



ASP8232
NON-CONFIDENTIAL SUMMARY



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EXECUTIVE SUMMARY

Preclinical and Phase 1 data:

- ASP8232 is a highly selective inhibitor of Vascular Adhesion Protein -1 (VAP-1)
- Primary indication is delaying progression of Diabetic Kidney Disease (DKD)
- ASP8232 effectively reduces albuminuria and ameliorates kidney histopathology in pre-clinical pharmacology experiments on top of ACEi/ARB treatment
- ASP8232 effectively blocks plasma VAP-1 activity in a concentration-dependent manner in rodents and humans
- ASP8232 is safe and well tolerated in healthy volunteers and in patients with renal impairment

Phase 2 data in patients with DKD:

- Treatment with ASP8232 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

ASP8232 - MECHANISM OF ACTION

- ASP8232 is a highly selective inhibitor of VAP-1.
- VAP-1 activity is implicated in multiple disorders and pathological processes that involve oxidative stress or inflammation, such as primary sclerosing cholangitis, tumour growth, graft-versus-host disease, multiple sclerosis, ischaemic brain injury, ophthalmological disorders, atherosclerosis and acute kidney injury.
- A causative role for VAP-1 in DKD has not yet been shown but is plausible because of the enzyme's effects on oxidative stress and inflammation.
- Epidemiological studies have shown that circulating concentrations of VAP-1 are associated with albuminuria and estimated glomerular filtration rate (eGFR) in patients with diabetes and that VAP-1 independently predicts cardiovascular mortality and progression of DKD to end-stage renal failure in these patients.

Two phase 1 studies completed

1. 8232-CL-0001: First in Man Umbrella protocol in Healthy Subjects: SAD, MAD, Food Effect, Itraconazole DDI
2. 8232-CL-0002: Phase 1b study: PK in renal impairment and exploratory safety study in Patients with DKD after 4 weeks dosing

Two Phase 2 studies completed (Proof of Concept Studies)

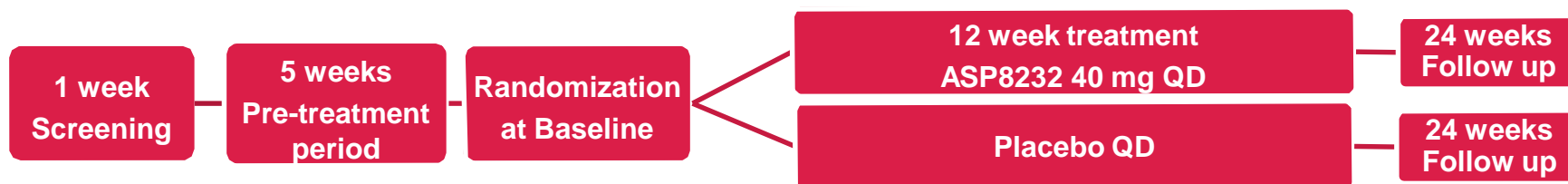
1. **8232-CL-0004 (ALBUM study) patients with DKD**
2. 8232-CL-3001 (VIDI study) patients with DME

Astellas Clinical Trial Data Disclosure:

<https://astellasclinicalstudyresults.com/hcp/compoundresult.aspx?PC=44>



8232-CL-0004 (ALBUM STUDY) PATIENTS WITH DKD - STUDY DESIGN



ASP8232, capsules, 40mg

- 1 capsule per day
- Treatment duration 12 weeks
- 1st dose taken at the site at Baseline visit
- 18 capsules per bottle

Placebo, capsules

- Matching ASP8232 in shape, color, taste, packaging, labeling

Standard of Care (ACEi, ARB, anti-diabetics, antihypertensives)

- **14 visits** over approximately 42 weeks



8232-CL-0004 (ALBUM STUDY) PATIENTS WITH DKD - KEY OBJECTIVES AND ENDPOINTS

Primary objective:

- To evaluate the efficacy of ASP8232 in reducing **Urinary Albumin to Creatinine Ratio (UACR)** in subjects with Type 2 Diabetes Mellitus (T2DM) and Chronic Kidney Disease (CKD) at 12 weeks compared to placebo.

Secondary objectives:

- To evaluate efficacy of ASP8232 in reducing the 24h urinary **albumin excretion rate (AER)**
- To evaluate the **safety and tolerability** of ASP8232
- To evaluate the **pharmacokinetics (PK)** of ASP8232

8232-CL-0004 (ALBUM STUDY) PATIENTS WITH DKD - KEY ELIGIBILITY CRITERIA

Inclusion

- eGFR (CKD-EPI) at screening of ≥ 25 and < 75 mL/min/1.73m²
- T2DM and anti-diabetic medication (oral and/or insulin) for ≥ 1 year prior to screening
- HbA1c level is $< 11.0\%$ (<97 mmol/mol) at screening
- Stable therapy with an ACE inhibitor or ARB for ≥ 3 months prior to screening
- Stable therapy with anti-hypertensive treatment, oral anti-diabetic agents and/or vitamin D receptor activators for ≥ 3 months prior to screening (when applicable)
- UACR is ≥ 200 and ≤ 3000 mg/g in a FMV sample at screening AND the geometric mean UACR of all FMV samples at visit 4 and at visit 5 is ≥ 200 and ≤ 3000 mg/g AND the UACR in at least 3 FMV samples at visit 4 and visit 5 is ≥ 200 mg/g

Exclusion

- Subject is on, or previously received, renal replacement therapy (e.g. dialysis or kidney transplantation).
- Renal impairment and/or albuminuria is considered to be of other origin than DKD
- Diagnosed with type 1 DM or DM with unclear etiology
- Sitting SBP < 90 or > 160 mmHg and/or DBP > 90 mmHg at screening

8232-CL-0004 (ALBUM STUDY) PATIENTS WITH DKD - BASELINE CHARACTERISTICS AND DEMOGRAPHICS (FAS)

		ASP8232 (n=60)	Placebo (n=60)
Sex	Male	43 (71.7%)	50 (83.3%)
	Female	17 (28.3%)	10 (16.7%)
Age		69.0	68.5
Race	White	56 (93.3%)	57 (95.0%)
Weight (kg)		92.80	94.82
BMI (kg/m ²)		32.28	32.20
Duration CKD (years)		4.98	5.46
Duration of T2DM (years)		16.34	16.24

8232-CL-0004 (ALBUM STUDY) PATIENTS WITH DKD - EFFICACY

The primary endpoint for the study was met. For the primary analysis, 7 isolated UACR values below detection limit were excluded.

- ◆ 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]).

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).

8232-CL-0004 (ALBUM STUDY) PATIENTS WITH DKD - SAFETY

Most Common TEAEs Reported in $\geq 5\%$ of Patients in Any Treatment Group (Safety Analysis Set)

	ASP8232 (n=64)	Placebo (n=61)
System Organ Class Adverse Event Preferred Term (MedDRA V 15.1)	ASP8232 (N=64)	Placebo (N=61)
Renal and urinary disorders Renal impairment	9 (14.1%)	1 (1.6%)
General disorders and administration site conditions Edema peripheral	6 (9.4%)	1 (1.6%)
Musculoskeletal and connective tissue disorders Back pain	2 (3.1%)	6 (9.8%)
Vascular disorders Hypertension	2 (3.1%)	6 (9.8%)
Blood and lymphatic system disorders Anaemia	4 (6.3%)	0

8232-CL-0004 (ALBUM STUDY) PATIENTS WITH DKD - PHARMACOKINETICS AND PHARMACODYNAMICS

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.

INTELLECTUAL PROPERTY

Patent covering ASP8232

- WO2012/124696 (filed on March 13, 2012)