# Clinical trial results:
# A Phase 2, Double-Blind, Randomized, Placebo Controlled Study to Evaluate the Efficacy and Safety of ASP8232 as Add-On Therapy to Angiotensin Converting Enzyme inhibitor (ACEi) or Angiotensin Receptor Blocker (ARB) in Reducing Albuminuria in Patients with Type 2 Diabetes and Chronic Kidney Disease

## Summary

| | |
|---|---|
| EudraCT number | 2014-002349-23 |
| Trial protocol | DK GB HU CZ DE BE IT NL ES PL |
| Global end of trial date | 15 March 2017 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 21 March 2018 |
| First version publication date | 21 March 2018 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | 8232-CL-0004 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02358096 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Astellas Pharma Europe BV |
| Sponsor organisation address | Sylviusweg 62, BE Leiden, Netherlands, 2333 |
| Public contact | Clinical Trial Disclosure, Astellas Pharma Europe BV, astellas.resultsdisclosure@astellas.com |
| Scientific contact | Clinical Trial Disclosure, Astellas Pharma Europe BV, astellas.resultsdisclosure@astellas.com |

Notes:

**Paediatric regulatory details**

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

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 15 March 2017 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 15 March 2017 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The main objective of the trial was to evaluate the efficacy of ASP8232 in reducing urinary albumin to creatinine ratio (UACR) in participants with Type 2 Diabetes Mellitus (T2DM) and Chronic Kidney Disease (CKD) at 12 weeks compared to placebo.

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, on the protection of human rights, and with the ethical principles that have their origin in the Declaration of Helsinki. Astellas ensures that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal, national and/or regional legislation related to the privacy and protection of personal information.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 17 March 2015 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Czech Republic: 20 |
| Country: Number of subjects enrolled | Denmark: 12 |
| Country: Number of subjects enrolled | Germany: 10 |
| Country: Number of subjects enrolled | Hungary: 23 |
| Country: Number of subjects enrolled | Italy: 9 |
| Country: Number of subjects enrolled | Netherlands: 7 |
| Country: Number of subjects enrolled | Poland: 19 |
| Country: Number of subjects enrolled | Spain: 19 |
| Country: Number of subjects enrolled | United Kingdom: 6 |
| Worldwide total number of subjects | 125 |
| EEA total number of subjects | 125 |

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) | 32 |
| From 65 to 84 years | 93 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 64 contracted sites in a total of 10 countries and regions. The randomization schedule was stratified by country. Participants selected for the study were suffering from Type 2 Diabetes Mellitus (T2DM) and Chronic Kidney Disease (CKD).

### Pre-assignment

Screening details:

Participants who met eligibility criteria were enrolled in the study. The study consisted of a screening period of 1 week, a 5-week pretreatment period, a 12-week treatment period and a 24-week follow-up period. Participants were randomized to 1 of the 2 treatments in a 1:1 ratio to ASP8232 or placebo.

### Period 1

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

Blinding implementation details:

Participants were randomly assigned to 1 of 2 treatment arms, ASP8232 or placebo in a double-blind fashion such that the investigator, sponsor's study management team, CRO staff, site staff and the participant did not know which treatment was being administered.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | ASP8232 |

Arm description:

Participants received  40 mg ASP8232 orally once a day for 84 consecutive days.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | ASP8232 |
| Investigational medicinal product code | ASP8232 |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received 40 mg of ASP8232 orally once a day. It was administered in the morning with or without food.

| | |
|---|---|
| **Arm title** | Placebo |

Arm description:

Participants received 40 mg matching placebo orally once a day for 84 consecutive days.

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

Dosage and administration details:

Participants received 40 mg of matching placebo orally once a day. It was administered in the morning with or without food

| **Number of subjects in period 1** | ASP8232 | Placebo |
|---|---|---|
| Started | 64 | 61 |
| Received Treatment | 64 | 61 |
| Completed | 58 | 59 |
| Not completed | 6 | 2 |
| Adverse event, serious fatal | 1 | - |
| Participant Randomized in Error | - | 1 |
| Consent withdrawn by subject | 5 | 1 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | ASP8232 |
| Reporting group description: | |
| Participants received 40 mg ASP8232 orally once a day for 84 consecutive days. | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Participants received 40 mg matching placebo orally once a day for 84 consecutive days. | |

| Reporting group values | ASP8232 | Placebo | Total |
|---|---|---|---|
| Number of subjects | 64 | 61 | 125 |
| Age categorical | | | |
| Units: Subjects | | | |
| Age continuous | | | |
| The analysis population consisted of all participants who were randomized to receive study treatment. | | | |
| Units: years | | | |
| arithmetic mean | 69.5 | 68.6 | |
| standard deviation | ± 7.4 | ± 6.7 | - |
| Gender categorical | | | |
| The analysis population consisted of all participants who were randomized to receive study treatment. | | | |
| Units: | | | |
| Male | 45 | 51 | 96 |
| Female | 19 | 10 | 29 |
| Race | | | |
| The analysis population consisted of all participants who were randomized to receive study treatment. | | | |
| Units: Subjects | | | |
| White | 60 | 58 | 118 |
| Black or African American | 1 | 0 | 1 |
| Asian | 2 | 2 | 4 |
| Other | 1 | 1 | 2 |
| Weight | | | |
| The analysis population consisted of all participants who were randomized to receive study treatment. | | | |
| Units: kilograms (kg) | | | |
| arithmetic mean | 92.84 | 94.74 | |
| standard deviation | ± 18.57 | ± 20.32 | - |
| Height | | | |
| The analysis population consisted of all participants who were randomized to receive study treatment. | | | |
| Units: centimeters (cm) | | | |
| arithmetic mean | 169.2 | 171.3 | |
| standard deviation | ± 9.0 | ± 8.6 | - |
| Body Mass Index (BMI) | | | |
| The analysis population consisted of all participants who were randomized to receive study treatment. | | | |
| Units: kg/m^2 | | | |
| arithmetic mean | 32.43 | 32.20 | |
| standard deviation | ± 5.75 | ± 6.40 | - |
| Duration of Chronic Kidney Disease (CKD) | | | |

| | | | |
|---|---|---|---|
| The analysis population was full analysis set (FAS), which consisted of all participants who were randomized and received at least one dose of study drug and had at least one post-baseline urinary albumin to creatinine ratio (UACR)/ albumin excretion rate (AER) measurement. The number of participants used for the analysis was ASP8232=60 and Placebo=60. Duration in years was calculated as: (randomization date - diagnosis date + 1) / 365.25. | | | |
| Units: Years<br>arithmetic mean<br>standard deviation | <br>4.98<br>± 4.42 | <br>5.46<br>± 4.20 | <br><br>- |
| Duration of Type 2 Diabetes Mellitus (T2DM) | | | |
| The analysis population was the FAS. The number of participants used for the analysis was ASP8232=60 and Placebo=60. Duration in years was calculated as: (randomization date - diagnosis date + 1) / 365.25. | | | |
| Units: Years<br>arithmetic mean<br>standard deviation | <br>16.34<br>± 7.73 | <br>16.24<br>± 7.04 | <br><br>- |
| Baseline for Percent Change in First Morning Void (FMV) Urinary Albumin to Creatinine Ratio (UACR) | | | |
| The analysis population was the FAS. Baseline was defined as the geometric mean (GM) of all UACR measurements corresponding to FMV urine samples returned on site at visits 4 and 5 during pretreatment period. The number of participants used for the analysis was ASP8232=60 and Placebo=60. | | | |
| Units: Year<br>geometric mean<br>full range (min-max) | <br>745.237<br>418.400 to 1229.835 | <br>686.911<br>388.400 to 1062.855 | <br><br>- |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | ASP8232 |
| Reporting group description: | |
| Participants received 40 mg ASP8232 orally once a day for 84 consecutive days. | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Participants received 40 mg matching placebo orally once a day for 84 consecutive days. | |

### Primary: Change From Baseline in Mean Change of Log-transformed Urinary Albumin to Creatinine Ratio (UACR) at Week 12 End of Treatment (EoT)

| | |
|---|---|
| End point title | Change From Baseline in Mean Change of Log-transformed Urinary Albumin to Creatinine Ratio (UACR) at Week 12 End of Treatment (EoT) |

End point description:

The UACR measured albumin and creatinine concentrations in urine across 3 samples of the first morning void (FMV) taken on three consecutive days prior to 11 study visits starting at visit 2 (Day -39) until visit 14 end of study (EoS) (Day 253). The mean was taken over the log transformed UACR measurements from FMV samples prior to the relevant visit (6 days samples for pretreatment as baseline and 3 days samples for treatment period). The post-baseline visits were defined as the geometric mean (GM) of the 3 UACR measurements corresponding to FMV urine samples collected for that visit. Only data from first morning void samples were used. The analysis population was the Full Analysis Set (FAS), which consisted of participants who were randomized and received at least one dose of study drug and had at least one post-baseline UACR measurement.

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

End point timeframe:

Baseline and end of treatment (EoT) (week 12)

| End point values | ASP8232 | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 55 | 56 | | |
| Units: Percent Change | | | | |
| number (not applicable) | | | | |
| Change from Baseline to Week 12 | -17.65 | 2.31 | | |

### Statistical analyses

| Statistical analysis title | ASP8232 vs Placebo |
|---|---|

Statistical analysis description:

Statistical analysis comparing change from baseline between ASP8232 vs Placebo. Estimates were obtained from a mixed model of repeated measures on the log-transformed UACR that includes treatment, visit, visit by treatment interaction and region as fixed class factors and baseline log transformed UACR as a continuous covariate. Least square mean (LSM) and the 95% CI were transformed back to the original scale and expressed as percentages. Only data from first morning void samples were used.

| | |
|---|---|
| Comparison groups | ASP8232 v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 111 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.033 |
| Method | Mixed models analysis |
| Parameter estimate | Percent Change |
| Point estimate | -19.51 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -34.01 |
| upper limit | -1.82 |

## Secondary: Percentage of Participants With > 30%/40%/50% Reduction in UACR From Baseline to Week 12 (EoT)

| | |
|---|---|
| End point title | Percentage of Participants With > 30%/40%/50% Reduction in UACR From Baseline to Week 12 (EoT) |

End point description:

The percentage of participants achieving a 30/40/50% reduction in GM of UACR from baseline to EoT were described using frequency tabulations. The FAS was used for analysis.

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

End point timeframe:

Baseline and end of treatment (EoT) (week 12)

| **End point values** | ASP8232 | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 60 | 60 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | | | | |
| Reduction > 30% | 36.7 | 21.7 | | |
| Reduction > 40% | 21.7 | 20.0 | | |
| Reduction > 50% | 11.7 | 11.7 | | |

## Statistical analyses

| **Statistical analysis title** | ASP8232 vs Placebo (Reduction > 30%) |
|---|---|

Statistical analysis description:

Statistical analysis comparing the percentage of reduction between ASP8232 vs Placebo. The percentage of participants with > 30% reduction in GM of UACR from baseline to EoT were analyzed using a logistic regression model including treatment as fixed factor and country and (mean) log transformed UACR at baseline as covariates.

| | |
|---|---|
| Comparison groups | ASP8232 v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.109 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.05 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.85 |
| upper limit | 4.94 |

| **Statistical analysis title** | ASP8232 vs Placebo (Reduction > 40%) |
|---|---|

Statistical analysis description:

Statistical analysis comparing the percentage of reduction between ASP8232 vs Placebo. The percentage of participants with > 40% reduction in GM of UACR from baseline to EoT were analyzed using a logistic regression model including treatment as fixed factor and country and (mean) log transformed UACR at baseline as covariates.

| | |
|---|---|
| Comparison groups | ASP8232 v Placebo |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.993 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.39 |
| upper limit | 2.56 |

| **Statistical analysis title** | ASP8232 vs Placebo (Reduction > 50%) |
|---|---|

Statistical analysis description:

Statistical analysis comparing the percentage of reduction between ASP8232 vs Placebo. The percentage of participants with > 50% reduction in GM of UACR from baseline to EoT were analyzed using a logistic regression model including treatment as fixed factor and country and (mean) log transformed UACR at baseline as covariates.

| | |
|---|---|
| Comparison groups | ASP8232 v Placebo |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.887 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.92 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.28 |
| upper limit | 2.98 |

## Secondary: Mean Change of Log-transformed Albumin Excretion Rate (AER) From Baseline to Week 12 (EoT)

| End point title | Mean Change of Log-transformed Albumin Excretion Rate (AER) From Baseline to Week 12 (EoT) |
|---|---|

End point description:

The AER was measured from urine collected 24 hours (h) before visit 6 (baseline), visit 8 (Day 29) and visit 11 (Day 85). The 24 h urine collection started on Day 1 before the scheduled visit up to and including the FMV on the day of the scheduled visit. The FAS was used for analysis.

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

End point timeframe:

Baseline and end of treatment (EoT) (week 12)

| **End point values** | ASP8232 | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 53 | 53 | | |
| Units: Percent Change | | | | |
| number (not applicable) | | | | |
| Change from Baseline in 24h AER at Week 12 (EoT) | -26.67 | -8.35 | | |

### Statistical analyses

| **Statistical analysis title** | ASP8232 vs Placebo |
|---|---|

Statistical analysis description:

Statistical analysis comparing the percent change in 24h AER at Week 12 (EoT) between ASP8232 vs Placebo. Estimates were obtained from a mixed model of repeated measures on the log-transformed UACR that includes treatment, visit, visit by treatment interaction and region as fixed class factors and baseline log transformed UACR as a continuous covariate.

| Comparison groups | ASP8232 v Placebo |
|---|---|
| Number of subjects included in analysis | 106 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.094 |
| Method | Mixed models analysis |
| Parameter estimate | Percent Change |
| Point estimate | -20 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -38.45 |
| upper limit | 3.99 |

## Secondary: Percentage of Participants With > 30%/40%/50% Reduction in AER From Baseline to Week 12 (EoT)

| | |
|---|---|
| End point title | Percentage of Participants With > 30%/40%/50% Reduction in AER From Baseline to Week 12 (EoT) |

End point description:

The percentage of participants achieving a 30/40/50% reduction in AER from baseline to EoT were described using frequency tabulations. The FAS was used for analysis.

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

End point timeframe:

Baseline and end of treatment (EoT) (week 12)

| **End point values** | ASP8232 | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 56 | 56 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | | | | |
| Reduction > 30% | 44.6 | 28.6 | | |
| Reduction > 40% | 33.9 | 23.2 | | |
| Reduction > 50% | 28.6 | 14.3 | | |

## Statistical analyses

| **Statistical analysis title** | ASP8232 vs Placebo (Reduction > 30%) |
|---|---|

Statistical analysis description:

Statistical analysis depicts AER Reduction of > 30%. The model included treatment as fixed factor, and country and baseline log transformed AER as covariates.

| | |
|---|---|
| Comparison groups | ASP8232 v Placebo |
| Number of subjects included in analysis | 112 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.072 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.93 |
| upper limit | 4.78 |

| **Statistical analysis title** | ASP8232 vs Placebo (Reduction > 40%) |
|---|---|
| Statistical analysis description: | |
| Statistical analysis depicts AER Reduction of > 40%. The model included treatment as fixed factor, and country and baseline log transformed AER as covariates. | |
| Comparison groups | ASP8232 v Placebo |
| Number of subjects included in analysis | 112 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.216 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.72 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.73 |
| upper limit | 4.04 |

| **Statistical analysis title** | ASP8232 vs Placebo (Reduction > 50%) |
|---|---|
| Statistical analysis description: | |
| Statistical analysis depicts AER Reduction of > 50%. The model includes treatment as fixed factor, and country and baseline log transformed AER as covariates. | |
| Comparison groups | ASP8232 v Placebo |
| Number of subjects included in analysis | 112 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.074 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.43 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.92 |
| upper limit | 6.44 |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to 28 days after last intake of study drug

Adverse event reporting additional description:

The safety analysis set (SAF) was used for the analysis and consisted of all randomized participants who received at least 1 dose of study drug. The treatment emergent adverse events (TEAEs) were defined as adverse events (AEs) observed after start of the administration of the test drug until 28 days after last intake of study drug.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 15.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | ASP8232 |

Reporting group description:

Participants received ASP8232 orally once a day for 84 consecutive days.

| | |
|---|---|
| Reporting group title | Placebo |

Reporting group description:

Participants received matching placebo orally once a day for 84 consecutive days.

| Serious adverse events | ASP8232 | Placebo | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 64 (4.69%) | 3 / 61 (4.92%) | |
| number of deaths (all causes) | 1 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Cardiac disorders | | | |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Aphasia | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 61 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 61 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Grand mal convulsion | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 61 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 61 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hemianopia homonymous | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 61 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 61 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 61 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 61 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Erysipelas | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia urinary tract infection | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 61 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | ASP8232 | Placebo | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 16 / 64 (25.00%) | 11 / 61 (18.03%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 2 / 64 (3.13%) | 6 / 61 (9.84%) | |
| occurrences (all) | 2 | 6 | |
| General disorders and administration site conditions | | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 6 / 64 (9.38%) | 1 / 61 (1.64%) | |
| occurrences (all) | 6 | 1 | |
| Renal and urinary disorders | | | |
| Renal impairment | | | |
| subjects affected / exposed | 9 / 64 (14.06%) | 1 / 61 (1.64%) | |
| occurrences (all) | 9 | 1 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 2 / 64 (3.13%) | 4 / 61 (6.56%) | |
| occurrences (all) | 2 | 4 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 05 January 2015 | The changes include: Substantial Amendment 1<br><br>● As the requirement for the mean UACR to be ≥ 200 mg/g at baseline ensured that participants were randomized with significant levels of albuminuria despite adequate treatment with angiotensin converting enzyme inhibitor (ACEi)/ARB, inclusion criterion 9 (FMV samples) was also to be met at visit 4 and 5.<br>● The criterion that prohibited sperm donation during the study period was a standard procedure in Astellas sponsored clinical trials and was deleted in error in the original protocol. It was re-introduced.<br>● As it was deemed important to repeat the electrocardiogram (ECG) during the 4-week follow-up visit, an ECG assessment was added to visit 12.<br>● There were no drug-related histopathological changes in the male reproductive organs in the 4-week and 13-week repeated dose studies in rats and monkeys. Therefore, it was concluded that the potential for effects on male fertility was low. Hence, the details of follow-up for pregnancy of partners of participating male patients were removed.<br>● Based on local requirements, certain events that occurred during a participant's participation in the clinical trial were to be reported as adverse events (AEs) or expedited as serious adverse events (SAEs). |
| 30 March 2015 | The changes include: Substantial Amendment 2<br><br>● In order to further characterize the pharmacokinetic and pharmacodynamic profile and long-term pharmacodynamic and pharmacodynamic profile of the investigational product ASP8232, the follow-up period was extended up to approximately 24 weeks after the EoT visit to cover approximately 5 times the mean terminal elimination halflife of 760 hours.<br>● In inclusion criteria 10, 11 and 12, the use of contraception for female participants of childbearing potential was extended until 24 weeks after the final study drug administration |
| 24 November 2015 | The changes include: Substantial Amendment 3<br><br>● In order to facilitate participants' enrollment into the study, the eGFR entry criterion was extended. The participant must have an eGFR (based on the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation) of ≥ 25 and < 75 mL/min/1.73 m2.<br>● Additional specification of study population for stable treatment for at least 3 months prior to screening was updated.<br>● Retesting of UACR measurement at visit 2 was allowed if value was between 100 and 200 mg/g. It was allowed to avoid the rejection of participants who were potentially valid candidates for the study, but appeared to be below 200 mg/g due to the day to day variability of albuminuria.<br>● Rescreening of the participants was allowed once per participant, if the participant was not randomized into this trial before.<br>● The previous criterion of at least 2 samples out of 3 per triplicate (at visit 4 and visit 5) was considered too strict, therefore this criterion was changed in order to facilitate enrollment. For a participant to be eligible, it is required that the geometric mean UACR of all visit 4 and visit 5 samples is ≥ 200 and ≤ 3000 mg/g AND in at least 3 FMV samples, and the UACR at visit 4 and visit 5 is ≥ 200 mg/g.<br>● Additional specifications of concomitant medication (and nonmedication therapies) were updated. Carvedilol was removed from the list of the prohibited drugs for pharmacokinetic interferences.<br>● Additional specification of previous and concomitant treatments was updated.<br>● Details of study completion date and number of patients participating in the study were updated. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

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

Seven isolated UACR data points and 1 AER datapoint below the lower limit of quantification (LLOQ) were detected after database softlock. Following database hardlock and study treatment unblinding, the team decided to exclude these values.

Notes: