat orally, once daily from Day 1 up to Week 52 in the Double-blind treatment phase.

Arm title	Double-blind Treatment Phase (Period 1): Atabecestat 10 mg

Arm description:

Subjects received 10 milligram (mg) of atabecestat orally, once daily from Day 1 up to Week 52 in the Double-blind treatment phase.

Arm type	Experimental
Investigational medicinal product name	Atabecestat, 10 mg
Investigational medicinal product code	
Other name	JNJ-54861911
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received 10 mg of atabecestat orally, once daily from Day 1 up to Week 52 in the Double-blind treatment phase.

Arm title	Double-blind Treatment Phase (Period 1): Atabecestat 25 mg

Arm description:

Subjects received 25 mg of atabecestat orally, once daily from Day 1 up to Week 52 in the Double-blind treatment phase.

Arm type	Experimental

Investigational medicinal product name	Atabecestat, 25 mg
Investigational medicinal product code	
Other name	JNJ-54861911
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received 25 mg of atabecestat orally, once daily from Day 1 up to Week 52 in the Double-blind treatment phase.

Number of subjects in period 1	Double-blind Treatment Phase (Period 1): Placebo	Double-blind Treatment Phase (Period 1): Atabecestat 10 mg	Double-blind Treatment Phase (Period 1): Atabecestat 25 mg
Started	35	29	26
Completed	29	26	22
Not completed	6	3	4
Consent withdrawn by subject	2	1	1
Physician decision	3	-	1
Adverse event, non-fatal	-	2	1
Subject refused further study treatment	1	-	1

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Open-label (OL) Phase (Period 2): Placebo to Atabecestat 5 mg

Arm description:

Subjects who were receiving placebo in the Double-blind treatment phase, received 5 mg atabecestat orally, once daily until registration of atabecestat or any safety issue in Open-label phase.

Arm type	Experimental
Investigational medicinal product name	Atabecestat, 5 mg
Investigational medicinal product code	
Other name	JNJ-54861911
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects who were receiving placebo in the Double-blind treatment phase, received the 5 mg atabecestat once daily until registration of atabecestat or any safety issue in Open-label phase.

Arm title	OL Phase (Period 2): Placebo to Atabecestat 25 mg

Arm description:

Subjects who were receiving placebo in the Double-blind treatment phase, received 25 mg atabecestat

orally, once daily until registration of atabecestat or any safety issue in Open-label phase.

Arm type	Experimental
Investigational medicinal product name	Atabecestat, 25 mg
Investigational medicinal product code	
Other name	JNJ-54861911
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects who were receiving placebo in the Double-blind treatment phase, received 25 mg atabecestat once daily until registration of atabecestat or any safety issue in Open-label phase.

Arm title	OL Phase (Period 2): Atabecestat 10 mg to Atabecestat 5 mg

Arm description:

Subjects who were receiving atabecestat 10 mg in the Double-blind treatment phase, received 5 mg atabecestat orally, once daily until registration of atabecestat or any safety issue in Open-label phase.

Arm type	Experimental
Investigational medicinal product name	Atabecestat 5 mg
Investigational medicinal product code	
Other name	JNJ-54861911
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects who were receiving atabecestat 10 mg in the Double-blind treatment phase, received 5 mg atabecestat once daily until registration of atabecestat or any safety issue in Open-label phase.

Arm title	OL Phase (Period 2): Atabecestat 25 mg to Atabecestat 25 mg

Arm description:

Subjects who were receiving atabecestat 25 mg in the Double-blind treatment phase continued to receive 25 mg atabecestat orally, once daily until registration of atabecestat or any safety issue in Open-label phase.

Arm type	Experimental
Investigational medicinal product name	Atabecestat 25 mg
Investigational medicinal product code	
Other name	JNJ-54861911
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects who were receiving atabecestat 25 mg in the Double-blind treatment phase continued to receive 25 mg atabecestat once daily until registration of atabecestat or any safety issue in Open-label phase.

Number of subjects in period 2	Open-label (OL) Phase (Period 2): Placebo to Atabecestat 5 mg	OL Phase (Period 2): Placebo to Atabecestat 25 mg	OL Phase (Period 2): Atabecestat 10 mg to Atabecestat 5 mg
Started	15	14	26
Completed	0	0	0
Not completed	15	14	26
Consent withdrawn by subject	2	4	-
Physician decision	-	-	1
At spouse request with PI agrement	-	-	1
Adverse event, non-fatal	2	2	-

Study terminated by sponsor	11	7	24
Subject not Compliant to Study Procedure	-	1	-

Number of subjects in period 2	OL Phase (Period 2): Atabecestat 25 mg to Atabecestat 25 mg
Started	22
Completed	0
Not completed	22
Consent withdrawn by subject	2
Physician decision	1
At spouse request with PI agrement	-
Adverse event, non-fatal	-
Study terminated by sponsor	19
Subject not Compliant to Study Procedure	-

Baseline characteristics

Reporting groups	
Reporting group title	Double-blind Treatment Phase (Period 1): Placebo
Reporting group description:	
Subjects received placebo matched to atabecestat orally, once daily from Day 1 up to Week 52 in the Double-blind treatment phase.	
Reporting group title	Double-blind Treatment Phase (Period 1): Atabecestat 10 mg
Reporting group description:	
Subjects received 10 milligram (mg) of atabecestat orally, once daily from Day 1 up to Week 52 in the Double-blind treatment phase.	
Reporting group title	Double-blind Treatment Phase (Period 1): Atabecestat 25 mg
Reporting group description:	
Subjects received 25 mg of atabecestat orally, once daily from Day 1 up to Week 52 in the Double-blind treatment phase.	

Reporting group values	Double-blind Treatment Phase (Period 1): Placebo	Double-blind Treatment Phase (Period 1): Atabecestat 10 mg	Double-blind Treatment Phase (Period 1): Atabecestat 25 mg
Number of subjects	35	29	26
Title for AgeCategorical			
Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	6	5	8
From 65 to 84 years	29	24	18
85 years and over	0	0	0
Title for AgeContinuous			
Units: years			
arithmetic mean	70.4	71.4	67.9
standard deviation	± 5.15	± 7.04	± 8.87
Title for Gender			
Units: subjects			
Female	19	16	12
Male	16	13	14

Reporting group values	Total		
Number of subjects	90		
Title for AgeCategorical			
Units: subjects			
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	19		
From 65 to 84 years	71		
85 years and over	0		
Title for AgeContinuous			
Units: years			
arithmetic mean			
standard deviation	-		

Title for Gender Units: subjects			
Female	47		
Male	43		

End points

End points reporting groups

Reporting group title	Double-blind Treatment Phase (Period 1): Placebo
Reporting group description:	
Subjects received placebo matched to atabecestat orally, once daily from Day 1 up to Week 52 in the Double-blind treatment phase.	
Reporting group title	Double-blind Treatment Phase (Period 1): Atabecestat 10 mg
Reporting group description:	
Subjects received 10 milligram (mg) of atabecestat orally, once daily from Day 1 up to Week 52 in the Double-blind treatment phase.	
Reporting group title	Double-blind Treatment Phase (Period 1): Atabecestat 25 mg
Reporting group description:	
Subjects received 25 mg of atabecestat orally, once daily from Day 1 up to Week 52 in the Double-blind treatment phase.	
Reporting group title	Open-label (OL) Phase (Period 2): Placebo to Atabecestat 5 mg
Reporting group description:	
Subjects who were receiving placebo in the Double-blind treatment phase, received 5 mg atabecestat orally, once daily until registration of atabecestat or any safety issue in Open-label phase.	
Reporting group title	OL Phase (Period 2): Placebo to Atabecestat 25 mg
Reporting group description:	
Subjects who were receiving placebo in the Double-blind treatment phase, received 25 mg atabecestat orally, once daily until registration of atabecestat or any safety issue in Open-label phase.	
Reporting group title	OL Phase (Period 2): Atabecestat 10 mg to Atabecestat 5 mg
Reporting group description:	
Subjects who were receiving atabecestat 10 mg in the Double-blind treatment phase, received 5 mg atabecestat orally, once daily until registration of atabecestat or any safety issue in Open-label phase.	
Reporting group title	OL Phase (Period 2): Atabecestat 25 mg to Atabecestat 25 mg
Reporting group description:	
Subjects who were receiving atabecestat 25 mg in the Double-blind treatment phase continued to receive 25 mg atabecestat orally, once daily until registration of atabecestat or any safety issue in Open-label phase.	

Primary: Number of Subjects with Treatment-emergent Adverse Events (TEAEs) and Serious TEAEs

End point title	Number of Subjects with Treatment-emergent Adverse Events (TEAEs) and Serious TEAEs[1]
End point description:	
An adverse event (AE) is any untoward medical occurrence in a subjects who received study drug without regard to possibility of causal relationship. TEAEs were events between administration of study drug and up to 3 years that were absent before treatment or that worsened relative to pre-treatment state. An serious adverse event (SAE) is an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Safety analysis set included all subjects who received at least 1 dose of study drug in the study (during Period 1 and 2).	
End point type	Primary
End point timeframe:	
Up to 3 years	

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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Double-blind Treatment Phase (Period 1): Placebo	Open-label (OL) Phase (Period 2): Placebo to Atabecestat 5 mg	Double-blind Treatment Phase (Period 1): Atabecestat 10 mg	OL Phase (Period 2): Placebo to Atabecestat 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	35	15	29	14
Units: Subjects				
Number of Subjects with TEAEs	22	10	15	11
Number of Subjects with Serious TEAEs	3	2	4	4

End point values	Double-blind Treatment Phase (Period 1): Atabecestat 25 mg	OL Phase (Period 2): Atabecestat 10 mg to Atabecestat 5 mg	OL Phase (Period 2): Atabecestat 25 mg to Atabecestat 25 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26	26	22	
Units: Subjects				
Number of Subjects with TEAEs	21	19	16	
Number of Subjects with Serious TEAEs	4	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Treatment Phase (Period 1): Percent Change from Baseline in Cerebrospinal Fluid (CSF) Amyloid Beta (ABeta) (1-37, 1-38, 1-40, 1-42) Levels

End point title	Double-blind Treatment Phase (Period 1): Percent Change from Baseline in Cerebrospinal Fluid (CSF) Amyloid Beta (ABeta) (1-37, 1-38, 1-40, 1-42) Levels

End point description:

The CSF samples were obtained for measuring levels of different ABeta fragments such as ABeta 1-37, ABeta 1-38, ABeta 1-40, ABeta 1-42. ABeta fragments of different length were produced by cleavage of the amyloid precursor protein (APP) by beta-secretase (BACE) and the gamma-secretase complex in the brain and excreted into CSF. Subjects were classified as 'Asymptomatic at Risk (AAR)' and 'Prodormal'. The Double-blind (DB) Safety Analysis Set included all subjects who received study treatment during Period 1. Here ‘n’ (number of subjects analysed) signifies those subjects who were evaluable for this endpoint at a given time point. For Arithmetic Mean and Standard Deviation (SD), 99999 indicates that data was not assessable as no subject was analysed for this endpoint at specified timepoints. For CSF ABeta 1-37 AAR at Week 52, 99999 indicates that SD could not be calculated for a single subject.

End point type	Secondary

End point timeframe:

Baseline, Double-blind (DB) Day 1 and DB Week 52

End point values	Double-blind Treatment Phase (Period 1): Placebo	Double-blind Treatment Phase (Period 1): Atabecestat 10 mg	Double-blind Treatment Phase (Period 1): Atabecestat 25 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	35	29	26	
Units: Percent change				
arithmetic mean (standard deviation)				
CSF ABeta 1-37: AAR: DB Day 1, n=0, 0, 0	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	
CSF ABeta 1-37: AAR: DB Week 52, n=4, 1, 1	-9.9 (± 7.32)	-65.4 (± 99999)	-90.0 (± 99999)	
CSF ABeta 1-37: Prodromal: DB Day 1, n=3, 0,0	6.1 (± 10.09)	99999 (± 99999)	99999 (± 99999)	
CSF ABeta 1-37: Prodromal: DB Week 52, n=8, 8, 5	-8.8 (± 17.75)	-62.0 (± 11.02)	-65.9 (± 23.16)	
CSF ABeta 1-38: AAR: DB Day 1, n=0, 0, 0	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	
CSF ABeta 1-38: AAR: DB Week 52, n=4, 3, 2	-9.3 (± 7.02)	-42.9 (± 17.49)	-83.5 (± 4.84)	
CSF ABeta 1-38: Prodromal: DB Day 1, n=3, 0, 0	10.2 (± 15.41)	99999 (± 99999)	99999 (± 99999)	
CSF ABeta 1-38: Prodromal: DB Week 52, n=10, 9, 10	-9.7 (± 16.52)	-58.6 (± 10.21)	-70.4 (± 23.53)	
CSF ABeta 1-40: AAR: DB Day 1, n=0, 0, 0	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	
CSF ABeta 1-40: AAR: DB Week 52, n=4, 3, 2	-9.7 (± 6.12)	-46.2 (± 18.22)	-84.6 (± 5.43)	
CSF ABeta 1-40: Prodromal: DB Day 1, n=3, 0, 0	8.6 (± 17.19)	99999 (± 99999)	99999 (± 99999)	
CSF ABeta 1-40: Prodromal: DB Week 52, n=12, 9, 10	-14.5 (± 20.48)	-60.7 (± 13.52)	-72.8 (± 22.30)	
CSF ABeta 1-42: AAR: DB Day 1, n=0, 0, 0	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	
CSF ABeta 1-42: AAR: DB Week 52, n=4, 3, 2	-10.1 (± 7.81)	-39.6 (± 24.28)	-76.7 (± 11.01)	
CSF ABeta 1-42: Prodromal: DB Day 1, n=3, 0, 0	8.0 (± 7.44)	99999 (± 99999)	99999 (± 99999)	
CSF ABeta 1-42: Prodromal: DB Week 52, n=12, 9, 10	-15.0 (± 20.51)	-52.5 (± 11.60)	-57.6 (± 31.42)	

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Treatment Phase (Period 1): Percent Change from Baseline in Cerebrospinal Fluid (CSF) Soluble Amyloid Precursor Protein (sAPP) Fragments (sAPP-alpha and sAPP-beta) Levels

End point title	Double-blind Treatment Phase (Period 1): Percent Change from Baseline in Cerebrospinal Fluid (CSF) Soluble Amyloid Precursor Protein (sAPP) Fragments (sAPP-alpha and sAPP-beta) Levels

End point description:

The CSF samples were obtained for measuring levels of different soluble amyloid precursor protein (sAPP) fragments (sAPP-alpha, sAPP-beta). Subjects were classified as 'Asymptomatic at Risk (AAR)' and 'Prodormal'. The DB Safety Analysis Set included all subjects who received study treatment during Period 1. Here ‘n’ (number of subjects analysed) signifies those subjects who were evaluable for this endpoint at a given time point. For Arithmetic Mean and Standard Deviation (SD), 99999 indicates that

data was not assessable as no subject was analysed for this endpoint at specified timepoints. For CSF sAPP-alpha and sAPP-Beta AAR at Week 52, 99999 indicates that Standard Deviation could not be calculated for a single subject.

End point type	Secondary

End point timeframe:

Baseline, DB Day 1 and DB Week 52

End point values	Double-blind Treatment Phase (Period 1): Placebo	Double-blind Treatment Phase (Period 1): Atabecestat 10 mg	Double-blind Treatment Phase (Period 1): Atabecestat 25 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	35	29	26	
Units: Percent change				
arithmetic mean (standard deviation)				
CSF sAPP-alpha: AAR: DB Day 1, n=0, 0, 0	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	
CSF sAPP-alpha: AAR: DB Week 52, n=4, 3, 1	-4.7 (± 12.78)	50.1 (± 13.67)	77.8 (± 99999)	
CSF sAPP-alpha: Prodromal: DB Day 1, n=3, 0, 0	0.9 (± 24.97)	99999 (± 99999)	99999 (± 99999)	
CSF sAPP-alpha: Prodromal: DB Week 52, n=12, 9, 11	-11.2 (± 14.01)	60.2 (± 24.03)	85.1 (± 39.35)	
CSF sAPP-Beta: AAR: DB Day 1, n=0, 0, 0	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	
CSF sAPP-Beta: AAR: DB Week 52, n=4, 3, 1	-10.8 (± 8.44)	-57.5 (± 8.06)	-90.8 (± 99999)	
CSF sAPP-Beta: Prodromal: DB Day 1, n=3, 0, 0	0.4 (± 18.93)	99999 (± 99999)	99999 (± 99999)	
CSF sAPP-Beta: Prodromal: DB Week 52, n=12, 9, 11	-11.7 (± 14.47)	-63.5 (± 5.19)	-73.0 (± 21.79)	

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Treatment Phase (Period 1): Percent Change from Baseline in Plasma Amyloid Beta (ABeta) (1-38, 1-40, 1-42) Levels

End point title	Double-blind Treatment Phase (Period 1): Percent Change from Baseline in Plasma Amyloid Beta (ABeta) (1-38, 1-40, 1-42) Levels

End point description:

Plasma samples were obtained for measuring levels of different ABeta fragments such as ABeta 1-38, ABeta 1-40, and ABeta 1-42. ABeta fragments of different length are produced by cleavage of the APP by beta-secretase (BACE) and the gamma-secretase complex in the different peripheral tissues, including white blood cells and can be measured in Plasma. Subjects were classified as 'Asymptomatic at Risk (AAR)' and 'Prodormal'. The DB Safety Analysis Set included all subjects who received study treatment during Period 1. Here 'n' (number of subjects analysed) signifies those subjects who were evaluable for this endpoint at a given time point. For Arithmetic Mean and Standard Deviation (SD), 99999 indicates that data was not assessable as no subject was analysed for this endpoint at specified timepoint. For Plasma ABeta 1-38 AAR at Week 52, ABeta 1-40 and 1-42 AAR at Day 1, 99999 indicates that SD could not be calculated for a single subject.

End point type	Secondary

End point timeframe:
Baseline, DB Day 1, DB Week 24, and DB Week 52

End point values	Double-blind Treatment Phase (Period 1): Placebo	Double-blind Treatment Phase (Period 1): Atabecestat 10 mg	Double-blind Treatment Phase (Period 1): Atabecestat 25 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	35	29	26	
Units: Percent change				
arithmetic mean (standard deviation)				
Plasma ABeta 1-38: AAR: DB Day 1, n=0, 0, 0	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	
Plasma ABeta 1-38: AAR: DB Week 24, n=2, 0, 0	-9.9 (± 0.83)	99999 (± 99999)	99999 (± 99999)	
Plasma ABeta 1-38: AAR: DB Week 52, n=1, 0, 0	-5.3 (± 99999)	99999 (± 99999)	99999 (± 99999)	
Plasma ABeta 1-38: Prodromal: DB Day 1, n=4, 0, 3	-5.0 (± 10.07)	99999 (± 99999)	-6.6 (± 13.56)	
Plasma ABeta 1-38:Prodromal: DB Week 24, n=4,0,0	3.0 (± 24.32)	99999 (± 99999)	99999 (± 99999)	
Plasma ABeta 1-38:Prodromal: DB Week 52, n=3,0,0	20.3 (± 35.48)	99999 (± 99999)	99999 (± 99999)	
Plasma ABeta 1-40: AAR: DB Day 1, n=1, 1, 4	19.2 (± 99999)	-4.9 (± 99999)	4.7 (± 40.27)	
Plasma ABeta 1-40: AAR: DB Week 24, n=5, 4, 4	-2.3 (± 12.38)	-75.2 (± 10.16)	-82.6 (± 5.59)	
Plasma ABeta 1-40: AAR: DB Week 52, n=5, 4, 4	0.0 (± 10.85)	-74.9 (± 6.76)	-80.8 (± 7.60)	
Plasma ABeta 1-40:Prodromal: DB Day 1, n=12,3,7	2.9 (± 15.48)	25.8 (± 66.03)	-24.2 (± 41.31)	
Plasma ABeta 1-40:Prodromal:DB Week 24, n=21,16,14	8.6 (± 18.57)	-68.6 (± 8.20)	-82.5 (± 7.38)	
Plasma ABeta 1-40:Prodromal:DB Week 52, n=18,15,13	10.5 (± 17.09)	-70.9 (± 9.24)	-75.3 (± 22.15)	
Plasma ABeta 1-42: AAR: DB Day 1, n=1, 0, 0	-5.9 (± 99999)	99999 (± 99999)	99999 (± 99999)	
Plasma ABeta 1-42: AAR: DB Week 24, n=3, 0, 0	-7.3 (± 9.33)	99999 (± 99999)	99999 (± 99999)	
Plasma ABeta 1-42: AAR: DB Week 52, n=3, 0, 0	-6.0 (± 2.69)	99999 (± 99999)	99999 (± 99999)	
Plasma ABeta 1-42:Prodromal:DB Day 1, n=4,0,0	-1.9 (± 5.54)	99999 (± 99999)	99999 (± 99999)	
Plasma ABeta 1-42:Prodromal:DB Week 24, n=8,0,0	15.9 (± 17.15)	99999 (± 99999)	99999 (± 99999)	
Plasma ABeta 1-42:Prodromal:DB Week 52, n=6,0,0	5.1 (± 17.68)	99999 (± 99999)	99999 (± 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Treatment Phase (Period 1): Percent Change from Baseline in Cerebrospinal Fluid (CSF) Tau Protein and Phosphorylated Tau (p-Tau) Protein Level

End point title	Double-blind Treatment Phase (Period 1): Percent Change from Baseline in Cerebrospinal Fluid (CSF) Tau Protein and Phosphorylated Tau (p-Tau) Protein Level

End point description:

The CSF samples were obtained for measuring levels of Tau protein and phosphorylated (p)-tau protein. The DB Safety Analysis Set included all subjects who received study treatment during Period 1. Here 'n' (number of subjects analysed) signifies those subjects who were evaluable for this endpoint at a given time point. For Arithmetic Mean and Standard Deviation (SD), 99999 indicates that data was not assessable as no subject was analysed for this endpoint at specified timepoint. For CSF Tau Protein and p-Tau Protein AAR at Week 52, 99999 indicates that SD could not be calculated for a single subject.

End point type	Secondary

End point timeframe:

Baseline, DB Day 1 and DB Week 52

End point values	Double-blind Treatment Phase (Period 1): Placebo	Double-blind Treatment Phase (Period 1): Atabecestat 10 mg	Double-blind Treatment Phase (Period 1): Atabecestat 25 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	35	29	26	
Units: Percent change				
arithmetic mean (standard deviation)				
CSF Tau Protein: AAR: DB Day 1, n=0, 0, 0	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	
CSF Tau Protein: AAR: DB Week 52, n=4, 3, 1	-1.4 (± 14.10)	3.2 (± 15.04)	22.4 (± 99999)	
CSF Tau Protein: Prodromal:DB Day 1, n=3,0,0	6.1 (± 6.82)	99999 (± 99999)	99999 (± 99999)	
CSF Tau Protein: Prodromal:DB Week 52, n=12,9,11	13.6 (± 45.55)	2.1 (± 13.82)	1.4 (± 8.20)	
CSF p-Tau Protein: AAR:DB Day 1, n=0,0,0	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	
CSF p-Tau Protein: AAR:DB Week 52, n=4,3,1	-4.6 (± 6.47)	-4.9 (± 1.40)	8.3 (± 99999)	
CSF p-Tau Protein: Prodromal:DB Day 1, n=3,0,0	-0.6 (± 7.81)	99999 (± 99999)	99999 (± 99999)	
CSF p-Tau Protein: Prodromal: Week 52, n=12,9,11	2.2 (± 12.93)	-2.7 (± 10.52)	-2.6 (± 8.52)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 3 years

Adverse event reporting additional description:

Safety analysis set included all subjects who received study treatment during Period 1 and 2.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Double-blind Treatment Phase (Period 1): Placebo

Reporting group description:

Subjects received placebo matched to atabecestat orally, once daily from Day 1 up to Week 52 in the Double-blind treatment phase.

Reporting group title	Double-blind Treatment Phase (Period 1): Atabecestat 10 mg

Reporting group description:

Subjects received 10 mg of atabecestat orally, once daily from Day 1 up to Week 52 in the Double-blind treatment phase.

Reporting group title	Double-blind Treatment Phase (Period 1): Atabecestat 25 mg

Reporting group description:

Subjects received 25 mg of atabecestat orally, once daily from Day 1 up to Week 52 in the Double-blind treatment phase.

Reporting group title	Open-label (OL) Phase (Period 2): Placebo to Atabecestat 5 mg

Reporting group description:

Subjects who were receiving placebo in the Double-blind treatment phase, received 5 mg atabecestat orally, once daily until registration of atabecestat or any safety issue in Open-label phase.

Reporting group title	OL Phase (Period 2): Placebo to Atabecestat 25 mg

Reporting group description:

Subjects who were receiving placebo in the Double-blind treatment phase, received 25 mg atabecestat orally, once daily until registration of atabecestat or any safety issue in Open-label phase.

Reporting group title	OL Phase (Period 2): Atabecestat 10 mg to Atabecestat 5 mg

Reporting group description:

Subjects who were receiving atabecestat 10 mg in the Double-blind treatment phase, received 5 mg atabecestat orally, once daily until registration of atabecestat or any safety issue in Open-label phase.

Reporting group title	OL Phase (Period 2): Atabecestat 25 mg to Atabecestat 25 mg

Reporting group description:

Subjects who were receiving atabecestat 25 mg in the Double-blind treatment phase continued to receive 25 mg atabecestat orally, once daily until registration of atabecestat or any safety issue in Open-label phase.

Serious adverse events	Double-blind Treatment Phase (Period 1): Placebo	Double-blind Treatment Phase (Period 1): Atabecestat 10 mg	Double-blind Treatment Phase (Period 1): Atabecestat 25 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 35 (8.57%)	4 / 29 (13.79%)	4 / 26 (15.38%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Investigations			
Hepatic Enzyme Increased			
subjects affected / exposed	0 / 35 (0.00%)	0 / 29 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases Increased			
subjects affected / exposed	0 / 35 (0.00%)	1 / 29 (3.45%)	0 / 26 (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
Injury, poisoning and procedural complications			
Burns Third Degree			
subjects affected / exposed	0 / 35 (0.00%)	0 / 29 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Craniocerebral Injury			
subjects affected / exposed	0 / 35 (0.00%)	0 / 29 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 35 (2.86%)	0 / 29 (0.00%)	0 / 26 (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
Thoracic Vertebral Fracture			
subjects affected / exposed	0 / 35 (0.00%)	1 / 29 (3.45%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist Fracture			
subjects affected / exposed	0 / 35 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocardial Ischaemia			

subjects affected / exposed	0 / 35 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	0 / 35 (0.00%)	1 / 29 (3.45%)	0 / 26 (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
Psychiatric disorders			
Psychotic Disorder			
subjects affected / exposed	0 / 35 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Calculus Urinary			
subjects affected / exposed	0 / 35 (0.00%)	1 / 29 (3.45%)	0 / 26 (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
Renal Colic			
subjects affected / exposed	0 / 35 (0.00%)	1 / 29 (3.45%)	0 / 26 (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
Ureteric Obstruction			
subjects affected / exposed	0 / 35 (0.00%)	1 / 29 (3.45%)	0 / 26 (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			
Foot Deformity			
subjects affected / exposed	1 / 35 (2.86%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			

subjects affected / exposed	0 / 35 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 29 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 35 (2.86%)	0 / 29 (0.00%)	0 / 26 (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	0 / 35 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Open-label (OL) Phase (Period 2): Placebo to Atabecestat 5 mg	OL Phase (Period 2): Placebo to Atabecestat 25 mg	OL Phase (Period 2): Atabecestat 10 mg to Atabecestat 5 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 15 (13.33%)	4 / 14 (28.57%)	0 / 26 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
Hepatic Enzyme Increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 26 (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
Transaminases Increased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 26 (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
Injury, poisoning and procedural complications			
Burns Third Degree			

subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Craniocerebral Injury			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thoracic Vertebral Fracture			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist Fracture			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 26 (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			
Myocardial Ischaemia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Psychotic Disorder			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Renal and urinary disorders			
Calculus Urinary			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Colic			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteric Obstruction			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Foot Deformity			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 26 (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
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 26 (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
Pyelonephritis			

subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 26 (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

Serious adverse events	OL Phase (Period 2): Atabecestat 25 mg to Atabecestat 25 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 22 (4.55%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Investigations			
Hepatic Enzyme Increased			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Transaminases Increased			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Burns Third Degree			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Craniocerebral Injury			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thoracic Vertebral Fracture			

subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Wrist Fracture			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Myocardial Ischaemia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Psychotic Disorder			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Calculus Urinary			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal Colic			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ureteric Obstruction			

subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Foot Deformity			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Double-blind Treatment Phase (Period 1): Placebo	Double-blind Treatment Phase (Period 1): Atabecestat 10 mg	Double-blind Treatment Phase (Period 1): Atabecestat 25 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 35 (48.57%)	11 / 29 (37.93%)	14 / 26 (53.85%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Basal Cell Carcinoma			
subjects affected / exposed	1 / 35 (2.86%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Skin Papilloma			
subjects affected / exposed	0 / 35 (0.00%)	0 / 29 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Squamous Cell Carcinoma			
subjects affected / exposed	0 / 35 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 35 (5.71%)	1 / 29 (3.45%)	0 / 26 (0.00%)
occurrences (all)	2	1	0
Hypotension			
subjects affected / exposed	0 / 35 (0.00%)	1 / 29 (3.45%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Orthostatic Hypotension			
subjects affected / exposed	0 / 35 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	0 / 35 (0.00%)	2 / 29 (6.90%)	0 / 26 (0.00%)
occurrences (all)	0	3	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 35 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal Pain			
subjects affected / exposed	0 / 35 (0.00%)	1 / 29 (3.45%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Confusional State			

subjects affected / exposed	1 / 35 (2.86%)	0 / 29 (0.00%)	1 / 26 (3.85%)
occurrences (all)	1	0	1
Delirium			
subjects affected / exposed	0 / 35 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Depression			
subjects affected / exposed	0 / 35 (0.00%)	0 / 29 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Depressive Symptom			
subjects affected / exposed	0 / 35 (0.00%)	2 / 29 (6.90%)	0 / 26 (0.00%)
occurrences (all)	0	2	0
Insomnia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 29 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	0	2
Nightmare			
subjects affected / exposed	1 / 35 (2.86%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 35 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Hepatic Enzyme Increased			
subjects affected / exposed	0 / 35 (0.00%)	0 / 29 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Intraocular Pressure Increased			
subjects affected / exposed	0 / 35 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Transaminases Increased			
subjects affected / exposed	0 / 35 (0.00%)	2 / 29 (6.90%)	0 / 26 (0.00%)
occurrences (all)	0	2	0
Weight Decreased			
subjects affected / exposed	1 / 35 (2.86%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			

Fall			
subjects affected / exposed	1 / 35 (2.86%)	2 / 29 (6.90%)	0 / 26 (0.00%)
occurrences (all)	1	2	0
Periorbital Haemorrhage			
subjects affected / exposed	0 / 35 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Tendon Rupture			
subjects affected / exposed	0 / 35 (0.00%)	0 / 29 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Nervous system disorders			
Complex Regional Pain Syndrome			
subjects affected / exposed	0 / 35 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	1 / 35 (2.86%)	0 / 29 (0.00%)	1 / 26 (3.85%)
occurrences (all)	1	0	1
Tension Headache			
subjects affected / exposed	0 / 35 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Ear Discomfort			
subjects affected / exposed	0 / 35 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Cataract			
subjects affected / exposed	6 / 35 (17.14%)	0 / 29 (0.00%)	2 / 26 (7.69%)
occurrences (all)	6	0	2
Dry Eye			
subjects affected / exposed	0 / 35 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Eye Pruritus			
subjects affected / exposed	0 / 35 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Keratitis			
subjects affected / exposed	1 / 35 (2.86%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Lacrimation Increased			

subjects affected / exposed	0 / 35 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Macular Fibrosis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Vitreous Floaters			
subjects affected / exposed	0 / 35 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 35 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	1 / 35 (2.86%)	1 / 29 (3.45%)	1 / 26 (3.85%)
occurrences (all)	1	1	1
Diverticulum Intestinal			
subjects affected / exposed	0 / 35 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Dysphagia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal Reflux Disease			
subjects affected / exposed	0 / 35 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Inguinal Hernia			
subjects affected / exposed	1 / 35 (2.86%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Actinic Keratosis			
subjects affected / exposed	1 / 35 (2.86%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Eczema			
subjects affected / exposed	0 / 35 (0.00%)	1 / 29 (3.45%)	1 / 26 (3.85%)
occurrences (all)	0	1	1
Hair Colour Changes			

subjects affected / exposed	2 / 35 (5.71%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	2	0	0
Nail Discolouration			
subjects affected / exposed	0 / 35 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	1 / 35 (2.86%)	1 / 29 (3.45%)	1 / 26 (3.85%)
occurrences (all)	1	1	2
Seborrhoeic Dermatitis			
subjects affected / exposed	2 / 35 (5.71%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	2	0	0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	0 / 35 (0.00%)	1 / 29 (3.45%)	1 / 26 (3.85%)
occurrences (all)	0	1	1
Muscle Spasms			
subjects affected / exposed	1 / 35 (2.86%)	1 / 29 (3.45%)	0 / 26 (0.00%)
occurrences (all)	1	1	0
Osteoarthritis			
subjects affected / exposed	1 / 35 (2.86%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Abscess Neck			
subjects affected / exposed	0 / 35 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Bacterial Blepharitis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Bronchitis			
subjects affected / exposed	1 / 35 (2.86%)	1 / 29 (3.45%)	2 / 26 (7.69%)
occurrences (all)	1	1	2
Candida Infection			

subjects affected / exposed	0 / 35 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Cystitis			
subjects affected / exposed	1 / 35 (2.86%)	1 / 29 (3.45%)	0 / 26 (0.00%)
occurrences (all)	1	1	0
Dermatophytosis of Nail			
subjects affected / exposed	0 / 35 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis Viral			
subjects affected / exposed	0 / 35 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	1 / 35 (2.86%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	2 / 35 (5.71%)	2 / 29 (6.90%)	2 / 26 (7.69%)
occurrences (all)	2	3	2
Pneumonia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 35 (2.86%)	0 / 29 (0.00%)	2 / 26 (7.69%)
occurrences (all)	1	0	2
Urinary Tract Infection			
subjects affected / exposed	0 / 35 (0.00%)	0 / 29 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	2

Non-serious adverse events	Open-label (OL) Phase (Period 2): Placebo to Atabecestat 5 mg	OL Phase (Period 2): Placebo to Atabecestat 25 mg	OL Phase (Period 2): Atabecestat 10 mg to Atabecestat 5 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 15 (66.67%)	11 / 14 (78.57%)	12 / 26 (46.15%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal Cell Carcinoma			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	0	2
Skin Papilloma			

subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Squamous Cell Carcinoma			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Hypotension			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Orthostatic Hypotension			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Malaise			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 15 (6.67%)	1 / 14 (7.14%)	0 / 26 (0.00%)
occurrences (all)	1	1	0
Oropharyngeal Pain			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Confusional State			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Delirium			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0

Depression			
subjects affected / exposed	2 / 15 (13.33%)	0 / 14 (0.00%)	0 / 26 (0.00%)
occurrences (all)	3	0	0
Depressive Symptom			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Nightmare			
subjects affected / exposed	2 / 15 (13.33%)	1 / 14 (7.14%)	0 / 26 (0.00%)
occurrences (all)	2	1	0
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Hepatic Enzyme Increased			
subjects affected / exposed	0 / 15 (0.00%)	3 / 14 (21.43%)	0 / 26 (0.00%)
occurrences (all)	0	3	0
Intraocular Pressure Increased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	0	2
Transaminases Increased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Weight Decreased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Periorbital Haemorrhage			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Tendon Rupture			

subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Complex Regional Pain Syndrome			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	0 / 15 (0.00%)	2 / 14 (14.29%)	3 / 26 (11.54%)
occurrences (all)	0	2	4
Tension Headache			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 26 (0.00%)
occurrences (all)	2	0	0
Ear and labyrinth disorders			
Ear Discomfort			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	0	2
Dry Eye			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Eye Pruritus			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Keratitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Lacrimation Increased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Macular Fibrosis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Vitreous Floaters			

subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			
subjects affected / exposed	1 / 15 (6.67%)	2 / 14 (14.29%)	1 / 26 (3.85%)
occurrences (all)	1	2	2
Diverticulum Intestinal			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Dysphagia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Gastrooesophageal Reflux Disease			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Inguinal Hernia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Actinic Keratosis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Eczema			
subjects affected / exposed	1 / 15 (6.67%)	1 / 14 (7.14%)	1 / 26 (3.85%)
occurrences (all)	2	1	1
Hair Colour Changes			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Nail Discolouration			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Pruritus			

subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Seborrhoeic Dermatitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Muscle Spasms			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Osteoarthritis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	1 / 26 (3.85%)
occurrences (all)	0	1	1
Infections and infestations			
Abscess Neck			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Bacterial Blepharitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 26 (0.00%)
occurrences (all)	2	0	0
Bronchitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	1 / 26 (3.85%)
occurrences (all)	1	0	1
Candida Infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Cystitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	1 / 26 (3.85%)
occurrences (all)	0	1	1
Dermatophytosis of Nail			

subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis Viral			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	1 / 26 (3.85%)
occurrences (all)	1	0	1
Nasopharyngitis			
subjects affected / exposed	1 / 15 (6.67%)	3 / 14 (21.43%)	3 / 26 (11.54%)
occurrences (all)	1	4	3
Pneumonia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	2 / 26 (7.69%)
occurrences (all)	0	1	2
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Urinary Tract Infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	1 / 26 (3.85%)
occurrences (all)	0	1	1

Non-serious adverse events	OL Phase (Period 2): Atabecestat 25 mg to Atabecestat 25 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 22 (50.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal Cell Carcinoma			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Skin Papilloma			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Squamous Cell Carcinoma			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Vascular disorders			

Hypertension subjects affected / exposed occurrences (all) Hypotension subjects affected / exposed occurrences (all) Orthostatic Hypotension subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0 0 / 22 (0.00%) 0 0 / 22 (0.00%) 0		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Malaise subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0 0 / 22 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Oropharyngeal Pain subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0 0 / 22 (0.00%) 0		
Psychiatric disorders Confusional State subjects affected / exposed occurrences (all) Delirium subjects affected / exposed occurrences (all) Depression subjects affected / exposed occurrences (all) Depressive Symptom subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0 0 / 22 (0.00%) 0 1 / 22 (4.55%) 1 0 / 22 (0.00%) 0		

Insomnia			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Nightmare			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Hepatic Enzyme Increased			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Intraocular Pressure Increased			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Transaminases Increased			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Weight Decreased			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Periorbital Haemorrhage			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Tendon Rupture			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Complex Regional Pain Syndrome			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		

Headache			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Tension Headache			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Ear Discomfort			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Eye disorders			
Cataract			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	2		
Dry Eye			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Eye Pruritus			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Keratitis			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Lacrimation Increased			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Macular Fibrosis			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Vitreous Floaters			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Diarrhoea			

subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Diverticulum Intestinal			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Dysphagia			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Gastrooesophageal Reflux Disease			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Inguinal Hernia			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Actinic Keratosis			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Eczema			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Hair Colour Changes			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Nail Discolouration			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Pruritus			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Seborrhoeic Dermatitis			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Nephrolithiasis			

subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	4		
Muscle Spasms			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Osteoarthritis			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Abscess Neck			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Bacterial Blepharitis			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Bronchitis			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Candida Infection			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Cystitis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Dermatophytosis of Nail			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Gastroenteritis Viral			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Influenza			

subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Pneumonia			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Urinary Tract Infection			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 October 2015	The overall reason for the amendment #1 was to clarify that subjects who had progressed to dementia (Clinical Dementia Rating Scale [CDR] greater than or equal to [>=]1) in the parent protocol (54861911ALZ2002) would not be enrolled in Study 54861911ALZ2004. In addition, in the case where the subject progressed to a dementia state during the study, the subject may have remained in the study, provided that the investigator judged that the potential benefits of treatment for this subject clearly outweighed the known and foreseeable risks and consent for continued participation was obtained from a representative determined in accordance with the local law.
08 April 2016	The overall reason for the amendment #2 was to reduce the 10 mg treatment to 5 mg of atabecestat for Treatment Period 2, to increase the frequency of hematology and chemistry assessments in the study, and other required changes which were relevant to the study.
26 October 2016	The overall reason for the amendment #4 was to specify that hepatic enzyme elevations were to be classified as "adverse drug reactions" (ADRs) and to clarify the reporting of those events that were considered serious. Additionally, the text was modified and updated related to dermatologic and ophthalmologic/Optical coherence tomography (OCT) examinations. The text related to re-consenting subjects who experienced cognitive decline was updated and clarified in sections regarding the informed consent process. An overall risk-benefit assessment was added in the protocol.
27 March 2017	The overall reason for the amendment #5 was to add new monitoring guidelines and stopping rules for liver enzymes during the first 3 months of treatment and to provide additional information on the management of elevated liver enzymes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
28 June 2018	Study was early terminated by the Sponsor.	-

Notes:

Limitations and caveats

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

The major limitation of this study was early termination of the study/program by the sponsor, which resulted in small numbers of subjects in groups, precluding meaningful interpretation of some of the analyses.

Notes: