



## Clinical trial results:

### A Randomized, Double-Blind, Delayed-Start Study of LY3314814 (AZD3293) in Early Alzheimer's Disease Dementia (Extension of Study AZES, The AMARANTH Study)

#### Summary

|                          |                            |
|--------------------------|----------------------------|
| EudraCT number           | 2016-003440-36             |
| Trial protocol           | HU DE PL ES BE GB FR IT RO |
| Global end of trial date | 02 October 2018            |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1           |
| This version publication date  | 27 June 2019 |
| First version publication date | 27 June 2019 |

#### Trial information

##### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | I8D-MC-AZFD |
|-----------------------|-------------|

##### Additional study identifiers

|                                    |                     |
|------------------------------------|---------------------|
| ISRCTN number                      | -                   |
| ClinicalTrials.gov id (NCT number) | NCT02972658         |
| WHO universal trial number (UTN)   | -                   |
| Other trial identifiers            | Trial Number: 16557 |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Eli Lilly and Company   |
| Sponsor organisation address | Lilly Corporate Center, Indianapolis, IN, United States, 46285                |
| Public contact               | Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 877CTLilly,     |
| Scientific contact           | Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 8772854559,     |
| Sponsor organisation name    | AstraZeneca UK Limited  |
| Sponsor organisation address | Charter Way, Macclesfield, Cheshire, United Kingdom, SK10 2NA                 |
| Public contact               | Available Mon - Fri 9 AM - 5 PM EST, AstraZeneca UK Limited, 44 1625-58-2828, |
| Scientific contact           | Available Mon - Fri 9 AM - 5 PM EST, AstraZeneca UK Limited, 44 1625-58-2828, |

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                       | 02 October 2018 |
| Is this the analysis of the primary completion data? | No              |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 02 October 2018 |
| Was the trial ended prematurely?                     | Yes             |

Notes:

## General information about the trial

Main objective of the trial:

This study is an extension of study I8D-MC-AZES (NCT02245737), the AMARANTH study. The purpose of this study is to evaluate the effectiveness of the study drug lanabecestat in participants with early Alzheimer's disease dementia at the time of entry into study I8D-MC-AZES.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 15 March 2017 |
| 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 | Puerto Rico: 1         |
| Country: Number of subjects enrolled | Romania: 2             |
| Country: Number of subjects enrolled | Hungary: 1             |
| Country: Number of subjects enrolled | United States: 94      |
| Country: Number of subjects enrolled | Japan: 39              |
| Country: Number of subjects enrolled | United Kingdom: 46     |
| Country: Number of subjects enrolled | Spain: 60              |
| Country: Number of subjects enrolled | Canada: 33             |
| Country: Number of subjects enrolled | Korea, Republic of: 13 |
| Country: Number of subjects enrolled | Belgium: 11            |
| Country: Number of subjects enrolled | Poland: 34             |
| Country: Number of subjects enrolled | France: 33             |
| Country: Number of subjects enrolled | Australia: 30          |
| Country: Number of subjects enrolled | Germany: 24            |
| Worldwide total number of subjects   | 421                    |
| EEA total number of subjects         | 211                    |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| 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)                      | 96  |
| From 65 to 84 years                       | 325 |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Participants who completed feeder study (AZES (NCT02245737)) were enrolled in this study.

### Pre-assignment

Screening details:

Participants who were randomized in Study AZES to either 20 mg or 50 mg of lanabecestat continued on the treatment allocation from the feeder study. Participants randomized to placebo in Study AZES were randomized in a blinded fashion, 1:1 ratio, to either lanabecestat 20 mg or 50 mg daily (QD), administered orally.

### Period 1

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

### Arms

|                              |                                      |
|------------------------------|--------------------------------------|
| Are arms mutually exclusive? | Yes                                  |
| <b>Arm title</b>             | AZES Placebo/AZFD Lanabecestat 20 mg |

Arm description:

Participants who received placebo in the feeder study (AZES) were randomized to receive lanabecestat 20 mg.

|  |                    |
|--|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | Lanabecestat       |
| Investigational medicinal product code |                    |
| Other name                             | LY3314814, AZD3293 |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

20 mg film-coated tablets of lanabecestat administered orally once a day.

|                  |   |
|------------------|---|
| <b>Arm title</b> | AZES Lanabecestat 20 mg/AZFD Lanabecestat 20 mg |
|------------------|---|

Arm description:

Participants who received lanabecestat 20 mg in the feeder study (AZES) were randomized to receive lanabecestat 20 mg. 1 participant was incorrectly marked as "Completed" rather than study terminated by Sponsor.

|  |                    |
|--|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | Lanabecestat       |
| Investigational medicinal product code |                    |
| Other name                             | LY3314814, AZD3293 |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

20 mg film-coated tablets of lanabecestat administered orally once a day.

|                  |                                      |
|------------------|--------------------------------------|
| <b>Arm title</b> | AZES Placebo/AZFD Lanabecestat 50 mg |
|------------------|--------------------------------------|

Arm description:

Participants who received placebo in the feeder study (AZES) were randomized to receive lanabecestat 50 mg.

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|   |   |
|---|---|
| Investigational medicinal product name                                    | Lanabecestat                                    |
| Investigational medicinal product code                                    |   |
| Other name  | LY3314814, AZD3293                              |
| Pharmaceutical forms  | Film-coated tablet                              |
| Routes of administration  | Oral use  |
| Dosage and administration details:  |   |
| 50 mg film-coated tablets of lanabecestat administered orally once a day. |   |
| <b>Arm title</b>  | AZES Lanabecestat 50 mg/AZFD Lanabecestat 50 mg |

Arm description:

Participants who received lanabecestat 50 mg in the feeder study (AZES) were randomized to receive lanabecestat 50 mg.

|  |                    |
|--|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | Lanabecestat       |
| Investigational medicinal product code |                    |
| Other name                             | LY3314814, AZD3293 |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

50 mg film-coated tablets of lanabecestat administered orally once a day.

| <b>Number of subjects in period 1</b>       | AZES Placebo/AZFD<br>Lanabecestat 20 mg | AZES Lanabecestat<br>20 mg/AZFD<br>Lanabecestat 20 mg | AZES Placebo/AZFD<br>Lanabecestat 50 mg |
|---|---|---|---|
| Started                                     | 76                                      | 139   | 75                                      |
| Received at least 1 Dose of Study drug      | 76                                      | 139   | 74                                      |
| Completed                                   | 0                                       | 1   | 0                                       |
| Not completed                               | 76                                      | 138   | 75                                      |
| Adverse event, serious fatal                | -                                       | -   | -                                       |
| Consent withdrawn by subject                | 4                                       | 4   | 1                                       |
| Other-selected by Investigator              | 1                                       | 1   | -                                       |
| Withdrawal due to Caregiver<br>Circumstance | 1                                       | 1   | 1                                       |
| Adverse event, non-fatal                    | -                                       | 3   | -                                       |
| Progressive Disease                         | -                                       | 1   | -                                       |
| Sponsor Decision                            | 70                                      | 127   | 72                                      |
| Lost to follow-up                           | -                                       | 1   | 1                                       |

| <b>Number of subjects in period 1</b>  | AZES Lanabecestat<br>50 mg/AZFD<br>Lanabecestat 50 mg |
|--|---|
| Started                                | 131   |
| Received at least 1 Dose of Study drug | 131   |
| Completed                              | 0   |
| Not completed                          | 131   |
| Adverse event, serious fatal           | 1   |
| Consent withdrawn by subject           | 6   |

|  |     |
|--|-----|
| Other-selected by Investigator           | -   |
| Withdrawal due to Caregiver Circumstance | -   |
| Adverse event, non-fatal                 | 2   |
| Progressive Disease                      | 1   |
| Sponsor Decision                         | 119 |
| Lost to follow-up                        | 2   |

## Baseline characteristics

### Reporting groups

|   |   |
|---|---|
| Reporting group title   | AZES Placebo/AZFD Lanabecestat 20 mg            |
| Reporting group description:<br>Participants who received placebo in the feeder study (AZES) were randomized to receive lanabecestat 20 mg.   |   |
| Reporting group title   | AZES Lanabecestat 20 mg/AZFD Lanabecestat 20 mg |
| Reporting group description:<br>Participants who received lanabecestat 20 mg in the feeder study (AZES) were randomized to receive lanabecestat 20 mg. 1 participant was incorrectly marked as "Completed" rather than study terminated by Sponsor. |   |
| Reporting group title   | AZES Placebo/AZFD Lanabecestat 50 mg            |
| Reporting group description:<br>Participants who received placebo in the feeder study (AZES) were randomized to receive lanabecestat 50 mg.   |   |
| Reporting group title   | AZES Lanabecestat 50 mg/AZFD Lanabecestat 50 mg |
| Reporting group description:<br>Participants who received lanabecestat 50 mg in the feeder study (AZES) were randomized to receive lanabecestat 50 mg.  |   |

| Reporting group values  | AZES Placebo/AZFD Lanabecestat 20 mg | AZES Lanabecestat 20 mg/AZFD Lanabecestat 20 mg | AZES Placebo/AZFD Lanabecestat 50 mg |
|---|--------------------------------------|---|--------------------------------------|
| Number of subjects  | 76                                   | 139   | 75                                   |
| Age categorical<br>Units: Subjects  |                                      |   |                                      |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |                                      |   |                                      |
| Age continuous  |                                      |   |                                      |
| Details are from AZES baseline.   |                                      |   |                                      |
| Units: years  |                                      |   |                                      |
| arithmetic mean   | 70.7                                 | 69.8  | 71.1                                 |
| standard deviation  | ± 6.6                                | ± 7.8   | ± 6.6                                |
| Gender categorical<br>Units: Subjects   |                                      |   |                                      |
| Female  | 35                                   | 76  | 40                                   |
| Male  | 41                                   | 63  | 35                                   |
| Ethnicity (NIH/OMB)<br>Units: Subjects  |                                      |   |                                      |
| Hispanic or Latino  | 7                                    | 4   | 4                                    |
| Not Hispanic or Latino  | 62                                   | 115   | 54                                   |
| Unknown or Not Reported   | 7                                    | 20  | 17                                   |

|  |   |       |       |
|--|---|-------|-------|
| Race (NIH/OMB)   |   |       |       |
| Units: Subjects  |   |       |       |
| American Indian or Alaska Native   | 0   | 0     | 0     |
| Asian  | 7   | 23    | 10    |
| Native Hawaiian or Other Pacific Islander  | 0   | 0     | 0     |
| Black or African American  | 0   | 2     | 1     |
| White  | 64  | 104   | 51    |
| More than one race   | 0   | 0     | 0     |
| Unknown or Not Reported  | 5   | 10    | 13    |
| Region of Enrollment   |   |       |       |
| Units: Subjects  |   |       |       |
| Puerto Rico  | 0   | 1     | 0     |
| Romania  | 1   | 1     | 0     |
| Hungary  | 1   | 0     | 0     |
| United States  | 23  | 35    | 13    |
| Japan  | 6   | 14    | 5     |
| United Kingdom   | 8   | 17    | 8     |
| Spain  | 10  | 21    | 8     |
| Canada   | 6   | 8     | 5     |
| South Korea  | 1   | 7     | 3     |
| Belgium  | 5   | 2     | 0     |
| Poland   | 6   | 8     | 6     |
| France   | 4   | 9     | 12    |
| Australia  | 3   | 13    | 8     |
| Germany  | 2   | 3     | 7     |
| ADAS-Cog13 (13-item Alzheimer's Disease Assessment Scale)  |   |       |       |
| ADAS-Cog13, a 13-item rating scale, measured the severity of cognitive dysfunction in persons with Alzheimer's disease (AD). Scores ranged from 0 to 85, with a higher score indicating worse cognitive functioning. Details are from AZES baseline. |   |       |       |
| Units: Units on a Scale  |   |       |       |
| arithmetic mean  | 27.9  | 29.6  | 27.0  |
| standard deviation   | ± 8.3   | ± 7.8 | ± 7.5 |
| <b>Reporting group values</b>  | AZES Lanabecestat<br>50 mg/AZFD<br>Lanabecestat 50 mg | Total |       |
| Number of subjects   | 131   | 421   |       |
| Age categorical  |   |       |       |
| Units: Subjects  |   |       |       |
| In utero   |   | 0     |       |
| Preterm newborn infants<br>(gestational age < 37 wks)  |   | 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)   |   | 0     |       |
| From 65-84 years   |   | 0     |       |
| 85 years and over  |   | 0     |       |



|  |       |     |  |
|--|-------|-----|--|
| Age continuous   |       |     |  |
| Details are from AZES baseline.  |       |     |  |
| Units: years   |       |     |  |
| arithmetic mean  | 70.1  |     |  |
| standard deviation   | ± 6.7 | -   |  |
| Gender categorical   |       |     |  |
| Units: Subjects  |       |     |  |
| Female   | 75    | 226 |  |
| Male   | 56    | 195 |  |
| Ethnicity (NIH/OMB)  |       |     |  |
| Units: Subjects  |       |     |  |
| Hispanic or Latino   | 3     | 18  |  |
| Not Hispanic or Latino   | 114   | 345 |  |
| Unknown or Not Reported  | 14    | 58  |  |
| Race (NIH/OMB)   |       |     |  |
| Units: Subjects  |       |     |  |
| American Indian or Alaska Native   | 0     | 0   |  |
| Asian  | 16    | 56  |  |
| Native Hawaiian or Other Pacific Islander  | 0     | 0   |  |
| Black or African American  | 0     | 3   |  |
| White  | 106   | 325 |  |
| More than one race   | 0     | 0   |  |
| Unknown or Not Reported  | 9     | 37  |  |
| Region of Enrollment   |       |     |  |
| Units: Subjects  |       |     |  |
| Puerto Rico  | 0     | 1   |  |
| Romania  | 0     | 2   |  |
| Hungary  | 0     | 1   |  |
| United States  | 23    | 94  |  |
| Japan  | 14    | 39  |  |
| United Kingdom   | 13    | 46  |  |
| Spain  | 21    | 60  |  |
| Canada   | 14    | 33  |  |
| South Korea  | 2     | 13  |  |
| Belgium  | 4     | 11  |  |
| Poland   | 14    | 34  |  |
| France   | 8     | 33  |  |
| Australia  | 6     | 30  |  |
| Germany  | 12    | 24  |  |
| ADAS-Cog13 (13-item Alzheimer's Disease Assessment Scale)  |       |     |  |
| ADAS-Cog13, a 13-item rating scale, measured the severity of cognitive dysfunction in persons with Alzheimer's disease (AD). Scores ranged from 0 to 85, with a higher score indicating worse cognitive functioning. Details are from AZES baseline. |       |     |  |
| Units: Units on a Scale  |       |     |  |
| arithmetic mean  | 27.1  |     |  |
| standard deviation   | ± 7.5 | -   |  |

## End points

### End points reporting groups

|   |   |
|---|---|
| Reporting group title   | AZES Placebo/AZFD Lanabecestat 20 mg            |
| Reporting group description:  |   |
| Participants who received placebo in the feeder study (AZES) were randomized to receive lanabecestat 20 mg.   |   |
| Reporting group title   | AZES Lanabecestat 20 mg/AZFD Lanabecestat 20 mg |
| Reporting group description:  |   |
| Participants who received lanabecestat 20 mg in the feeder study (AZES) were randomized to receive lanabecestat 20 mg. 1 participant was incorrectly marked as "Completed" rather than study terminated by Sponsor. |   |
| Reporting group title   | AZES Placebo/AZFD Lanabecestat 50 mg            |
| Reporting group description:  |   |
| Participants who received placebo in the feeder study (AZES) were randomized to receive lanabecestat 50 mg.   |   |
| Reporting group title   | AZES Lanabecestat 50 mg/AZFD Lanabecestat 50 mg |
| Reporting group description:  |   |
| Participants who received lanabecestat 50 mg in the feeder study (AZES) were randomized to receive lanabecestat 50 mg.  |   |

### Primary: Change From Baseline Analysis on the 13-item Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-Cog13)

|  |  |
|--|--|
| End point title  | Change From Baseline Analysis on the 13-item Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-Cog13) <sup>[1]</sup> |
| End point description:   |  |
| <p>ADAS-Cog13 is a psychometric instrument that evaluates word recall, ability to follow commands, constructional praxis, naming, ideational praxis, orientation, word recognition, memory, comprehension of spoken language, word-finding, and language ability, with a measure of delayed word recall and concentration/ distractibility. The total score of the 13-item scale ranges from 0 to 85, with an increase in score indicating cognitive worsening. Least Squares (LS) mean was determined by mixed-model repeated measures (MMRM) model with factors for treatment, visit, treatment*visit, baseline efficacy score, baseline efficacy score-by-visit interaction, disease status at baseline, APOE4 (apolipoprotein E4) status, AChEI (acetylcholinesterase inhibitor) use at baseline, age at baseline, and pooled country. Analysis Population Description (APD): All AZFD participants who received at least one dose of study drug and have baseline and at least one post-baseline data for ADAS-Cog13 measure.</p> |  |
| End point type   | Primary  |
| End point timeframe:   |  |
| AZES Baseline through AZFD Week 26   |  |

#### 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: Because the feeder study AZES was stopped for futility, the original primary efficacy analysis (Delayed Start analysis) was replaced with MMRM analysis across AZES and AZFD. No comparisons between treatment groups were made.

| End point values                    | AZES Placebo/AZFD Lanabecestat 20 mg | AZES Lanabecestat 20 mg/AZFD Lanabecestat 20 mg | AZES Placebo/AZFD Lanabecestat 50 mg | AZES Lanabecestat 50 mg/AZFD Lanabecestat 50 mg |
|-------------------------------------|--------------------------------------|---|--------------------------------------|---|
| Subject group type                  | Reporting group                      | Reporting group                                 | Reporting group                      | Reporting group                                 |
| Number of subjects analysed         | 76                                   | 139   | 75                                   | 131   |
| Units: Units on a scale             |                                      |   |                                      |   |
| least squares mean (standard error) | 9.61 (± 1.60)                        | 9.25 (± 1.21)                                   | 8.41 (± 1.65)                        | 10.41 (± 1.25)                                  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Delayed Start Analysis on the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory Instrumental Items (ADCS-iADL)

|  |   |
|--|---|
| End point title  | Change From Baseline in Delayed Start Analysis on the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory Instrumental Items (ADCS-iADL) |
| End point description:<br>The ADCS-ADL is a 23-item inventory developed as a rater-administered questionnaire answered by the participant's caregiver. The ADCS-ADL measures both basic and instrumental activities of daily living by participants. The range for the ADCS-iADL is 0-59 with higher scores reflecting better performance. LS Mean was determined by MMRM with factors for treatment, visit, treatment*visit, baseline efficacy score, baseline efficacy score-by-visit interaction, disease status at baseline, APOE4 status, AChEI use at baseline, age at baseline, and pooled country.<br>APD: All AZFD participants who received at least one dose of study drug and have baseline and at least one post-baseline data for ADCS-iADL measure. |   |
| End point type   | Secondary   |
| End point timeframe:<br>AZES Baseline through AZFD Week 26   |   |

| End point values                    | AZES<br>Placebo/AZFD<br>Lanabecestat<br>20 mg | AZES<br>Lanabecestat<br>20 mg/AZFD<br>Lanabecestat<br>20 mg | AZES<br>Placebo/AZFD<br>Lanabecestat<br>50 mg | AZES<br>Lanabecestat<br>50 mg/AZFD<br>Lanabecestat<br>50 mg |
|-------------------------------------|---|---|---|---|
| Subject group type                  | Reporting group                               | Reporting group   | Reporting group                               | Reporting group   |
| Number of subjects analysed         | 76  | 139   | 74  | 129   |
| Units: Units on a scale             |   |   |   |   |
| least squares mean (standard error) | -9.19 (± 1.47)                                | -8.45 (± 1.10)  | -7.37 (± 1.51)                                | -7.48 (± 1.14)  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Delayed Start Analysis on the Functional Activities Questionnaire (FAQ) Score

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Delayed Start Analysis on the Functional Activities Questionnaire (FAQ) Score |
|-----------------|---|

End point description:

FAQ is a 10-item, caregiver-questionnaire and was administered to the study partner and asked to rate the participant's ability to perform a variety of activities ranging from writing checks, assembling tax records, shopping, playing games, food preparation, traveling, keeping appointments, traveling out of

neighborhood, keeping track of current events and understanding media. FAQ total score was calculated by adding the scores from each of the 10 items. Each activity is rated on a scale from 0 to 3 (Never did and would have difficulty now =1; Never did but could do now =0; Normal =0; Has difficulty but does by self =1; Requires assistance =2; Dependent =3). FAQ scale is 0 to 30, with higher scores indicating greater impairment. LS Mean was determined by MMRM.

APD: All AZFD participants who received at least one dose of study drug and have baseline and at least one post-baseline data for FAQ score.

|                                    |           |
|------------------------------------|-----------|
| End point type                     | Secondary |
| End point timeframe:               |           |
| AZES Baseline through AZFD Week 26 |           |

| End point values                    | AZES<br>Placebo/AZFD<br>Lanabecestat<br>20 mg | AZES<br>Lanabecestat<br>20 mg/AZFD<br>Lanabecestat<br>20 mg | AZES<br>Placebo/AZFD<br>Lanabecestat<br>50 mg | AZES<br>Lanabecestat<br>50 mg/AZFD<br>Lanabecestat<br>50 mg |
|-------------------------------------|---|---|---|---|
| Subject group type                  | Reporting group                               | Reporting group   | Reporting group                               | Reporting group   |
| Number of subjects analysed         | 76  | 137   | 74  | 130   |
| Units: Units on a scale             |   |   |   |   |
| least squares mean (standard error) | 6.28 (± 0.98)                                 | 7.09 (± 0.76)   | 6.73 (± 1.01)                                 | 6.91 (± 0.79)   |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Delayed Start Analysis on the Integrated Alzheimer's Disease Rating Scale (iADRS) Score

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Delayed Start Analysis on the Integrated Alzheimer's Disease Rating Scale (iADRS) Score |
|-----------------|---|

End point description:

The iADRS is a composite that measures both cognition and function. The iADRS comprises scores from the ADAS-Cog and the ADCS-iADL. The iADRS is calculated as a linear combination of the total scores of the ADAS-Cog13 (score range 0 to 85 with higher scores reflecting worse performance) and the ADCS-iADL (score range from 0-59 with higher scores reflecting better performance). The iADRS score ranges from 0 to 144 with higher scores indicating greater impairment. LS Mean was determined by MMRM with factors for treatment, visit, treatment\*visit, baseline efficacy score, baseline efficacy score-by-visit interaction, disease status at baseline, APOE4 status, AChEI use at baseline, age at baseline, and pooled country.

APD: All AZFD participants who received at least one dose of study drug and have baseline and at least one post-baseline data for iADRS.

|                                    |           |
|------------------------------------|-----------|
| End point type                     | Secondary |
| End point timeframe:               |           |
| AZES Baseline through AZFD Week 26 |           |

| End point values                    | AZES<br>Placebo/AZFD<br>Lanabecestat<br>20 mg | AZES<br>Lanabecestat<br>20 mg/AZFD<br>Lanabecestat<br>20 mg | AZES<br>Placebo/AZFD<br>Lanabecestat<br>50 mg | AZES<br>Lanabecestat<br>50 mg/AZFD<br>Lanabecestat<br>50 mg |
|-------------------------------------|---|---|---|---|
| Subject group type                  | Reporting group                               | Reporting group   | Reporting group                               | Reporting group   |
| Number of subjects analysed         | 76  | 138   | 72  | 123   |
| Units: Units on a scale             |   |   |   |   |
| least squares mean (standard error) | -18.85 ( $\pm$<br>2.58)                       | -17.57 ( $\pm$<br>1.97)                                     | -15.37 ( $\pm$<br>2.76)                       | -18.37 ( $\pm$<br>2.09)                                     |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Delayed Start Analysis on the Mini-Mental Status Examination (MMSE)

|  |   |
|--|---|
| End point title  | Change From Baseline in Delayed Start Analysis on the Mini-Mental Status Examination (MMSE) |
| End point description:   |   |
| <p>The MMSE is an instrument used to assess a participant's cognitive function. The MMSE assesses orientation to time and place, immediate and delayed recall of words, attention and calculation, language (naming, comprehension and repetition), and spatial ability (copying a figure). The range for MMSE total Score is 0 to 30, with a higher score indicating better cognitive performance. LS Mean was determined by MMRM methodology with factors for treatment, visit, treatment*visit, baseline efficacy score, baseline efficacy score-by-visit interaction, disease status at baseline, APOE4 status, AChEI use at baseline, age at baseline, and pooled country.</p> <p>APD: All AZFD participants who received at least one dose of study drug and have baseline and at least one post-baseline data for MMSE.</p> |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| AZES Baseline through AZFD Week 26   |   |

| End point values                    | AZES<br>Placebo/AZFD<br>Lanabecestat<br>20 mg | AZES<br>Lanabecestat<br>20 mg/AZFD<br>Lanabecestat<br>20 mg | AZES<br>Placebo/AZFD<br>Lanabecestat<br>50 mg | AZES<br>Lanabecestat<br>50 mg/AZFD<br>Lanabecestat<br>50 mg |
|-------------------------------------|---|---|---|---|
| Subject group type                  | Reporting group                               | Reporting group   | Reporting group                               | Reporting group   |
| Number of subjects analysed         | 76  | 139   | 75  | 131   |
| Units: Units on a scale             |   |   |   |   |
| least squares mean (standard error) | -5.84 ( $\pm$ 0.71)                           | -5.73 ( $\pm$ 0.54)   | -4.72 ( $\pm$ 0.72)                           | -5.25 ( $\pm$ 0.56)   |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Delayed Start Analysis on the ADAS-Cog13

|                 |  |
|-----------------|--|
| End point title | Delayed Start Analysis on the ADAS-Cog13 |
|-----------------|--|

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**End point description:**

ADAS-Cog13 (13-item version of ADAS Cog) is a psychometric instrument that evaluates word recall, ability to follow commands, constructional praxis, naming, ideational praxis, orientation, word recognition, memory, comprehension of spoken language, word-finding, and language ability, with a measure of delayed word recall and concentration/ distractibility. The total score of the 13-item scale ranges from 0 to 85, with an increase in score indicating cognitive worsening. Least Squares (LS) mean was determined by mixed-model repeated measures (MMRM) model with factors for treatment, visit, treatment\*visit, baseline efficacy score, baseline efficacy score-by-visit interaction, disease status at baseline, APOE4 (apolipoprotein E4) status, AChEI (acetylcholinesterase inhibitor) use at baseline, age at baseline, and pooled country.

APD: All AZFD participants who received at least one dose of study drug and have baseline and at least one post-baseline data for ADAS-Cog13 measure.

---

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

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**End point timeframe:**

AZES Baseline through AZFD Week 52

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| End point values                    | AZES<br>Placebo/AZFD<br>Lanabecestat<br>20 mg | AZES<br>Lanabecestat<br>20 mg/AZFD<br>Lanabecestat<br>20 mg | AZES<br>Placebo/AZFD<br>Lanabecestat<br>50 mg | AZES<br>Lanabecestat<br>50 mg/AZFD<br>Lanabecestat<br>50 mg |
|-------------------------------------|---|---|---|---|
| Subject group type                  | Reporting group                               | Reporting group   | Reporting group                               | Reporting group   |
| Number of subjects analysed         | 76  | 139   | 75  | 131   |
| Units: Units on a scale             |   |   |   |   |
| least squares mean (standard error) | 16.64 (± 3.45)                                | 12.40 (± 2.25)  | 16.79 (± 2.47)                                | 15.05 (± 2.06)  |

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**Statistical analyses**

No statistical analyses for this end point

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## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up To 156 Weeks

Adverse event reporting additional description:

All AZFD participants who received at least one dose of study drug.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 21.1 |
|--------------------|------|

### Reporting groups

|                       |   |
|-----------------------|---|
| Reporting group title | AZES Lanabecestat 20 mg/AZFD Lanabecestat 20 mg |
|-----------------------|---|

Reporting group description:

Participants who received Lanabecestat 20 mg in the feeder study (AZES) received Lanabecestat 20 mg in AZFD.

|                       |   |
|-----------------------|---|
| Reporting group title | AZES Lanabecestat 50 mg/AZFD Lanabecestat 50 mg |
|-----------------------|---|

Reporting group description:

Participants who received Lanabecestat 50 mg in the feeder study (AZES) received Lanabecestat 50 mg in AZFD.

|                       |                                      |
|-----------------------|--------------------------------------|
| Reporting group title | AZES Placebo/AZFD Lanabecestat 20 mg |
|-----------------------|--------------------------------------|

Reporting group description:

Participants who received placebo in the feeder study (AZES) received Lanabecestat 20 mg in AZFD.

|                       |                                      |
|-----------------------|--------------------------------------|
| Reporting group title | AZES Placebo/AZFD Lanabecestat 50 mg |
|-----------------------|--------------------------------------|

Reporting group description:

Participants who received placebo in the feeder study (AZES) received Lanabecestat 50 mg in AZFD.

| Serious adverse events  | AZES Lanabecestat 20 mg/AZFD Lanabecestat 20 mg | AZES Lanabecestat 50 mg/AZFD Lanabecestat 50 mg | AZES Placebo/AZFD Lanabecestat 20 mg |
|---|---|---|--------------------------------------|
| Total subjects affected by serious adverse events                   |   |   |                                      |
| subjects affected / exposed   | 8 / 139 (5.76%)                                 | 7 / 131 (5.34%)                                 | 3 / 76 (3.95%)                       |
| number of deaths (all causes)                                       | 0   | 1   | 0                                    |
| number of deaths resulting from adverse events                      | 0   | 0   | 0                                    |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |   |   |                                      |
| breast cancer in situ   |   |   |                                      |
| alternative dictionary used: MedDRA 21.1                            |   |   |                                      |
| subjects affected / exposed   | 1 / 139 (0.72%)                                 | 0 / 131 (0.00%)                                 | 0 / 76 (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                                |
| breast cancer metastatic  |   |   |                                      |
| alternative dictionary used: MedDRA 21.1                            |   |   |                                      |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 1 / 139 (0.72%) | 0 / 131 (0.00%) | 0 / 76 (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          |
| laryngeal squamous cell carcinoma               |                 |                 |                |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                |
| subjects affected / exposed                     | 0 / 139 (0.00%) | 0 / 131 (0.00%) | 1 / 76 (1.32%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Investigations                                  |                 |                 |                |
| electrocardiogram repolarisation abnormality    |                 |                 |                |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                |
| subjects affected / exposed                     | 0 / 139 (0.00%) | 0 / 131 (0.00%) | 0 / 76 (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          |
| weight decreased                                |                 |                 |                |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                |
| subjects affected / exposed                     | 0 / 139 (0.00%) | 1 / 131 (0.76%) | 0 / 76 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Injury, poisoning and procedural complications  |                 |                 |                |
| fall  |                 |                 |                |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                |
| subjects affected / exposed                     | 0 / 139 (0.00%) | 1 / 131 (0.76%) | 1 / 76 (1.32%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| femoral neck fracture                           |                 |                 |                |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                |
| subjects affected / exposed                     | 1 / 139 (0.72%) | 0 / 131 (0.00%) | 1 / 76 (1.32%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| femur fracture                                  |                 |                 |                |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                |



|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 139 (0.00%) | 1 / 131 (0.76%) | 0 / 76 (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          |
| radiation proctitis                             |                 |                 |                |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                |
| subjects affected / exposed                     | 0 / 139 (0.00%) | 0 / 131 (0.00%) | 0 / 76 (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                               |                 |                 |                |
| bradycardia                                     |                 |                 |                |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                |
| subjects affected / exposed                     | 0 / 139 (0.00%) | 1 / 131 (0.76%) | 0 / 76 (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          |
| Nervous system disorders                        |                 |                 |                |
| ischaemic stroke                                |                 |                 |                |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                |
| subjects affected / exposed                     | 1 / 139 (0.72%) | 0 / 131 (0.00%) | 0 / 76 (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          |
| optic neuritis                                  |                 |                 |                |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                |
| subjects affected / exposed                     | 1 / 139 (0.72%) | 0 / 131 (0.00%) | 0 / 76 (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          |
| Gastrointestinal disorders                      |                 |                 |                |
| colitis   |                 |                 |                |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                |
| subjects affected / exposed                     | 1 / 139 (0.72%) | 0 / 131 (0.00%) | 0 / 76 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| enteritis                                       |                 |                 |                |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                |

|  |                 |                 |                |
|--|-----------------|-----------------|----------------|
| subjects affected / exposed  | 1 / 139 (0.72%) | 0 / 131 (0.00%) | 0 / 76 (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          |
| oesophageal motility disorder<br>alternative dictionary used:<br>MedDRA 21.1 |                 |                 |                |
| subjects affected / exposed  | 0 / 139 (0.00%) | 1 / 131 (0.76%) | 0 / 76 (0.00%) |
| occurrences causally related to treatment / all                              | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all                                   | 0 / 0           | 0 / 0           | 0 / 0          |
| small intestinal obstruction<br>alternative dictionary used:<br>MedDRA 21.1  |                 |                 |                |
| subjects affected / exposed  | 0 / 139 (0.00%) | 0 / 131 (0.00%) | 0 / 76 (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  |                 |                 |                |
| depression<br>alternative dictionary used:<br>MedDRA 21.1                    |                 |                 |                |
| subjects affected / exposed  | 1 / 139 (0.72%) | 0 / 131 (0.00%) | 0 / 76 (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          |
| neuropsychiatric symptoms<br>alternative dictionary used:<br>MedDRA 21.1     |                 |                 |                |
| subjects affected / exposed  | 0 / 139 (0.00%) | 1 / 131 (0.76%) | 0 / 76 (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                              |                 |                 |                |
| back pain<br>alternative dictionary used:<br>MedDRA 21.1                     |                 |                 |                |
| subjects affected / exposed  | 0 / 139 (0.00%) | 1 / 131 (0.76%) | 0 / 76 (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 chest pain<br>alternative dictionary used:<br>MedDRA 21.1    |                 |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 139 (0.00%) | 1 / 131 (0.76%) | 0 / 76 (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                     |                 |                 |                |
| diverticulitis                                  |                 |                 |                |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                |
| subjects affected / exposed                     | 0 / 139 (0.00%) | 1 / 131 (0.76%) | 0 / 76 (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          |
| influenza                                       |                 |                 |                |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                |
| subjects affected / exposed                     | 0 / 139 (0.00%) | 0 / 131 (0.00%) | 0 / 76 (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                                       |                 |                 |                |
| alternative dictionary used: MedDRA 21.1        |                 |                 |                |
| subjects affected / exposed                     | 0 / 139 (0.00%) | 1 / 131 (0.76%) | 0 / 76 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0          |

| Serious adverse events  | AZES Placebo/AZFD<br>Lanabecestat 50 mg |  |  |
|---|---|--|--|
| Total subjects affected by serious adverse events                   |   |  |  |
| subjects affected / exposed   | 5 / 74 (6.76%)                          |  |  |
| number of deaths (all causes)                                       | 0                                       |  |  |
| number of deaths resulting from adverse events                      | 0                                       |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |   |  |  |
| breast cancer in situ   |   |  |  |
| alternative dictionary used: MedDRA 21.1                            |   |  |  |
| subjects affected / exposed   | 0 / 74 (0.00%)                          |  |  |
| occurrences causally related to treatment / all                     | 0 / 0                                   |  |  |
| deaths causally related to treatment / all                          | 0 / 0                                   |  |  |
| breast cancer metastatic  |   |  |  |
| alternative dictionary used: MedDRA 21.1                            |   |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 0 / 74 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| laryngeal squamous cell carcinoma               |                |  |  |
| alternative dictionary used: MedDRA 21.1        |                |  |  |
| subjects affected / exposed                     | 0 / 74 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Investigations                                  |                |  |  |
| electrocardiogram repolarisation abnormality    |                |  |  |
| alternative dictionary used: MedDRA 21.1        |                |  |  |
| subjects affected / exposed                     | 1 / 74 (1.35%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| weight decreased                                |                |  |  |
| alternative dictionary used: MedDRA 21.1        |                |  |  |
| subjects affected / exposed                     | 0 / 74 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Injury, poisoning and procedural complications  |                |  |  |
| fall  |                |  |  |
| alternative dictionary used: MedDRA 21.1        |                |  |  |
| subjects affected / exposed                     | 0 / 74 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| femoral neck fracture                           |                |  |  |
| alternative dictionary used: MedDRA 21.1        |                |  |  |
| subjects affected / exposed                     | 0 / 74 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| femur fracture                                  |                |  |  |
| alternative dictionary used: MedDRA 21.1        |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 0 / 74 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| radiation proctitis                             |                |  |  |
| alternative dictionary used: MedDRA 21.1        |                |  |  |
| subjects affected / exposed                     | 1 / 74 (1.35%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Cardiac disorders                               |                |  |  |
| bradycardia                                     |                |  |  |
| alternative dictionary used: MedDRA 21.1        |                |  |  |
| subjects affected / exposed                     | 0 / 74 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Nervous system disorders                        |                |  |  |
| ischaemic stroke                                |                |  |  |
| alternative dictionary used: MedDRA 21.1        |                |  |  |
| subjects affected / exposed                     | 0 / 74 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| optic neuritis                                  |                |  |  |
| alternative dictionary used: MedDRA 21.1        |                |  |  |
| subjects affected / exposed                     | 0 / 74 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastrointestinal disorders                      |                |  |  |
| colitis   |                |  |  |
| alternative dictionary used: MedDRA 21.1        |                |  |  |
| subjects affected / exposed                     | 0 / 74 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| enteritis                                       |                |  |  |
| alternative dictionary used: MedDRA 21.1        |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 0 / 74 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| oesophageal motility disorder                   |                |  |  |
| alternative dictionary used: MedDRA 21.1        |                |  |  |
| subjects affected / exposed                     | 0 / 74 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| small intestinal obstruction                    |                |  |  |
| alternative dictionary used: MedDRA 21.1        |                |  |  |
| subjects affected / exposed                     | 1 / 74 (1.35%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Psychiatric disorders                           |                |  |  |
| depression                                      |                |  |  |
| alternative dictionary used: MedDRA 21.1        |                |  |  |
| subjects affected / exposed                     | 0 / 74 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| neuropsychiatric symptoms                       |                |  |  |
| alternative dictionary used: MedDRA 21.1        |                |  |  |
| subjects affected / exposed                     | 1 / 74 (1.35%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Musculoskeletal and connective tissue disorders |                |  |  |
| back pain                                       |                |  |  |
| alternative dictionary used: MedDRA 21.1        |                |  |  |
| subjects affected / exposed                     | 0 / 74 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| musculoskeletal chest pain                      |                |  |  |
| alternative dictionary used: MedDRA 21.1        |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 0 / 74 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Infections and infestations                     |                |  |  |
| diverticulitis                                  |                |  |  |
| alternative dictionary used: MedDRA 21.1        |                |  |  |
| subjects affected / exposed                     | 0 / 74 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| influenza                                       |                |  |  |
| alternative dictionary used: MedDRA 21.1        |                |  |  |
| subjects affected / exposed                     | 1 / 74 (1.35%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| pneumonia                                       |                |  |  |
| alternative dictionary used: MedDRA 21.1        |                |  |  |
| subjects affected / exposed                     | 0 / 74 (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 %

| <b>Non-serious adverse events</b>                     | AZES Lanabecestat<br>20 mg/AZFD<br>Lanabecestat 20 mg | AZES Lanabecestat<br>50 mg/AZFD<br>Lanabecestat 50 mg | AZES Placebo/AZFD<br>Lanabecestat 20 mg |
|---|---|---|---|
| Total subjects affected by non-serious adverse events |   |   |   |
| subjects affected / exposed                           | 23 / 139 (16.55%)                                     | 17 / 131 (12.98%)                                     | 11 / 76 (14.47%)                        |
| Injury, poisoning and procedural complications        |   |   |   |
| fall  |   |   |   |
| alternative dictionary used: MedDRA 21.1              |   |   |   |
| subjects affected / exposed                           | 7 / 139 (5.04%)                                       | 5 / 131 (3.82%)                                       | 4 / 76 (5.26%)                          |
| occurrences (all)                                     | 8   | 8   | 4                                       |
| Gastrointestinal disorders                            |   |   |   |
| diarrhoea   |   |   |   |
| alternative dictionary used: MedDRA 21.1              |   |   |   |

|   |                       |                      |                     |
|---|-----------------------|----------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)  | 8 / 139 (5.76%)<br>8  | 6 / 131 (4.58%)<br>6 | 2 / 76 (2.63%)<br>2 |
| Psychiatric disorders<br>depression<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)            | 3 / 139 (2.16%)<br>3  | 2 / 131 (1.53%)<br>2 | 4 / 76 (5.26%)<br>4 |
| Infections and infestations<br>nasopharyngitis<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all) | 8 / 139 (5.76%)<br>10 | 5 / 131 (3.82%)<br>7 | 1 / 76 (1.32%)<br>1 |

|  |   |  |  |
|--|---|--|--|
| <b>Non-serious adverse events</b>  | AZES Placebo/AZFD<br>Lanabecestat 50 mg |  |  |
| Total subjects affected by non-serious<br>adverse events<br>subjects affected / exposed  | 8 / 74 (10.81%)                         |  |  |
| Injury, poisoning and procedural<br>complications<br>fall<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all) | 3 / 74 (4.05%)<br>3                     |  |  |
| Gastrointestinal disorders<br>diarrhoea<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)                   | 2 / 74 (2.70%)<br>2                     |  |  |
| Psychiatric disorders<br>depression<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 74 (0.00%)<br>0                     |  |  |
| Infections and infestations<br>nasopharyngitis<br>alternative dictionary used:<br>MedDRA 21.1<br>subjects affected / exposed<br>occurrences (all)            | 3 / 74 (4.05%)<br>3                     |  |  |





## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 06 February 2018 | Amendment (a): Amended to<br>-Extend the study additional year from original protocol.<br>-Provided Clarification of when temporary discontinuation would be considered due to vasogenic edema. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

An independent assessment concluded the trial was not likely to meet the primary endpoint upon completion and therefore, trial stopped for futility. Because of this futility, the originally planned delayed-start analysis was not performed.

Notes: