Name of Sponsor/Company: Astellas Pharma Europe BV, Sylviusweg 62, 2333BE Leiden, The Netherlands		
Name of Finished Product: ASP8232		
Name of Active Ingredient: ASP8232		

SYNOPSIS

Title of Study: 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

Investigators/Coordinating Investigator: [redacted]

Study Centers: This multicenter study was conducted at 64 contracted sites in a total of 10 countries; 56 sites screened patients and 46 sites had patients who attended visit 6.

Publication Based on the Study: Not applicable

Study Period: 1Q2015 to 1Q2017

Study Initiation Date (Date of First Enrollment): 17 Mar 2015

Study Completion Date (Date of Last Evaluation): 15 Mar 2017

Phase of Development: Phase 2

Objectives:

Primary Objective: To evaluate the efficacy of ASP8232 in reducing urinary albumin to creatinine ratio (UACR) in patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) at 12 weeks compared to placebo

Secondary Objectives:

- To evaluate the efficacy of ASP8232 in reducing the 24 h urinary albumin excretion rate (AER) in patients with T2DM and CKD at 12 weeks compared to placebo
- To evaluate the safety and tolerability of ASP8232
- To evaluate the pharmacokinetics of ASP8232
- To evaluate pharmacodynamics of ASP8232 by assessing soluble vascular adhesion protein (sVAP-1) plasma concentration and inhibition of VAP-1 activity and total antioxidant status (TAS) in serum

Exploratory Objectives:

- To evaluate effect of ASP8232 on quality of life as measured by kidney disease and quality of life (KDQOL™)-36 and patient global impression of change (PGIC)
- To evaluate the effect of ASP8232 on disease-related biomarkers, e.g. markers associated with micro-inflammation or endothelial dysfunction

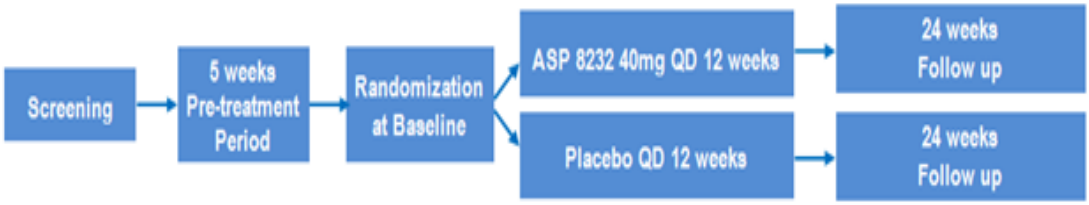
- To evaluate the effect of ASP8232 on estimated glomerular filtration rate (eGFR)
- To evaluate the effect of ASP8232 on metabolomics parameters
- To evaluate the effect of ASP8232 on UACR at 12 weeks after end of treatment

Methodology:

This was a double-blind, randomized, parallel-group, placebo-controlled, phase 2, proof of concept study to evaluate the efficacy of ASP8232 in reducing albuminuria after 12 weeks of treatment in patients suffering from T2DM and CKD.

The study consisted of screening period up to 1 week, a 5-week pretreatment period, a 12-week treatment period and a 24-week follow-up period Figure 1. The follow-up period was extended to a 24-week from the original 12-week duration during Protocol Amendment 2. Most randomized patients were enrolled under Protocol Amendment 2 or later. Protocol Amendment 2 was implemented shortly after the first patients were randomized under Protocol Amendment 1, meaning with the exception of any dropouts that would have occurred, all patients would have undergone a 24-week follow-up period.

Figure 1 Study Flow Chart



After signing informed consent, the screening examinations including blood and urine samplings were performed as per the schedule of assessment. The patients provided one first morning void (FMV) urine sample within the next three days for assessment of UACR to fulfill the criteria of required UACR value.

After screening, the patients entered a 5-week pretreatment period to ensure stabilization of their current treatment regime (antidiabetics, antihypertensives, dietary measures, etc.) to reduce the variability of UACR baseline value. UACR baseline value was assessed as the geometric mean of all separate FMV samples, taken 2 days before, 1 day before and on the morning of the scheduled visit 4 and the same applied to visit 5. Additionally, the patients provided a 24 h urine sample collected at baseline (visit 6) for determination of 24 h urine AER.

Patients were randomized to 1 of the 2 treatment arms in a 1:1 ratio to take either ASP8232 (40 mg) or placebo once daily for 12 weeks (84 days). The patients received the allocated treatment in one constant daily dose starting on the day of the randomization visit. After randomization at visit 6 (Day [D]1), all patients returned to the investigative site at visits 7 to 11 (D15, D29, D43, D57 and D85)/end of treatment (EoT) as per schedule of assessments.

At visits 8 (D29) and 11 (D85), the patients were also requested to collect 24 hours urine as follows:

- FMV samples for UACR determination were collected 3 days before, 2 days before and 1 day before the scheduled visit. These were stored in separate refrigerated containers and brought to the site on the scheduled visit.

- Twenty-four hour urine collection was to start after the FMV collection on the morning 1 day before the scheduled visit until and including the FMV on the morning of the scheduled visit. The 24 h urine was collected in a separate container and was brought to the site on the scheduled visit.

All patients returned for an initial (safety) follow-up at visit 12, 4 weeks after EoT, visit 13, 12 weeks after EoT, and for a final follow-up at visit 14, which was the end of study (EoS) and 24 weeks after EoT. The main purpose of visit 14 was to assess the UACR and eGFR.

For UACR measurements at visits 12 and 13, patients collected FMV samples 2 days before, 1 day before and on the morning of these scheduled visits and brought these samples in separate containers to the study center.

Number of Patients (Planned, Enrolled and Analyzed):

A total of 110 subjects were planned (55 per treatment group) for the study. A total of 406 patients signed the informed consent for this study. Of these, 281 were screen failures at study visit 1. One hundred twenty-five subjects were randomized to study treatment (64 in ASP8232 group and 61 in placebo group) and were further analyzed.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

A patient was deemed eligible for the study if all of the following criteria were met:

1. Independent Ethics Committee-approved written informed consent and privacy language as per national regulations were obtained from the patient prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. The patient was male or female ≥ 18 and ≤ 85 years of age.
3. Patient had an eGFR (based on the Chronic Kidney Disease Epidemiology Collaboration equation) at screening of ≥ 25 and < 75 mL/min/1.73 m^2.
4. Patient had a documented diagnosis of T2DM and received antidiabetic medication (oral and/or parenteral) for at least 1 year prior to screening.
5. Patient's HbA1c level was < 11.0% (< 97 mmol/mol) at screening.
6. Patient was on a stable therapy with an ACEi or ARB for at least 3 months prior to screening.
7. Patient who received antihypertensive treatment, noninsulin antidiabetic agents and/or vitamin D receptor activators at screening needed to be on stable therapy for at least 3 months prior to screening. Subjects on insulin therapy could have the insulin type/dose/schedule adjusted even during the 3 months prior to screening.
8. If the patient had been subjected to specific dietary interventions then this should have been stable over the past 3 months prior to screening visit.
9. Patient's UACR was ≥ 200 and ≤ 3000 mg/g in a FMV sample at screening and the geometric mean UACR of all FMV samples at visit 4 and visit 5 samples was ≥ 200 and ≤ 3000 mg/g and the UACR in at least 3 FMV samples at visit 4 and visit 5 was ≥ 200 mg/g.
10. Female patient was either:

Of nonchildbearing potential:

- postmenopausal (defined as at least 1 year without any menses) prior to screening, or
- documented surgically sterile or status post hysterectomy (at least 1 month prior to screening)

Or, if of childbearing potential:

- had a negative pregnancy test at screening, and
- used 2 forms of birth control* (at least 1 of which was a barrier method) starting at screening and throughout the study period and for 24 weeks after the final study drug administration.

11. Female patient was not breastfeeding at screening or during the study period, and for 24 weeks after the final study drug administration.
12. Female patient must not have donated ova and male patient must not donate sperm starting at screening and throughout the study period, and for 24 weeks after the final study drug administration.
13. Patient agreed not to participate in another interventional study after signing the informed consent and until the end of study visit had been completed.
14. In the opinion of the investigator, patient had the ability and willingness to return for all scheduled visits and perform all assessments.

*Acceptable forms of birth control included:

- Established use of oral, injected or implanted hormonal methods of contraception.
- Placement of an intrauterine device or intrauterine system.
- Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.

Exclusion Criteria:

Patients were excluded from participation in the study if any of the following applied:

1. Patient had received investigational therapy within 28 days prior to screening.
2. Patient had other condition which, in the investigator's opinion, made the patient unsuitable for study participation.
3. Patient was on, or previously received, renal replacement therapy (e.g., dialysis or kidney transplantation).
4. Patient had significant obstructive uropathy (clinically symptomatic, or causing recent or repeated infections or planned for surgical intervention) or other causes of renal impairment not related to parenchymal renal disorder and/or disease of the kidney; or patient currently had or had in the past renal disease secondary to malignancy.
5. Patient's renal impairment and/or albuminuria was considered to be of other origin than diabetic kidney disease.
6. Patient had known (auto-) immune disorder and/or received immunosuppression for more than 2 weeks, cumulatively, within 12 weeks prior to screening or anticipated need for immuno-suppressive therapy during the study.

7. Patient had active urinary tract infection which required treatment or clinically significant infection at the time of screening or randomization.
8. Patient was diagnosed with type 1 diabetes mellitus or diabetes mellitus with unclear etiology.
9. Patient had a sitting systolic blood pressure < 90 or > 160 mmHg and/or a diastolic blood pressure > 90 mmHg at screening.
10. Female patient who was pregnant or lactating or had a positive pregnancy test within 72 hours prior to screening and/or randomization or had been pregnant within 6 months before screening assessment or breast-feeding within 3 months before screening or who was planning to become pregnant within the total study period.
11. Patient had a known or suspected hypersensitivity to ASP8232, or any components of the formulation used.
12. Patient was an employee of the Astellas Group or contract research organization involved in the study.

Waivers to the inclusion and exclusion criteria were NOT allowed.

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

The patients were randomized (1:1) to 1 of the 2 treatment arms at visit 6:ASP8232 (40 mg) capsules and ASP8232-matched placebo capsules.

Patients self-administered ASP8232 (40 mg) or placebo capsules orally once daily for 84 consecutive days. The capsules were taken in the morning with or without food.

Batch Numbers:

- 40 mg ASP8232 patient kit (PATK) placebo to match (PTM): [redacted]
- 40 mg ASP8232 PATK: [redacted]

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

ASP8232 40 mg once daily or placebo was administered for 84 days.

Reference Product, Dose and Mode of Administration:

Not Applicable.

Criteria for Evaluation:

Efficacy:

Primary Efficacy Endpoint:

- Mean change of log transformed UACR from baseline to EoT (D85).

Secondary Efficacy Endpoints:

- The proportion of subjects with > 30%/40%/50% reduction in UACR from baseline to EoT (D85)
- Mean change of log transformed AER from baseline to EoT (D85)

- The proportion of subjects with > 30%/40%/50% reduction in AER from baseline to EoT (D85)

Exploratory Efficacy Endpoints:

- Mean change of eGFR from baseline to EoT (D85)
- The change from baseline in (mean) log-transformed UACR at week 24 and week 36/EoS
- Mean change of KDQOL total score from baseline to end of treatment (D85)

Safety:

- Nature, frequency and severity of adverse events (AEs)
- Vital signs
- 12-lead electrocardiogram (ECG) measurements
- Safety laboratory tests: biochemistry, hematology and urinalysis

Pharmacokinetics:

- ASP8232 plasma concentrations

Pharmacodynamics:

- Change from baseline of sVAP-1 concentration, of inhibition of VAP-1 activity and of TAS

Statistical Methods:

For continuous variables, descriptive statistics included the number of patients (n), mean, standard deviation (SD), median, minimum and maximum. In addition, for pharmacokinetic concentrations, the coefficient of variation and the geometric mean was calculated. Frequencies and percentages were displayed for categorical data. Percentages by categories were based on the number of patients with no missing data, i.e., were added up to 100%.

Summaries and analyses were presented for each treatment group. Statistical comparisons were made using 2-sided tests at α=0.05 significance level unless specifically stated otherwise.

Efficacy analysis was conducted on the full analysis set (FAS) and per protocol set (PPS). The primary efficacy analysis was performed on the FAS. The PPS was used to assess the robustness of the results from the statistical tests based on the FAS. The secondary and exploratory analyses were conducted on the FAS and PPS.

Descriptive statistics were provided for plasma concentrations of ASP8232 and metabolites by time point and by treatment group, for the patients in the pharmacokinetic analysis set (PKAS) and pharmacodynamic analysis set (PDAS).

The coding dictionary for this study was Medical Dictionary for Regulatory Activities v15.1 which was used to summarize AEs by system organ class (SOC) and preferred term (PT). The number and percentage of patients with treatment-emergent AEs (TEAEs), as classified by SOC and PT were summarized for each treatment group. All AEs were presented in a listing of individual data.

Summary of Results/Conclusions:

During the study, 406 patients were screened and 125 patients were randomized to study treatment (64 in ASP8232 group and 61 in placebo group). Overall, 59 patients (92.2%) in the ASP8232 group and 57 patients

(93.4%) in the placebo group remained on study treatment. For one clinical site ([redacted]), data integrity issues were observed and Clinical Quality Assurance performed a For-Cause audit of this site. It was decided to exclude all patients [redacted] in site [redacted] from FAS and PPS. The patient disposition is presented in Table 1 and Figure 2.

A total of 26 patients (20.8%) had 1 or more protocol deviations in the study; the most common protocol deviation was "received excluded concomitant treatment" 11 patients (8.8%).

In general, treatment groups were similar with respect to baseline characteristics, including diagnosis of the target disease. The study included more male patients (93 [77.5%]) than the female patients (27 [22.5%]). Overall mean age at randomization of 68.7 years was comparable among ASP8232 and placebo; the age range of patients was 47 to 84 years. All randomized patients were treated with an ACEi or ARB (or combination thereof) during the study.

All patients enrolled in this study had a history of T2DM and chronic renal failure and all patients in the SAF received previous medications for CKD and T2DM.

Efficacy/Pharmacokinetic/Pharmacodynamic Results:

Efficacy:

- The primary endpoint for the study was met. The primary analysis performed on the mean change of log transformed UACR from baseline to EoT was statistically significant (-19.51% compared to placebo; [95% CI: -34.01, -1.82]; P = 0.033). The percent change from baseline in UACR was greater with ASP8232 (-17.65%; [95% CI: -28.64, -4.97]) than with placebo (2.31%; [95% CI: -11.35, 18.07]) Table 3. For the primary analysis, 7 isolated UACR values below detection limit were excluded.
  - The secondary endpoint analysis of 24 h urinary albumin excretion was consistent with the primary endpoint. The placebo-adjusted reduction in albuminuria for the ASP8232 group was greater although not statistically significant (-20.00% compared to placebo; [95% CI: -38.45, 3.99]; P = 0.094).
  - Subgroup analyses performed on the primary endpoint, by stratification of UACR and eGFR at baseline, did not reveal any clinically relevant differences between subgroups.
  - Several sensitivity analyses confirmed a quantitatively similar effect on albuminuria.
  - Ad-hoc sensitivity analyses showed that changes in UACR were not unduly influenced by changes in urine creatinine; percent change of albuminuria in FMV samples at week 12 showed a greater reduction in the ASP8232 group compared to placebo (-25.67%; [95% CI: -39.03, -9.38]; P = 0.004).
  - The albuminuria reduction compared to placebo was sustained up to 12 weeks after EoT, but diminished at 24 weeks after EoT. There was a greater proportion of responders with a > 30% reduction in FMV UACR and AER from baseline to week 12 in the ASP8232 group compared to the placebo group (P = 0.109 and 0.072, respectively) Table 4 and Table 5.
  - The eGFR change from baseline to week 12 was greater for the ASP8232 group than placebo. The difference was evident at week 2 and disappeared during the follow-up period. This is consistent with a mild and reversible eGFR lowering effect. In addition, the discrepancy between eGFR assessed using cystatin C and eGFR using creatinine is consistent with the inhibitory effect of ASP8232 on tubular creatinine secretion.
  - Changes in quality-of-life metrics (KDQOL, PGIC) from baseline to EoT were generally comparable across both treatment groups.

Pharmacokinetics:

- ASP8232 pre-dose concentrations were steady throughout the remaining treatment period.
- The ASP8232 plasma concentrations decreased rapidly after end of treatment followed by a gradual decrease. The ASP8232 concentrations were detectable in plasma, 24 weeks after EoT.

Pharmacodynamics:

VAP-1 Activity in Plasma:

- A strong and nearly complete reduction in plasma VAP-1 activity at week 2 which remained constant until week 12 (EoT) was evident following treatment with ASP8232. After week 12, VAP-1 activity increased gradually throughout the remaining treatment period, 24 weeks after EoT, to levels close to baseline.
- VAP-1 activity was [redacted] of baseline when measured at all visits in the treatment period corresponding to an inhibition of [redacted]

TAS Concentration in Serum

- TAS increased slightly during treatment in the ASP8232 group.

Safety Results:

Treatment with ASP8232 was well-tolerated with an acceptable safety profile in patients with T2DM and CKD. An overview of TEAEs is presented in Table 6

The overall incidence of TEAEs was generally comparable between ASP8232 and placebo groups (60.9% and 55.7%, respectively).

The most commonly reported TEAE was renal impairment (9 [14.1%] patients in ASP8232 group and 1 [1.6%] patient in placebo group). Other common AEs that met the 5% threshold in any treatment group included hypertension, peripheral edema, anemia, and back pain. The imbalance in the incidence of TEAEs observed across treatment groups may be due to differences in baseline characteristics or confounded by multiple comorbidities, intercurrent conditions and concomitant medications. The imbalance in AEs related to renal function may also be explained by ASP8232 inhibition of tubular creatinine excretion and a potential reversible and functional eGFR reduction. The most common TEAEs reported in ≥ 5% of patients in any treatment group are presented in Table 7

Most TEAEs were mild to moderate in severity in the ASP8232 and placebo group. A total of 3 severe TEAEs were reported during the study (2 in the ASP8232 group [dry mouth and cerebrovascular accident] and 1 in the placebo group [erysipelas]). Dry mouth was considered as related to study drug.

The incidence of drug-related TEAEs was higher in the ASP8232 group (16 [25.0%]) compared to placebo (4 [6.6%]). The most frequently reported drug-related TEAEs were in the SOC of investigations and renal and urinary disorders (total 7 [5.6%]; 6 patients in the ASP8232 group and 1 in the placebo group).

One patient in the ASP8232 group died during the study as a result of cardiac arrest and respiratory failure. This occurred near the end of the follow-up period and was considered not related to study drug.

The overall incidence of serious TEAEs was similar in both treatment groups (3 [4.7%] in ASP8232 and 3 [4.9%] in placebo group). None of the reported serious TEAEs were considered to be related to study drug.

There were a total of 2 TEAEs reported leading to permanent discontinuation of study drug. Both in the ASP8232 group: 1 due to decreased eGFR and the other due to renal impairment. Both TEAEs were considered to be possibly related to study drug and were reported as recovered/recovering at the last available assessment.

In general, no clinically significant differences in change from baseline were found for clinical laboratory evaluations other than relevant endpoints and vital signs.

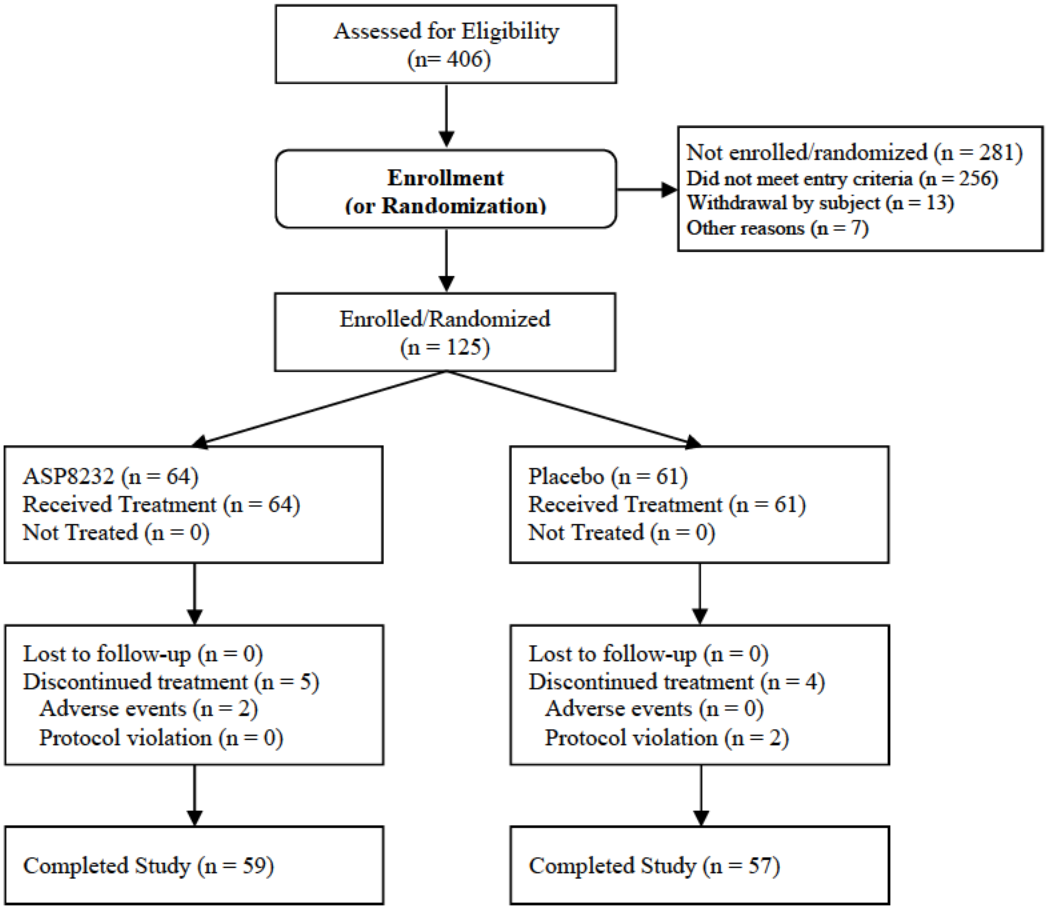
Mean changes from baseline to EoT in ECG parameters were comparable between the ASP8232 and placebo groups. No clinically relevant treatment-emergent ECG abnormalities were observed in this study.

CONCLUSIONS:

Treatment with ASP8232, a specific VAP-1 inhibitor, resulted in statistically significant reduction of residual albuminuria in patients with DKD on stable ACEi/ARB treatment compared to placebo during 12 weeks treatment. Treatment with ASP8232 was well-tolerated with an acceptable safety profile, with no SAEs related to study drug reported.

Date of Report: 23 Oct 2017

Figure 2 **Disposition of Subjects**



Source: End-of-Text Tables 12.1.1.1, 12.1.1.3, 12.1.1.4 and 12.1.1.5

Table 1 Patient Disposition and Discontinuation

Parameters	Category	ASP8232 (N=64)	Placebo (N=61)	Total (N=125)
	Subjects with informed consent			406
	Discontinued before randomization			281
	Randomized			125
Treatment discontinuation	Yes	5 (7.8%)	4 (6.6%)	9 (7.2%)
	No	59 (92.2%)	57 (93.4%)	116 (92.8%)
Primary reason for discontinuation †	Completed	59 (92.2%)	57 (93.4%)	116 (92.8%)
	Randomized/registered but never received/dispensed study drug	0	0	0
	Adverse event	2 (3.1%)	0	2 (1.6%)
	Death	0	0	0
	Lost to Follow-up	0	0	0
	Protocol Violation	0	2 (3.3%)	2 (1.6%)
	Withdrawal by Subject	3 (4.7%)	2 (3.3%)	5 (4.0%)
	Study Terminated by Sponsor	0	0	0
	Physician Decision	0	0	0
	Non-Compliance with Study Drug	0	0	0
	Pregnancy	0	0	0
	Other	0	0	0

† Only the primary reason for discontinuation was collected.

Sources: End-of-Text Tables 12.1.1.1 and 12.1.1.4

Table 2 Summary of Demographic and Baseline Characteristics for Patients in the Full analysis Set

Parameter Category/ Statistics	ASP8232 (n =60)	Placebo (n = 60)	Total (n = 120)
Sex, n (%)			
Male	43 (71.7)	50 (83.3)	93 (77.5)
Female	17 (28.3)	10 (16.7)	27 (22.5)
Race, n (%)			
White	56 (93.3)	57 (95.0)	113 (94.2)
Black or African American	1 (1.7)	0	1 (0.8)
Asian	2 (3.3)	2 (3.3)	4 (3.3)
Other	1 (1.7)	1 (1.7)	2 (1.7)
Age, years			
Mean (SD)	69.0 (7.2)	68.5 (6.6)	68.7 (6.9)
Median	69.5	69.0	69.0
Min - Max	47 - 84	56 - 82	47 - 84
EudraCT age category, n (%)			
≥ 18 to ≤ 64 years	14 (23.3)	18 (30.0)	32 (26.7)
≥ 65 to ≤ 84 years	46 (76.7)	42 (70.0)	88 (73.3)
≥ 85 years	0	0	0
Weight (kg)			
Mean (SD)	92.80 (19.03)	94.82 (20.49)	93.81 (19.72)
Median	90.85	92.20	19.70
Min – Max	63.4 – 153.0	53.5 – 146.1	53.5 – 153.0
Height (cm)			
Mean (SD)	169.5 (9.1)	171.4 (8.7)	170.4 (8.9)
Median	169.5	171.0	170.0
Min – Max	150 - 187	146 - 189	146 – 189
BMI (kg/m^2)			
Mean (SD)	32.28 (5.82)	32.20 (6.46)	32.24 (6.12)
Median	30.83	31.14	31.02
Min – Max	21.94 – 49.39	22.59 – 56.77	21.94 – 56.77
Duration of CKD (Years) †			
Mean (SD)	4.98 (4.42)	5.46 (4.20)	5.22 (4.30)
Median	4.05	4.40	4.20
Min – Max	0.4 – 27.6	0.3 – 18.4	0.3 – 27.6
Duration of T2DM (Years) †			
Mean (SD)	16.34 (7.73)	16.24 (7.04)	16.29 (7.36)
Median	16.15	16.00	16.05
Min – Max	3.0 – 33.8	2.7 – 32.0	2.7 – 33.8

All subjects who were randomized and received at least 1 dose of study drug and had at least 1 post baseline UACR measurement (Full Analysis Set)

† Duration in years was calculated as: (randomization date - diagnosis date + 1) / 365.25.

BMI: body mass index (weight [kg]/height [m^2]); CKD: chronic kidney disease; Max: maximum; Min: minimum; T2DM: type 2 diabetes mellitus

Sources: End-of-Text Tables 12.1.2.1.1 and 12.1.2.2.1

Table 3 Analysis of Change from Baseline and Percent Change in FMV UACR (FAS)

Visit/Statistic	ASP8232	Placebo	ASP8232 vs. Placebo
Baseline†			
n	60	60	
Geometric Mean (Q1, Q3)	745.237 (418.400, 1229.835)	686.911 (388.400, 1062.855)	
Week 12/LOCF‡			
n	60	60	
Geometric Mean (Q1, Q3)	611.458 (346.955, 965.475)	701.798 (427.160, 1166.750)	
Week 36/LOCF (24 weeks after EoT)‡			
n	56	58	
Geometric Mean (Q1, Q3)‡	658.045 (325.595, 1215.005)	671.560 (359.740, 1315.150)	
Change from Baseline to Week 12§			
n	55	56	
Percent Change	-17.65	2.31	-19.51
95% CI	(-28.64, -4.97)	(-11.35, 18.07)	(-34.01, -1.82)
P-value			P = 0.033

CI: confidence interval; EoT: end of treatment; FAS: full analysis set; FMV: first morning void; GM: geometric mean; LSM: least square mean; UACR: urinary albumin to creatinine ratio

The full analysis set (FAS) consisted of all patients who were randomized and received at least one dose of study drug and had at least one post baseline UACR measurement. This was the primary analysis set for efficacy analyses.

† Baseline was defined as the GM of all UACR measurements corresponding to FMV urine samples returned on site at visits 4 and 5 during pretreatment period.

‡ Postbaseline visits were defined as the GM of the 3 UACR measurements corresponding to FMV urine samples collected for that visit.

§ 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. LSM and their 95% CI were transformed back to the original scale and expressed as percentages. Only data from FMV samples are used.

Source: End-of-Text Tables 12.3.1.1.1 and 12.3.1.2.1

Table 4 Logistic Regression for the Percentage of Reduction in UACR from Baseline to Week 12/LOCF: FAS

Category	Statistic	ASP8232 (n=60)	Placebo (n=60)
Reduction > 30%	Responders (%)	22 (36.7%)	13 (21.7%)
	Odds Ratio† 95% CI P-value	2.05 (0.85, 4.94) P = 0.109	
Reduction > 40%	Responders (%)	13 (21.7%)	12 (20.0%)
	Odds Ratio† 95% CI P-value	1.00 (0.39, 2.56) P = 0.993	
Reduction > 50%	Responders (%)	7 (11.7%)	7 (11.7%)
	Odds Ratio† 95% CI P-value	0.92 (0.28, 2.98) P = 0.887	

† Odds ratio, 95% CI and p-value were from a logistic regression model that included treatment as fixed factor, and region and baseline log transformed UACR as covariates. An odds ratio greater than 1 represents ASP8232 having more patients with the specified reduction than placebo.

Values below detection limit were not used.

The full analysis set (FAS) consisted of all patients who were randomized and received at least one dose of study drug and had at least one post baseline UACR measurement.

The model included treatment as fixed factor, and country and baseline log transformed UACR as covariates. Baseline was defined as the GM of all UACR measurements corresponding to FMV urine samples returned on site at visits 4 and 5 during pretreatment period. Postbaseline visits were defined as the GM of the 3 UACR measurements corresponding to FMV urine samples collected for that visit. Only data from FMV samples were used. When the assessment at week 12 was not available, LOCF was used to impute the end of treatment value.

CI: confidence interval; FAS: full analysis set; FMV: first morning void; GM: geometric mean;
LOCF: last observation carried forward; UACR: urinary albumin to creatinine ratio

Source: End-of-Text Table 12.3.2.1.2.1

Table 5 Analysis of Change from Baseline and Percent Change in 24 h AER at Week 12/EoT: FAS

Visit/Statistic	ASP8232	Placebo	ASP8232 vs Placebo
Baseline†			
n	58	59	
Geometric Mean (Q1, Q3)	989.76 (605.00, 1663.00)	950.26 (603.00, 1664.00)	
Week 12/LOCF‡			
n	58	57	
Geometric Mean (Q1, Q3)	718.77 (362.00, 1232.00)	948.37 (555.00, 1915.00)	
Change from Baseline to Week 12§			
n	53	53	
Percent Change	-26.67	-8.35	-20.00
95% Confidence Interval	(-39.40, -11.27)	(-24.33, 1102)	(-38.45,3.99)
P-value			P = 0.094

The full analysis set (FAS) consisted of all patients who were randomized and received at least one dose of study drug and had at least one post baseline AER measurement.
AER: albumin excretion rate; CI: confidence interval; EoT: end of treatment; FAS: full analysis set; FMV: first morning void; GM: geometric mean; LSM: least square mean; UACR: urine albumin to creatinine ratio
† Baseline was defined as the GM of all UACR measurements corresponding to FMV urine samples returned on site at visits 4 and 5 during pretreatment period.
‡ Postbaseline visits were defined as the GM of the 3 UACR measurements corresponding to FMV urine
§ 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 (LS) means and their 95% CI were transformed back to the original scale and expressed as percentages.

Source: End-of-Text Table 12.3.2.2.1.1, Table 12.3.2.2.2.1

Table 6 Overview of TEAEs and Death (Safety Analysis Set)

	ASP8232(N = 64)	Placebo (N = 61)
Any TEAE	39 (60.9%)	34 (55.7%)
Drug-related† TEAEs	16 (25.0%)	4 (6.6%)
Deaths‡	1 (1.6%)	0
Serious TEAEs	3 (4.7%)	3 (4.9%)
Drug-related† Serious TEAEs	0	0
TEAEs Leading to Discontinuation	2 (3.1%)	0
Drug-related† TEAEs Leading to Discontinuation	2 (3.1%)	0

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

TEAE: treatment-emergent adverse event

TEAEs were defined as an AE observed after starting administration of the test drug/comparative drug until 28 days after last intake of study drug.

† Possible or probable, as assessed by the Investigator, or records where relationship is missing.

‡All reported deaths after the first study drug administration.

Source: End-of-Text Table 12.6.1.1

Table 7 Most Common TEAEs Reported in ≥ 5% of Patients in Any Treatment Group (Safety Analysis Set)

MedDRA v15.1 System Organ Class Preferred Term	ASP8232 (n = 64) n (%)	Placebo (n = 61) n (%)
All Systems		
Overall	18 (28.1)	11 (18.0)
Renal and Urinary Disorders	9 (14.1)	1 (1.6)
Renal impairment	9 (14.1)	1 (1.6)
General Disorders and Administration Site Conditions	6 (9.4)	1 (1.6)
Edema peripheral	6 (9.4)	1 (1.6)
Blood and Lymphatic System Disorders	4 (6.3)	0
Anemia	4 (6.3)	0
Musculoskeletal and Connective Tissue Disorders	2 (3.1)	6 (9.8)
Back pain	2 (3.1)	6 (9.8)
Vascular Disorders	4 (6.3)	7 (11.5)
Hypertension	2 (3.1)	6 (9.8)

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

AE: adverse event; TEAE: treatment-emergent adverse event.

Source: End-of-Text Table 12.6.1.11.