Name of Sponsor/Company: Astellas Pharma Europe BV (APEB)		
Name of Finished Product: Not applicable		
Name of Active Ingredient: ASP8232		

SYNOPSIS

Title of Study:

A phase 1 study to evaluate the effect of renal impairment on the pharmacokinetics, pharmacodynamics and safety of ASP8232 (Part 1) and a multiple dose, placebo-controlled exploratory safety, pharmacokinetic and pharmacodynamic study in type 2 diabetes mellitus subjects with chronic kidney disease (part 2)

Investigators/Coordinating Investigator:

Prof. Dr. med. [redacted]

Study Centers:

This multinational, multicenter clinical study was conducted at 3 contracted sites in 3 countries (Bulgaria, Moldova and Romania)

Publication Based on the Study:

Not applicable

Study Period:

3Q2013 to 3Q2014

Study Initiation Date (Date of First Enrollment):

16 Sep 2013

Study Completion Date (Date of Last Evaluation):

09 Sep 2014

Phase of Development:

Phase 1

Objectives:

Part 1: Single Dose

Primary Objective

- To compare the single dose pharmacokinetics of ASP8232 in healthy subjects and subjects with renal impairment.

Secondary Objectives

- To obtain concentration-response relationship data for ASP8232, both in terms of free and total concentration, by measuring the inhibitory effect of ASP8232 on the activity of plasma vascular adhesion protein-1 (VAP-1) and the effect of ASP8232 on Total Antioxidant Status (TAS).
- To compare the single dose pharmacodynamics (inhibition of VAP-1 activity, TAS) of ASP8232 in healthy subjects and subjects with renal impairment.
- To evaluate the safety and tolerability of single dose ASP8232 in healthy subjects and subjects with renal impairment.

Exploratory Objective

- To assess the change from baseline of the Urinary Albumin-to-Creatinine Ratio (UACR) following a single dose of ASP8232.

Part 2: Multiple Dose

Primary Objective

- To evaluate the safety and tolerability of multiple dose ASP8232 in type 2 diabetes mellitus (T2DM) subjects with chronic kidney disease (CKD).

Secondary Objectives

- To assess multiple dose pharmacokinetics of ASP8232 in T2DM subjects with CKD.
- To obtain the concentration-response relationship data for ASP8232, both in terms of free and total concentration, by measuring the inhibitory effect of ASP8232 on the activity of plasma VAP-1 and the effect of ASP8232 on TAS.
- To assess multiple dose pharmacodynamics (inhibition of VAP-1 activity, TAS) of ASP8232 in T2DM subjects with CKD.
- To assess the change from baseline of 24-hour urinary albumin excretion after multiple doses of ASP8232 versus placebo in T2DM subjects with CKD.

Exploratory Objective

- To assess the change from baseline of the UACR after multiple doses of ASP8232 versus placebo in T2DM subjects with CKD.

Methodology:

Overall

This clinical study was divided in 2 parts. Part 1 included renal impaired subjects matched (with regard to age, weight and sex) to healthy subjects. In part 2, subjects with confirmed or known T2DM and CKD were included.

Part 1: Single Dose

Part 1 was a phase 1, open-label clinical study to compare the pharmacokinetics, pharmacodynamics and safety and tolerability of ASP8232 in healthy subjects and subjects with renal impairment.

This part of the clinical study included 40 subjects (16 healthy subjects, 8 subjects with mild renal impairment, 8 subjects with moderate renal impairment and 8 subjects with severe renal impairment). The cohort of subjects with severe renal impairment (n = 8) was to include at a minimum 3 male and 3 female subjects. As a result of pharmacokinetic data from the severe renal impaired cohort (> 3-fold increase in mean C_{max} or mean AUC), 8 male or female subjects with moderate renal impairment and 8 male or female subjects with mild renal impairment were also included in part 1 of the clinical study.

Sufficient healthy subjects were recruited (additional 8 subjects) to ensure appropriately matched healthy subjects for all renal impaired subjects (matched for age, sex and weight). It was determined that 1 renal impaired subject who didn't have a match per clinical study protocol criteria was acceptable as there were sufficient healthy subjects to meet clinical study objectives.

Renal function was classified at clinical study entry according to estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) equation:

- $\geq$ 80 mL/min per 1.73 m^2 for subjects with normal renal function.
- 60 to < 80 mL/min per 1.73 m^2 for subjects with mild renal impairment.
- 30 to < 60 mL/min per 1.73 m^2 for subjects with moderate renal impairment.
- 15 to < 30 mL/min per 1.73 m^2 for subjects with severe renal impairment.

Eligible subjects were residential for 9 days. On day -1, subjects were admitted to the clinical unit. Upon confirmation of eligibility on day -1, subjects received a single oral dose of [redacted] ASP8232 on day 1, after a fast of at least 10 hours, with a standard lunch 4 hours postdose. Dosing was followed by a 168-hour blood and urine pharmacokinetic/pharmacodynamic sampling period. Subjects were discharged on day 8, provided that there were no medical reasons for a longer stay in the clinical unit. Subjects returned to the clinical unit on day 10 (216 hours postdose), day 12 (264 hours postdose), day 14 (312 hours postdose), day 21 (480 hours postdose), day 28 (648 hours postdose) and day 42 (984 hours postdose) for ambulant visits during which blood pharmacokinetic/pharmacodynamic samples were collected. This part of the clinical study was completed with an end-of-study visit (ESV) after collection of the last pharmacokinetic sample on day 56 (1320 hours postdose).

Safety, pharmacokinetic (plasma and urine samples for ASP8232analysis) and pharmacodynamic assessments (plasma and serum samples to measure ASP8232 effect on VAP-1 activity and TAS, respectively, and urine samples to measure the effect of ASP8232 on UACR), were performed throughout this part of the clinical study.

Part 2: Multiple Dose

Part 2 was an exploratory multiple dose placebo-controlled clinical study to evaluate the pharmacokinetics, pharmacodynamics and safety and tolerability of multiple doses of ASP8232 in T2DM subjects with CKD.

This part of the clinical study included 15 male or female subjects with confirmed or known T2DM and CKD randomized in a 2:1 ratio of ASP8232 to matching placebo, thus 10 subjects were exposed to ASP8232 and 5 subjects were exposed to matching placebo. At least 5 subjects should have been > 65 years of age.

At clinical study entry, subjects should have had moderate to severe renal impairment. In order to balance recruitment, at least 3 subjects were planned for each of the specified intervals:

- 15 to < 30 mL/min per 1.73 m^2
- 30 to < 45 mL/min per 1.73 m^2
- 45 to < 60 mL/min per 1.73 m^2

Eligible subjects were admitted to the clinical unit on day -2 in order to collect pharmacodynamic urine samples before start of dosing on day 1. Subjects were administered multiple oral doses of ASP8232 or placebo for 28 days. Subjects received a [redacted] ASP8232 or matching placebo on day 1, followed by [redacted] ASP8232 or matching placebo from days 2 to 28. Dosing within the clinical unit was conducted 5 minutes after the completion of a light breakfast, with a standard lunch 4 hours postdose. Subjects were discharged on day 8, provided that there were no medical reasons for a longer stay in the clinical unit. Subjects returned to the clinical unit on days 14 and 21, days 27 to 29, and ESV (between 14 and 28 days after the day 29 visit) during which blood pharmacokinetic/pharmacodynamic and urine pharmacodynamic samples were collected.

Safety assessments, pharmacokinetic assessments (plasma and urine samples for ASP8232 analysis) and pharmacodynamic assessments (plasma samples to measure ASP8232 effect on VAP-1 activity, serum samples for TAS and urine samples for UACR) were performed throughout this part of the clinical study.

Number of Patients (Planned, Enrolled and Analyzed):

Part 1: Single Dose

In total, 81 subjects provided written informed consent and were subsequently screened. Of these, 41 subjects discontinued before allocation to study drug (screen failures). As a result, 40 subjects (16 healthy subjects, 8 subjects with mild renal impairment, 8 subjects with moderate renal impairment and 8 subjects with severe renal impairment) were allocated to ASP8232. All 40 (100.0%) subjects received study drug and completed the clinical study (i.e., subjects received a single dose of ASP8232) and were included in the safety analysis set (SAF), pharmacokinetic analysis set (PKAS) and pharmacodynamic analysis set (PDAS).

Part 2: Multiple Dose

In total, 33 subjects provided written informed consent and were subsequently screened. Of these, 18 subjects discontinued before randomization to study drug (screen failures). As a result, 15 subjects were randomized to study drug (10 subjects randomized to ASP8232 and 5 subjects randomized to matching placebo). All 15 (100.0%) subjects received study drug and completed the clinical study (i.e., subjects received multiple doses of ASP8232 or placebo for 28 days) and were included in the SAF and PDAS. All 10 (100.0%) subjects who received ASP8232 were included in the PKAS.

Diagnosis and Main Criteria for Inclusion:

Part 1: Single Dose

Healthy male or female subjects, or male or female subjects with renal impairment, 35 to 80 years of age, inclusive, with a body mass index within the range of 18.5 to 29.9 kg/m^2, inclusive, who provided written informed consent and to whom all of the inclusion and none of the exclusion criteria applied, were eligible for inclusion in this clinical study. Subjects had predose eGFR values (based on the MDRD method) ≥ 80 mL/min per 1.73 m^2 for healthy subjects or 15 to < 30 , 30 to < 60 or 60 to < 80 mL/min per 1.73 m^2 for subjects with severe, moderate or mild renal impairment. Subjects were allowed to have occasionally used paracetamol (up to 2 g/day) and a stable low dose aspirin for prophylactic use. Subjects with renal impairment were not to be included in the clinical study if he/she had not been on a stable dose of allowed concomitant medications for at least 2 weeks prior to day 1 and/or for whom dose changes were likely to occur during the clinical study. Regular use of metabolism inducers (e.g., barbiturates, rifampin) within the 3 months prior to admission to the clinical unit was not allowed.

Part 2: Multiple Dose

Male or female subjects with either known or confirmed T2DM and CKD for at least 1 year, 35 to 80 years of age, inclusive, with a body mass index within the range of 18.5 to 29.9 kg/m^2, inclusive, who provided written informed consent and to whom all of the inclusion and none of the exclusion criteria applied, were eligible for inclusion in this clinical study. Subject had eGFR values (based on the MDRD method) between 15 and 60 mL/min per 1.73 m^2. Subjects were on a stable therapy with angiotensin converting enzyme inhibitors or angiotensin receptor blocker for at least 3 months, and on a stable antihyperglycemia therapy, e.g., with metformin, sulphanylureas, thiazolidinediones or dipeptidyl peptidase-4 inhibitor. Subjects were not to be included in the clinical study if he/she had not been on a stable dose of allowed concomitant medications for at least 2 weeks prior to day 1 and/or for whom dose changes were likely to occur during the clinical study. Regular use of metabolism inducers (e.g., barbiturates, rifampin) within the 3 months prior to admission to the clinical unit was not allowed.

Test Product, Dose and Mode of Administration, Batch Numbers:

ASP8232 and placebo-to-match capsules were provided to each clinical unit already packaged into individual patient kits.

Part 1: Single Dose

ASP8232 was administered as [redacted] ASP8232 capsules.

Batch numbers:

[redacted]

Part 2: Multiple Dose

ASP8232 was administered as [redacted] capsules on day 1 and [redacted] capsule on days 2 to 28.

The placebo-to-match for ASP8232 capsules was identical in appearance to ASP8232 capsules.

Batch numbers:

- [redacted] ASP8232 capsules:
  [redacted]
- Placebo-to-match [redacted] ASP8232 capsules:
  [redacted]
- [redacted] ASP8232 capsules:
  [redacted]
- Placebo-to-match [redacted] ASP8232 capsules:
  [redacted]

Reference Product, Dose and Mode of Administration, Batch Numbers:

Not applicable

Duration of Treatment (or Duration of Study, if applicable):

Part 1: Single Dose

On day -1, subjects were admitted to the clinical unit. Subjects received a single oral dose of ASP8232 on day 1. Subjects were discharged on day 8 and returned to the clinical unit on day 10 (216 hours postdose), day 12 (264 hours postdose), day 14 (312 hours postdose), day 21 (480 hours postdose), day 28 (648 hours postdose) and day 42 (984 hours postdose) for ambulant visits, and on day 56 (1320 hours postdose) for an ESV.

Part 2: Multiple Dose

Eligible subjects were admitted to the clinical unit on day -2 and received multiple oral doses of ASP8232 and matching placebo from days 1 to 28. Subjects were discharged on day 8 and returned to the clinical unit on days 14 and 21, days 27 to 29 for ambulant visits, and between 14 and 28 days after the day 29 visit for an ESV.

Criteria for Evaluation:

Pharmacokinetic Endpoints

Part 1: Single Dose

- ASP8232 (plasma)
  - Primary: AUC_{inf}, AUC_{last}, $AUC_{last,u}$, $AUC_{inf,u}$, C_{max}, $C_{max,u}$
  - Secondary: CL/F, CL_u/F, f_u, t_{lag}, t_{max}, $t_{½}$, V_z/F, $V_{z,u}/F$

- ASP8232 (urine)
  - Secondary: CL_R, $CL_{R,u}$, Ae_{24}, Ae_{24}%, Ae_{last}, Ae_{last}%, Ae_{inf}, Ae_{inf}%

Part 2: Multiple Dose

Pharmacokinetic endpoints were considered secondary:

- ASP8232 (plasma): f_u, C_{trough}, $C_{trough,u}$ (days 2, 5, 8, 14, 21)

Pharmacodynamic Endpoints

Part 1: Single Dose

- Secondary:
  - VAP-1 activity (plasma): R_{max}, R_{max}%, $t_{max,R}$, $R_{avg,24}$
  - TAS (serum): R_{max}, R_{max}%, $t_{max,R}$, $R_{avg,24}$
- Exploratory
  - UACR: urinary albumin (mg/dL)/urine creatinine (g/dL) = UACR in mg/g

Part 2: Multiple Dose

- Secondary:
  - 24-hour Urinary Albumin Excretion Rate (UAER)
- Exploratory:
  - UACR: urinary albumin (mg/dL)/urine creatinine (g/dL) = UACR in mg/g
  - Urinary metabolomics (results reported separately)

Safety Endpoints

In part 1, safety endpoints were considered secondary endpoints and in part 2, safety endpoints were considered primary endpoints.

Safety assessments included the nature, frequency and severity of adverse events (AEs), vital signs (blood pressure, pulse and body temperature), clinical laboratory tests (hematology, biochemistry and urinalysis) and routine 12-lead electrocardiogram (ECG).

Statistical Methods:

The pharmacokinetic parameters were calculated using noncompartmental methods according to the Astellas Global Non-compartmental Analysis Manual Version 1.0 (16 Jul 2013). The pharmacokinetic and pharmacodynamic parameters were calculated using Phoenix® software (Pharsight Corp. Mountain View, California, United States) version 6.2.1.

Pharmacokinetics

Concentrations and pharmacokinetic parameters were summarized using the following descriptive statistics: number of data, arithmetic mean, SD, coefficient of variation (%CV), median, range (minimum and maximum). For C_{max} and AUC (part 1) and C_{trough} (part 2), the geometric mean was also calculated.

Part 1: Single Dose

The primary pharmacokinetic parameters in part 1 were C_{max}, $C_{max,u}$, AUC_{inf}, $AUC_{inf,u}$, AUC_{last} and $AUC_{last,u}$. An analysis of variance on natural log-transformed pharmacokinetic parameters with renal function status as fixed effect was used to assess the effect of renal impairment on the pharmacokinetics of ASP8232. An analysis of covariance (ANCOVA) model was also performed to assess the impact of sex, age and weight as exploratory analysis with renal function status and sex as fixed effects, and age and weight as covariates. Descriptive statistics were provided for ASP8232 pharmacokinetic parameters for each renal function group separately.

An exploratory analysis was performed to investigate the relationship between the pharmacokinetic parameters of ASP8232 and the eGFR (calculated using the MDRD formula).

Part 2: Multiple Dose

The pharmacokinetic analysis was performed by an explorative population pharmacokinetic modeling approach.

The statistical analysis was limited to descriptive statistics of concentrations.

Pharmacodynamics

Concentrations, percent change from baseline, percent of baseline and pharmacodynamic parameters were summarized using standard descriptive statistics and %CV.

Part 1: Single Dose

Baseline for VAP-1 activity was defined as the mean of a maximum of 4 measurements (19, 17 and 15 hours prior to dosing and predose). Values of VAP-1 activity below 0 were set to zero (0).

Baseline for TAS was defined as the mean of a maximum of 4 measurements (19, 17 and 15 hours prior to dosing and predose). If 1 or more of these 4 measurements was missing, the baseline was calculated as the mean of all non-missing measurements or was taken as the single measurement in the case of having only 1 result available. Concentrations of TAS below the level of quantification (BLQ) were set to missing for calculating descriptive statistics and in the estimation of individual pharmacodynamic parameters. For the summary statistics by renal function group, in case at least half of the individual data at a given time point were BLQ, the SD and arithmetic %CV were not calculated.

Baseline for UACR was defined as the mean of 2 measurements (day -1 and predose). If 1 of these measurements was missing, the baseline was taken as the single available measurement.

Part 2: Multiple Dose

Baseline for VAP-1 activity was defined as the mean of a maximum of 3 measurements (19, 17 and 15 hours prior to dosing). Values of VAP-1 activity below 0 were set to zero (0).

Baseline for TAS was defined as the mean of a maximum of 4 measurements (19, 17 and 15 hours prior to dosing and predose). Concentrations of TAS BLQ were set to 0 for calculating descriptive statistics. For the summary statistics by treatment group, in case at least half of the individual data at a given time point were BLQ, the SD and %CV were not calculated. If at least 1 value was BLQ, the geometric mean was not calculated.

Baseline for UACR was defined as the geometric mean of 3 assessments (day -3, day -2 and predose [day 1]). Baseline for UAER was defined as the -24 to 0 hour assessment on day 1. To assess the effect of treatment on each of UACR and UAER, an ANCOVA was performed. Values were natural log-transformed before statistical analysis. Changes in the log-transformed UACR and UAER from baseline (at each time point, excluding measurements at predose and at the ESV) were assessed with the use of the ANCOVA model, with treatment, time and treatment by time interaction as fixed effects, subject as random effect and the log-transformed baseline UACR and UAER value as a covariate.

LS means for the factor treatment, the estimated LS means difference (ASP8232-placebo) and its 90% CI on the log scale were constructed and p-values for the fixed effects presented. All raw statistical output is included in the statistical appendices. For UACR and UAER, the LS means of each of ASP8232 and placebo, the difference between the LS means and its associated 90% CI were back-transformed to obtain the results in the original scale.

As an exploratory analysis, an ANCOVA model was used to assess the impact of treatment on UACR and UAER on the change from baseline at the last 2 times (for UACR) and last time (for UAER) of assessment (i.e., the last assessment up to 648 hours and ESV for UACR and the last assessment up to 648 to 672 hours postdose for UAER). This model included treatment as fixed effect and the log-transformed baseline UACR and UAER value as a covariate. Only observations for the last assessment were included in the model.

Safety

AEs were coded using MedDRA version 15.1. The number and percentage of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), TEAEs leading to discontinuation, and TEAEs related to study drug were summarized by SOC, preferred term and renal function group (part 1) and treatment group (part 2). All AEs are listed.

For quantitative laboratory measurements descriptive statistics were used to summarize results and change from baseline by renal function group (part 1), treatment group (part 2) and time point. Laboratory data are displayed in listings.

Descriptive statistics were used to summarize vital sign results and changes from baseline by renal function group (part 1), treatment group (part 2) and time point. Vital signs data are displayed in listings.

The 12-lead ECG results with normal, not clinically significant abnormal, and clinically significant abnormal results as assessed by investigator, as well as abnormalities in change from baselines are summarized by renal function group (part 1), treatment group (part 2) and time point.

Summary of Results/Conclusions:

Demographics for healthy subjects and subjects with renal impairment (part 1), and T2DM subjects with CKD (part 2) can be found in [Table 1 and Table 2, respectively].

Pharmacokinetic Results:

Part 1: Single Dose

Plasma Pharmacokinetics

[redacted]

Urine Pharmacokinetics

[redacted]

Part 2: Multiple Dose

[redacted]

Pharmacodynamic Results:

Part 1: Single Dose

[redacted]

[redacted]

Part 2: Multiple Dose

[redacted]

Safety Results:

There were no deaths, SAEs or AEs leading to permanent discontinuation of the study drug during the conduct of the clinical study. None of the TEAEs was considered by the investigator to be related to the study drug [Table 12 (part 1) and Table 13 (part 2)].

In part 1, a total of 7 TEAEs were reported for 6 (15.0%) subjects (2 TEAEs reported for 1 [6.3%] subject in the healthy subject dose group, 4 TEAEs reported for 4 [50.0%] subjects in the mild renal impairment dose group and 1 TEAE reported for 1 [12.5%] subject in the severe renal impairment dose group) who received ASP8232. All TEAEs were considered by the investigator to be mild in severity and not related to study drug.

In part 2, a total of 5 TEAEs were reported for 3 (20.0%) subjects (2 TEAEs reported for 1 [20.0%] subject who received placebo and 3 TEAEs reported for 2 [20.0%] subjects who received ASP8232). The investigator considered 3 TEAEs to be mild in severity and 2 TEAEs to be moderate in severity, and all TEAEs to be not related to study drug.

In part 1, alkaline phosphatase values > 1.5 × upper limit of normal were reported for a subject at baseline, and remained stable during treatment. These values were considered by the investigator to be clinically significant.

In part 2, a TEAE of increased blood creatinine was reported for a subject. Values were reported to be above the normal range (screening: 370 µmol/L; highest value 485 µmol/L on day 6), but were not considered by the investigator to be clinically significant.

In part 1, a single 12-lead ECG measurement was considered by the investigator to be abnormal, clinically significant. The abnormality was reported as a TEAE of ventricular extrasystoles [Table 14].

In part 2, systolic blood pressure (SBP) values > 160 mmHg were reported for a subject. The highest value of 192 mmHg on day 14 (312 hours postdose) (the subject's mean SBP at screening was 134 mmHg) was considered by the investigator to be clinically significant. This was reported as a TEAE of hypertension [Table 15].

No other abnormal values observed in any of the clinical laboratory values, vital signs or 12-lead ECGs were considered by the investigator to be clinically significant.

CONCLUSIONS:

Pharmacokinetics

[redacted]

Pharmacodynamics

[redacted]

[redacted]

Safety

There were no deaths, SAEs or AEs leading to permanent discontinuation of the study drug during the conduct of the clinical study. None of the TEAEs was considered by the investigator to be related to the study drug. No treatment-related effects were found in vital signs measurements, 12-lead ECG and laboratory values.

Overall Conclusions

[redacted]

Date of Report: Reissued, 01 Apr 2016

Table 1 Summary of Demographics and Other Baseline Characteristics for Subjects in Part 1, Single Dose (Safety Analysis Set)

Parameter Category/Statistics	Healthy Subjects (n = 16)	Subjects with Renal Impairment†			Total (n = 40)
		Mild (n = 8)	Moderate (n = 8)	Severe (n = 8)	
Sex, n (%)					
Male	9 (56.3)	5 (62.5)	5 (62.5)	5 (62.5)	24 (60.0)
Female	7 (43.8)	3 (37.5)	3 (37.5)	3 (37.5)	16 (40.0)
Race, n (%)					
White	16 (100.0)	8 (100.0)	8 (100.0)	8 (100.0)	40 (100.0)
Age (years)‡					
Mean (SD)	52.5 (10.6)	54.3 (14.6)	66.4 (7.6)	50.6 (10.8)	55.3 (12.1)
Median	54.5	55.5	67.5	51.5	56.5
Min – Max	35 – 70	35 – 75	52 – 74	36 – 64	35 – 75
Age Group, n (%)					
≤ 65 years	14 (87.5)	6 (75.0)	4 (50.0)	8 (100.0)	32 (80.0)
> 65 years	2 (12.5)	2 (25.0)	4 (50.0)	0	8 (20.0)
Weight (kg)					
Mean (SD)	76.18 (12.65)	81.61 (11.83)	75.38 (10.80)	76.50 (16.39)	77.17 (12.69)
Median	76.00	83.50	78.70	79.50	79.10
Min – Max	56.0 – 95.0	58.0 – 94.7	55.9 – 87.9	56.0 – 101.0	55.9 – 101.0
Height (cm)					
Mean (SD)	169.6 (11.7)	167.0 (5.6)	160.0 (8.9)	171.6 (8.2)	167.5 (10.1)
Median	167.5	165.5	159.5	170.0	166.5
Min – Max	147 – 185	162 – 180	145 – 172	163 – 190	145 – 190
BMI (kg/m^2)					
Mean (SD)	26.50 (3.93)	29.34 (4.61)	29.46 (3.69)	25.85 (4.67)	27.53 (4.31)
Median	25.68	30.33	30.63	25.37	27.17
Min – Max	21.3 – 33.7	20.6 – 34.0	23.3 – 33.3	20.9 – 33.4	20.6 – 34.0
Waist/hip Ratio					
Mean (SD)	0.93 (0.18)	0.90 (0.13)	0.93 (0.07)	0.88 (0.13)	0.91 (0.14)
Median	0.90	0.90	0.90	0.85	0.90
Min – Max	0.7 – 1.4	0.7 – 1.1	0.8 – 1.0	0.7 – 1.1	0.7 – 1.4

Table continued on next page

Parameter Category/Statistics	Healthy Subjects (n = 16)	Subjects with Renal Impairment†			Total (n = 40)
		Mild (n = 8)	Moderate (n = 8)	Severe (n = 8)	
eGFR (mL/min per 1.73 m^2)§					
Mean (SD)	104.2 (13.3)	69.6 (6.7)	45.5 (5.9)	23.6 (5.0)	69.4 (33.6)
Median	103.5	69.5	43.0	25.0	69.5
Min – Max	83 – 130	61 – 78	38 – 55	17 – 29	17 – 130
UACR (mg/g)¶					
Mean (SD)	4.1 (2.4)	229.6 (523.7)	32.8 (42.7)	854.9 (684.8)	225.1 (492.7)
Median	3.4	9.1	8.1	450.8	6.2
Q1 – Q3	2.4 – 5.1	2.2 – 148.5	4.6 – 60.0	335.9 – 1488.6	3.1 – 148.8
Min – Max	1 – 9	2 – 1515	4 – 114	329 – 1959	1 – 1959
UACR Category, n (%)††					
Normal	16 (100.0)	5 (62.5)	5 (62.5)	0	26 (65.0)
Microalbuminuria	0	2 (25.0)	3 (37.5)	0	5 (12.5)
Macroalbuminuria	0	1 (12.5)	0	8 (100.0)	9 (22.5)

The safety analysis set consisted of all enrolled subjects who received at least 1 dose of study drug.

BMI: body mass index (weight [kg]/height [m^2]); eGFR: estimated glomerular filtration rate; Max: maximum recorded values; Min: minimum recorded values; UACR: urinary albumin-to-creatinine ratio.

† Degree of renal impairment.

‡ Age calculated at the date of signing the informed consent form.

§ Calculated with the Modification of Diet in Renal Disease formula.

¶ Geometric mean of the measurements on day -1 and predose.

†† Normal: < 30 mg/g; microalbuminuria ≥ 30 to < 300 mg/g; macroalbuminuria ≥ 300 mg/g.

Source: Part 1, Single Dose End-of-Text Table 12.1.2.1.1

Table 2 Summary of Demographics and Other Baseline Characteristics for Subjects in Part 2, Multiple Dose (Safety Analysis Set)

Parameter Category/Statistics	ASP8232 (n = 10)	Placebo (n = 5)	Total (n = 15)
Sex, n (%)			
Male	6 (60.0)	5 (100.0)	11 (73.3)
Female	4 (40.0)	0	4 (26.7)
Race, n (%)			
White	10 (100.0)	5 (100.0)	15 (100.0)
Age (years)†			
Mean (SD)	61.2 (9.8)	54.0 (16.8)	58.8 (12.4)
Median	63.0	53.0	61.0
Min – Max	41 – 76	36 – 79	36 – 79
Age Group n, (%)			
≤ 65 years	6 (60.0)	4 (80.0)	10 (66.7)
> 65 years	4 (40.0)	1 (20.0)	5 (33.3)
Weight (kg)			
Mean (SD)	80.95 (11.97)	87.12 (8.86)	83.01 (11.12)
Median	83.00	86.00	86.00
Min – Max	59.0 – 100.0	78.0 – 101.0	59.0 – 101.0
Height (cm)			
Mean (SD)	166.8 (8.0)	175.0 (6.9)	169.5 (8.4)
Median	164.0	174.0	168.0
Min – Max	155 – 184	168 – 184	155 – 184
BMI (kg/m^2)			
Mean (SD)	29.12 (4.03)	28.50 (2.97)	28.91 (3.61)
Median	29.94	29.83	29.83
Min – Max	22.2 – 33.8	24.1 – 31.2	22.2 – 33.8
Waist/hip Ratio			
Mean (SD)	0.96 (0.12)	1.0 (0.10)	0.97 (0.11)
Median	1.00	1.00	1.00
Min – Max	0.7 – 1.1	0.9 – 1.1	0.7 – 1.1
eGFR (mL/min per 1.73 m^2)‡			
Mean (SD)	40.3 (15.2)	41.6 (13.6)	40.7 (14.2)
Median	37.0	37.0	37.0
Min – Max	16 – 59	27 – 56	16 – 59
UACR (mg/g)§			
Mean (SD)	978.4 (602.7)	1631.7 (2473.7)	1196.2 (1443.4)
Median	950.9	256.9	906.9
Q1 – Q3	658.1 – 1410.2	237.7 – 1588.8	256.9 – 1588.8
Min – Max	22 – 1945	149 – 5926	22 – 5926
UACR Category, n (%)¶			
Normal	1 (10.0)	0	1 (6.7)
Microalbuminuria	0	3 (60.0)	3 (20.0)
Macroalbuminuria	9 (90.0)	2 (40.0)	11 (73.3)
UAER (mg/L)††			
Mean (SD)	898.8 (698.7)	1898.0 (2480.7)	1231.8 (1519.8)
Median	852.7	527.5	831.8
Q1 – Q3	306.5 – 1257.8	294.2 – 2502.6	294.2 – 1424.0
Min – Max	30 – 2406	168 – 5998	30 – 5998

Table continued on next page

Parameter Category/Statistics	ASP8232 (n = 10)	Placebo (n = 5)	Total (n = 15)
UAER Category, n (%)‡‡			
Microalbuminuria	2 (20.0)	2 (40.0)	4 (26.7)
Macroalbuminuria	8 (80.0)	3 (60.0)	11 (73.3)

The safety analysis set consisted of all enrolled subjects who received at least 1 dose of study drug.

BMI: body mass index (weight [kg]/height [m^2]); eGFR: estimated glomerular filtration rate; Max: maximum recorded values; Min: minimum recorded values; UACR: urinary albumin-to-creatinine ratio; UAER: urinary albumin excretion rate.

† Age calculated at the date of signing the informed consent form.

‡ Calculated with the Modification of Diet in Renal Disease formula.

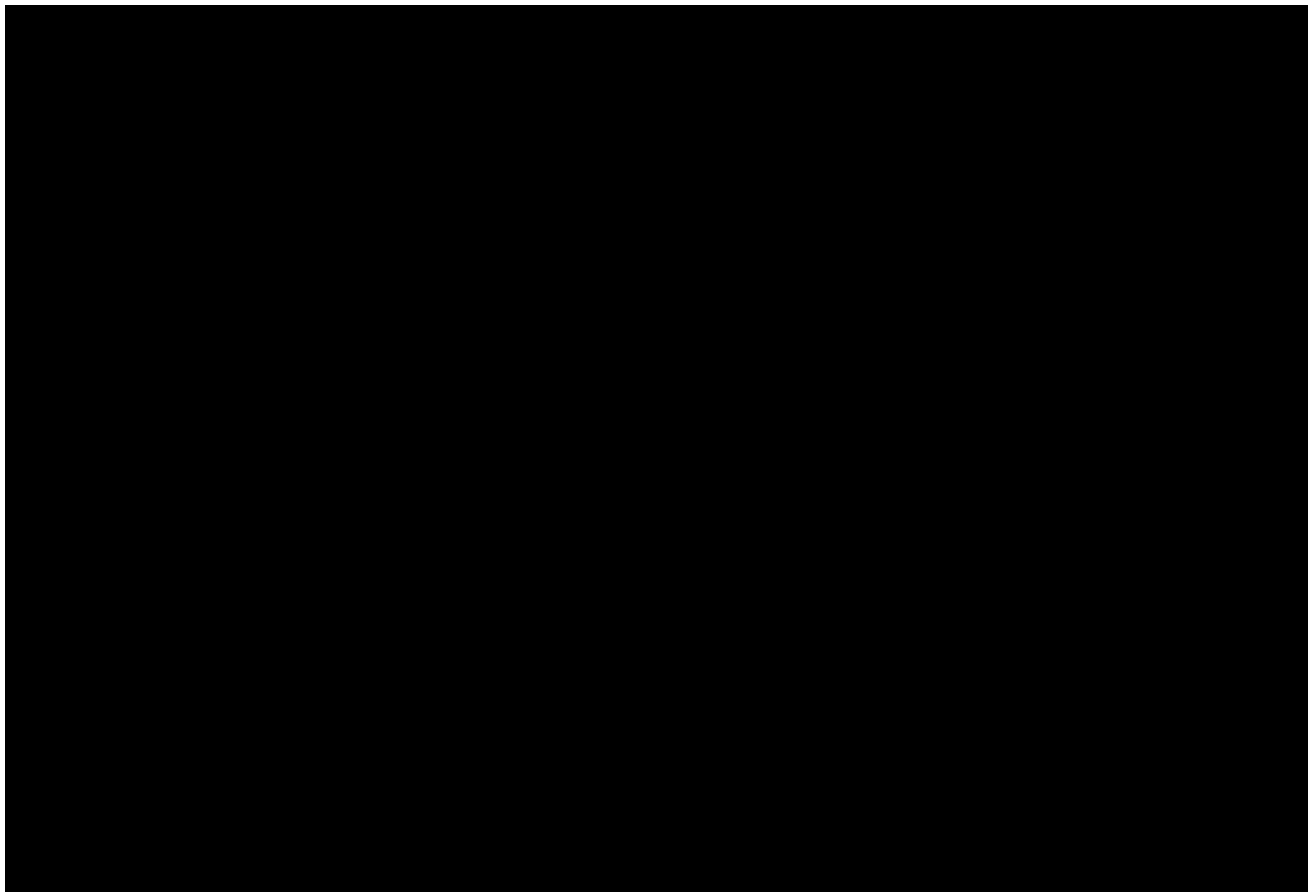
§ Geometric mean of the day -3, day -2 and predose (day 1) assessments.

¶ Normal: < 30 mg/g; microalbuminuria ≥ 30 to < 300 mg/g; macroalbuminuria ≥ 300 mg/g.

†† Assessment on day -1 (-24 to 0 hours relative to dosing on day 1).

‡‡ Normal: < 30 mg/L; microalbuminuria ≥ 30 to < 300 mg/L; macroalbuminuria ≥ 300 mg/L.

Source: Part 2, Multiple Dose End-of-Text Table 12.1.2.1.1



PK and PD Results Tables 4 -11 and Figures 1 – 3 (Pages 18 – 28) were removed.

Table 12 Overview of Treatment-emergent Adverse Events in Part 1, Single Dose (Safety Analysis Set)

Parameter	Healthy Subjects (n = 16) n (%) E	Subjects with Renal Impairment†			Total (n = 40) n (%) E
		Mild (n = 8) n (%) E	Moderate (n = 8) n (%) E	Severe (n = 8) n (%) E	
TEAEs	1 (6.3) 2	4 (50.0) 4	0	1 (12.5) 1	6 (15.0) 7
Drug-related TEAEs	0	0	0	0	0
Deaths	0	0	0	0	0
Serious TEAEs	0	0	0	0	0
Drug-related serious TEAEs	0	0	0	0	0
TEAEs leading to permanent discontinuation of study drug	0	0	0	0	0
Drug-related TEAEs leading to permanent discontinuation of study drug	0	0	0	0	0

The safety analysis set consisted of all enrolled subjects who received at least 1 dose of study drug.

A treatment-emergent adverse event was defined as an adverse event which started or worsened after first study drug intake.

A related TEAE was defined as a TEAE of possible or probable relationship, as assessed by the investigator, or records where relationship is missing.

E: number of events; TEAE: treatment-emergent adverse event.

† Degree of renal impairment.

Source: Part 1, Single Dose End-of-Text Table 12.6.1.1

Table 13 Overview of Treatment-emergent Adverse Events in Part 2, Multiple Dose (Safety Analysis Set)

Parameter	ASP8232 (n = 10) n (%) E	Placebo (n = 5) n (%) E	Total (n = 15) n (%) E
TEAEs	2 (20.0) 3	1 (20.0) 2	3 (20.0) 5
Drug-related TEAEs	0	0	0
Deaths	0	0	0
Serious TEAEs	0	0	0
Drug-related serious TEAEs	0	0	0
TEAEs leading to permanent discontinuation of study drug	0	0	0
Drug-related TEAEs leading to permanent discontinuation of study drug	0	0	0

The safety analysis set consisted of all enrolled subjects who received at least 1 dose of study drug.

A treatment-emergent adverse event was defined as an adverse event which started or worsened after first study drug intake.

A related TEAE was defined as a TEAE of possible or probable relationship, as assessed by the investigator, or records where relationship is missing.

E: number of events; TEAE: treatment-emergent adverse event.

Source: Part 2, Multiple Dose End-of-Text Tables 12.6.1.1 and 12.6.1.6

Table 14 Incidence of Subjects with Treatment-emergent Adverse Events in Part 1, Single Dose (Safety Analysis Set)

MedDRA v15.1 System Organ Class Preferred Term	Healthy Subjects (n = 16) n (%)	Subjects with Renal Impairment†			Total (n = 40) n (%)
		Mild (n = 8) n (%)	Moderate (n = 8) n (%)	Severe (n = 8) n (%)	
Overall	1 (6.3)	4 (50.0)	0	1 (12.5)	6 (15.0)
Cardiac Disorders	1 (6.3)	0	0	0	1 (2.5)
Ventricular extrasystoles	1 (6.3)	0	0	0	1 (2.5)
Infections and Infestations	0	1 (12.5)	0	0	1 (2.5)
Nasopharyngitis	0	1 (12.5)	0	0	1 (2.5)
Nervous System Disorders	0	1 (12.5)	0	1 (12.5)	2 (5.0)
Headache	0	1 (12.5)	0	0	1 (2.5)
Syncope	0	0	0	1 (12.5)	1 (2.5)
Vascular Disorders	0	2 (25.0)	0	0	2 (5.0)
Hypertension	0	1 (12.5)	0	0	1 (2.5)
Hypertensive crisis	0	1 (12.5)	0	0	1 (2.5)

The safety analysis set consisted of all enrolled subjects who received at least 1 dose of study drug.

A treatment-emergent adverse event was defined as an adverse event which started or worsened after first study drug intake.

† Degree of renal impairment.

Source: Part 1, Single Dose End-of-Text Table 12.6.1.2

Table 15 Incidence of Subjects with Treatment-emergent Adverse Events in Part 2, Multiple Dose (Safety Analysis Set)

MedDRA v15.1 System Organ Class Preferred Term	ASP8232 (n = 10) n (%)	Placebo (n = 5) n (%)	Total (n = 15) n (%)
Overall	2 (20.0)	1 (20.0)	3 (20.0)
Investigations	1 (10.0)	0	1 (6.7)
Blood creatinine increased	1 (10.0)	0	1 (6.7)
Metabolism and Nutrition Disorders	0	1 (20.0)	1 (6.7)
Hyperkalaemia	0	1 (20.0)	1 (6.7)
Nervous System Disorders	1 (10.0)	0	1 (6.7)
Dizziness	1 (10.0)	0	1 (6.7)
Vascular Disorders	1 (10.0)	0	1 (6.7)
Hypertension	1 (10.0)	0	1 (6.7)

The safety analysis set consisted of all enrolled subjects who received at least 1 dose of study drug.

A treatment-emergent adverse event was defined as an adverse event which started or worsened after first study drug intake.

Source: Part 2, Multiple Dose End-of-Text Table 12.6.1.2