



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 agreement | - | - | 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 agreement | - |
| 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. A 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 'Prodromal'. 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 'Prodromal'. 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 'Prodromal'. 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 | 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 occurrences (all) | 1 / 35 (2.86%) 1 | 0 / 29 (0.00%) 0 | 0 / 26 (0.00%) 0 |
| Skin Papilloma subjects affected / exposed occurrences (all) | 0 / 35 (0.00%) 0 | 0 / 29 (0.00%) 0 | 1 / 26 (3.85%) 1 |
| Squamous Cell Carcinoma subjects affected / exposed occurrences (all) | 0 / 35 (0.00%) 0 | 0 / 29 (0.00%) 0 | 0 / 26 (0.00%) 0 |
| Vascular disorders Hypertension subjects affected / exposed occurrences (all) | 2 / 35 (5.71%) 2 | 1 / 29 (3.45%) 1 | 0 / 26 (0.00%) 0 |
| Hypotension subjects affected / exposed occurrences (all) | 0 / 35 (0.00%) 0 | 1 / 29 (3.45%) 1 | 0 / 26 (0.00%) 0 |
| Orthostatic Hypotension subjects affected / exposed occurrences (all) | 0 / 35 (0.00%) 0 | 0 / 29 (0.00%) 0 | 0 / 26 (0.00%) 0 |
| General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) | 0 / 35 (0.00%) 0 | 0 / 29 (0.00%) 0 | 0 / 26 (0.00%) 0 |
| Malaise subjects affected / exposed occurrences (all) | 0 / 35 (0.00%) 0 | 2 / 29 (6.90%) 3 | 0 / 26 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 0 / 35 (0.00%) 0 | 0 / 29 (0.00%) 0 | 0 / 26 (0.00%) 0 |
| Oropharyngeal Pain subjects affected / exposed occurrences (all) | 0 / 35 (0.00%) 0 | 1 / 29 (3.45%) 1 | 0 / 26 (0.00%) 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 occurrences (all) | 2 / 35 (5.71%) 2 | 0 / 29 (0.00%) 0 | 0 / 26 (0.00%) 0 |
| Nail Discolouration subjects affected / exposed occurrences (all) | 0 / 35 (0.00%) 0 | 0 / 29 (0.00%) 0 | 0 / 26 (0.00%) 0 |
| Pruritus subjects affected / exposed occurrences (all) | 1 / 35 (2.86%) 1 | 1 / 29 (3.45%) 1 | 1 / 26 (3.85%) 2 |
| Seborrhoeic Dermatitis subjects affected / exposed occurrences (all) | 2 / 35 (5.71%) 2 | 0 / 29 (0.00%) 0 | 0 / 26 (0.00%) 0 |
| Renal and urinary disorders Nephrolithiasis subjects affected / exposed occurrences (all) | 0 / 35 (0.00%) 0 | 0 / 29 (0.00%) 0 | 0 / 26 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Back Pain subjects affected / exposed occurrences (all) | 0 / 35 (0.00%) 0 | 1 / 29 (3.45%) 1 | 1 / 26 (3.85%) 1 |
| Muscle Spasms subjects affected / exposed occurrences (all) | 1 / 35 (2.86%) 1 | 1 / 29 (3.45%) 1 | 0 / 26 (0.00%) 0 |
| Osteoarthritis subjects affected / exposed occurrences (all) | 1 / 35 (2.86%) 1 | 0 / 29 (0.00%) 0 | 0 / 26 (0.00%) 0 |
| Infections and infestations Abscess Neck subjects affected / exposed occurrences (all) | 0 / 35 (0.00%) 0 | 0 / 29 (0.00%) 0 | 0 / 26 (0.00%) 0 |
| Bacterial Blepharitis subjects affected / exposed occurrences (all) | 0 / 35 (0.00%) 0 | 0 / 29 (0.00%) 0 | 0 / 26 (0.00%) 0 |
| Bronchitis subjects affected / exposed occurrences (all) | 1 / 35 (2.86%) 1 | 1 / 29 (3.45%) 1 | 2 / 26 (7.69%) 2 |
| Candida Infection | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 35 (0.00%) 0 | 0 / 29 (0.00%) 0 | 0 / 26 (0.00%) 0 |
| Cystitis | | | |
| subjects affected / exposed occurrences (all) | 1 / 35 (2.86%) 1 | 1 / 29 (3.45%) 1 | 0 / 26 (0.00%) 0 |
| Dermatophytosis of Nail | | | |
| subjects affected / exposed occurrences (all) | 0 / 35 (0.00%) 0 | 0 / 29 (0.00%) 0 | 0 / 26 (0.00%) 0 |
| Gastroenteritis Viral | | | |
| subjects affected / exposed occurrences (all) | 0 / 35 (0.00%) 0 | 0 / 29 (0.00%) 0 | 0 / 26 (0.00%) 0 |
| Influenza | | | |
| subjects affected / exposed occurrences (all) | 1 / 35 (2.86%) 1 | 0 / 29 (0.00%) 0 | 0 / 26 (0.00%) 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed occurrences (all) | 2 / 35 (5.71%) 2 | 2 / 29 (6.90%) 3 | 2 / 26 (7.69%) 2 |
| Pneumonia | | | |
| subjects affected / exposed occurrences (all) | 0 / 35 (0.00%) 0 | 0 / 29 (0.00%) 0 | 0 / 26 (0.00%) 0 |
| Upper Respiratory Tract Infection | | | |
| subjects affected / exposed occurrences (all) | 1 / 35 (2.86%) 1 | 0 / 29 (0.00%) 0 | 2 / 26 (7.69%) 2 |
| Urinary Tract Infection | | | |
| subjects affected / exposed occurrences (all) | 0 / 35 (0.00%) 0 | 0 / 29 (0.00%) 0 | 1 / 26 (3.85%) 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 occurrences (all) | 0 / 15 (0.00%) 0 | 0 / 14 (0.00%) 0 | 2 / 26 (7.69%) 2 |
| Skin Papilloma | | | |

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

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

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 0 / 14 (0.00%) 0 | 0 / 26 (0.00%) 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 occurrences (all) | 1 / 15 (6.67%) 1 | 0 / 14 (0.00%) 0 | 0 / 26 (0.00%) 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 occurrences (all) | 0 / 15 (0.00%) 0 | 1 / 14 (7.14%) 1 | 0 / 26 (0.00%) 0 |
| Seborrhoeic Dermatitis subjects affected / exposed occurrences (all) | 0 / 15 (0.00%) 0 | 0 / 14 (0.00%) 0 | 0 / 26 (0.00%) 0 |
| Renal and urinary disorders Nephrolithiasis subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 0 / 14 (0.00%) 0 | 0 / 26 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Back Pain subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 0 / 14 (0.00%) 0 | 0 / 26 (0.00%) 0 |
| Muscle Spasms subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 0 / 14 (0.00%) 0 | 0 / 26 (0.00%) 0 |
| Osteoarthritis subjects affected / exposed occurrences (all) | 0 / 15 (0.00%) 0 | 1 / 14 (7.14%) 1 | 1 / 26 (3.85%) 1 |
| Infections and infestations Abscess Neck subjects affected / exposed occurrences (all) | 0 / 15 (0.00%) 0 | 1 / 14 (7.14%) 1 | 0 / 26 (0.00%) 0 |
| Bacterial Blepharitis subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 2 | 0 / 14 (0.00%) 0 | 0 / 26 (0.00%) 0 |
| Bronchitis subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 0 / 14 (0.00%) 0 | 1 / 26 (3.85%) 1 |
| Candida Infection subjects affected / exposed occurrences (all) | 0 / 15 (0.00%) 0 | 1 / 14 (7.14%) 1 | 0 / 26 (0.00%) 0 |
| Cystitis subjects affected / exposed occurrences (all) | 0 / 15 (0.00%) 0 | 1 / 14 (7.14%) 1 | 1 / 26 (3.85%) 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) | 0 / 22 (0.00%) 0 | | |
| Hypotension subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | | |
| Orthostatic Hypotension subjects affected / exposed occurrences (all) | 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 occurrences (all) | 2 / 22 (9.09%) 2 | | |
| Nightmare subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | | |
| Investigations Alanine Aminotransferase Increased subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | | |
| Hepatic Enzyme Increased subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | | |
| Intraocular Pressure Increased subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | | |
| Transaminases Increased subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | | |
| Weight Decreased subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | | |
| Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | | |
| Periorbital Haemorrhage subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | | |
| Tendon Rupture subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | | |
| Nervous system disorders Complex Regional Pain Syndrome subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 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 occurrences (all) | 0 / 22 (0.00%) 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 [\geq]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: