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)			

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 ● 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. ● 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. ● 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. ● 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. ● 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 ● 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. ● 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 ● 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. ● Additional specification of study population for stable treatment for at least 3 months prior to screening was updated. ● 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. ● Rescreening of the participants was allowed once per participant, if the participant was not randomized into this trial before. ● 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. ● Additional specifications of concomitant medication (and nonmedication therapies) were updated. Carvedilol was removed from the list of the prohibited drugs for pharmacokinetic interferences. ● Additional specification of previous and concomitant treatments was updated. ● 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: