Supplemental Table 1. Comparison of trial design for AMETHYST-DN, OPAL-HK, and TOURMALINE

	AMETHYST-DN [18, 20]	OPAL-HK [19]	TOURMALINE
Design	52-week, phase 2, open-label, randomized study. The study had a run-in period of up to 4weeks, an 8-week treatment phase followed by a long-term maintenance phase of up to 44 weeks	12-week, phase 3, two-phase, single-blind, randomized withdrawal study. After the initial 4-week treatment phase, eligible patients entered a randomized withdrawal phase, and continued patiromer treatment or were switched to placebo for 8 weeks.	4-week, phase 4, open-label, randomized trial that evaluated patiromer administered without food versus with food
Patients	Adults with T2DM, CKD and hyperkalemia who were receiving RAASi	Patients with CKD and hyperkalemia who were receiving RAASi	Patients with hyperkalemia.
Patiromer dose	Patients with mild hyperkalemia (serum potassium >5.0–5.5 mEq/L) received patiromer at 8.4 g to 25.2 g/day, while those with moderate hyperkalemia (>5.5–<6.0 mEq/L) received 16.8 g to 33.6 g/day. Patiromer was titrated during the treatment period to reach and maintain serum potassium ≤5.0 mEq/L.	Patients with mild hyperkalemia (serum potassium 5.1–<5.5 mEq/L) received patiromer at 8.4 g, while those with moderate-to-severe hyperkalemia (≥5.5–<6.5 mEq/L) received 18.6 g/day. Patiromer was titrated to achieve and maintain serum potassium within the target range (3.8–<5.1mEq/L).	Patiromer was administered at a starting dose of 8.4 g/day and titrated in increments of 8.4 g/day (to a maximum of 25.2 g/day) to reach and maintain serum potassium levels in the target range of 3.8–5.0 mEq/L.
Main Inclusion criteria	1. Age 30 - 80 years old at screening 2. T2DM diagnosed after age 30 which has been treated with oral medications or insulin for at least 1 year 3. CKD: eGFR 15 - <60 mL/min/1.73m2 4. uACR: (Cohorts 1 and 2 only): ≥ 30 mg/g	1. Males and females ages 18 - 80 2. CKD - eGFR 15 to <60 mL/min/1.73m^2 3. Serum K+ 5.1 to <6.5 mEq/L 4. Receiving an ACE Inhibitor, an ARB, or an AA medication	5. Potassium concentration >5.0 mEq/L 6. Stable RAASi medication, if taking 7. Medications taken on a chronic basis are given once daily or twice daily

	5. Serum K+ values: Cohorts 1 and 2: 4.3 - 5.0 mEq/L at screening AND 4.5 - 5.0 mEq/L at randomisation AND >5.0 - <6.0 mEq/L at randomization to patiromer; Cohort 3: >5.0 - <6.0 mEq/L 6. Receiving an ACEI and/or ARB for at least 28 days prior to screening 7. SBP ≥130 - <180 mmHg AND average DBP ≥80 - <110 mmHg		
Main Exclusion criteria	1. Type 1 diabetes mellitus 2. HBa1C >12% (Cohort 1 and 2) 3. Emergency treatment for T2DM within the last 3 months 4. SBP >180 mmHg or DBP >110 mmHg 5. serum magnesium <1.4 mg/dL (<0.58 mmol/L) 6. uACR ≥10000 mg/g (Cohort 1 and 2) 7. Renal artery stenosis, diabetic gastroparesis, non-diabetic CKD 8. History of gastrointestinal disorders 9. NYHA Class III or IV heart failure 10. BMI ≥40 kg/m^2 11. Unstable angina, unresolved acute coronary syndrome, cardiac arrest or clinically significant ventricular arrhythmias, TIA or stroke, IV cardiac medication	1. Auto-immune related CKD 2. Uncontrolled Type 1 diabetes or HbA1c >10.0% 3. NYHA class IV heart failure 4. Major surgery or heart or kidney transplant in the past 3 months 5. Significant cardiovascular or cerebrovascular events in the past 2 months 6. BMI ≥ 40 kg/m^2	1. Expected need for dialysis 2. Major organ transplant 3. History of conditions associated with pseudohyperkalemia 4. History of gastrointestinal disorders 5. Cancer or unstable medical condition

	12. Kidney transplant, cancer, alcoholism, or drug/chemical abuse, raised liver enzymes 13. New or changed prescriptions for loop and thiazide diuretics or other antihypertensive medications 14. Use of polymer-based drugs, phosphate binders, other potassium binders, lithium, potassium sparing medications, potassium supplements, bicarbonate or baking soda	

AA: aldosterone antagonist; ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blocker; BMI: body mass index; CKD: chronic kidney disease; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration; HbA1c: haemoglobin A1c; K+: potassium; NYHA: New York Heart Association; RAASi: renin angiotensin aldosterone system inhibitors; SBP: systolic blood pressure; T2DM: Type 2 diabetes mellitus; uACR: urine albumin creatinine ratio.

Supplemental Table 2. Non-fatal treatment-emergent adverse events leading to treatment discontinuation, with onset during the first four weeks, by System Organ Class and Preferred Term

Adverse event	n (%) of patients	
	Patients with Stage 3b–5 CKD (n=421)	**Patients with Stage 1–3a CKD (n=211)**
≥ 1 AE leading to discontinuation of patiromer[a,b]	24 (6)	5 (2)
Renal and urinary disorders		
Worsening renal function	5 (1)	0
Acute kidney injury	1 (0.2)	0
Gastrointestinal disorders		
Vomiting	3 (0.7)	0
Diarrhea	2 (0.5)	1 (0.5)
Constipation	2 (0.5)	0
Flatulence	2 (0.5)	0
Nausea	1 (0.2)	0
Abdominal pain	1 (0.2)	0
Abdominal distension	0	1 (0.5)

Abdominal pain upper	0	1 (0.5)
Cardiac disorders		
Angina pectoris	1 (0.2)	0
Atrial fibrillation	0	1 (0.5)
General disorders and administration site conditions		
Fatigue	1 (0.2)	0
Vascular disorders		
Hypertensive crisis	1 (0.2)	0
Metabolism and Nutrition Disorders		
Hypokalemia	2 (0.5)	0
Anorexia	1 (0.2)	0
Infections and infestations		
Urinary tract infection	1 (0.2)	0
Musculoskeletal and connective tissue disorders		
Muscle spasms	1 (0.2)	0
Immune system disorders		
Hypersensitivity	0	1 (0.5)
Investigations		
Glomerular filtration rate decreased	2 (0.5)	0

[a]Some patients may have discontinued patiromer due to >1 adverse event.

[b]In 9 patients, these events were adjudicated by the investigator to be treatment-related: abdominal pain (one patient), constipation (two patients), diarrhea (two patients),

flatulence (two patients), vomiting (two patients); none of these events were serious or severe.

AE, adverse event; CKD, chronic kidney disease.

Supplemental Table 3: Serious treatment-emergent adverse events with onset during the first four weeks, by System Organ Class and Preferred Term

No. of patients (%)	Patients with CKD stage 3b–5 (n=421)	Patients with CKD stage 1–3a (n=211)
≥1 serious adverse event[a]	**16 (4)**	**3 (1)**
Cardiac disorders	**4 (1.0)**	**1 (0.5)**
Atrial fibrillation	1 (0.2)	1 (0.5)
Angina pectoris	1 (0.2)	0
Cardiorespiratory arrest[b]	1 (0.2)	0
Myocardial infarction[b]	1 (0.2)	0
Renal and urinary disorders	**5 (1)**	**(0)**
Worsening renal function	4 (1)	0
Acute kidney injury	1 (0.2)	0
Infections and infestations	**2 (0.5)**	**1 (0.5)**
Arteriosclerotic gangrene	0	1 (0.5)
Escherichia bacteremia	1 (0.2)	0
Gastrointestinal infection	1 (0.2)	0
Urinary tract infection	1 (0.2)	0
Vascular disorders	**2 (0.5)**	**1 (0.5)**
Diabetic vascular disorder[b]	0	1 (0.5)
Hypertensive crisis	1 (0.2)	0

Intermittent claudication	1 (0.2)	0
Blood and lymphatic system disorders	**1 (0.2)**	**0**
Anemia	1 (0.2)	0
Gastrointestinal disorders	**1 (0.2)**	**0**
Mesenteric artery thrombosis[b]	1 (0.2)	0
General disorders and administration site conditions	**1 (0.2)**	**0**
Sudden cardiac death[b]	1 (0.2)	0
Investigations	**1 (0.2)**	0
Anticoagulation drug level below therapeutic level	1 (0.2)	0
Metabolism and nutrition disorders	**1 (0.2)**	0
Gout	1 (0.2)	0

[a] No serious adverse events were considered related to treatment with patiromer.

[b] Adverse event led to death.

CKD, chronic kidney disease.

Supplemental Table 4. Mean (SD) serum calcium, phosphate and magnesium at baseline, Week 4 and change from baseline to Week 4 (safety population; N=632)

	Patients with Stage 3b–5 CKD (n=421)	**Patients with Stage 1–3a CKD (n=211)**
Mean (SD) serum Ca^{2+}, mg/dL		
Baseline[a]	9.21 (0.65)	9.51 (0.51)
Week 4[a]	9.23 (0.63)	9.55 (0.50)
Change from baseline to Week 4	−0.005 (0.55)	+0.043 (0.50)
Mean (SD) serum Mg^{2+}, mg/dL		
Baseline[a]	2.14 (0.31)	2.0 (0.24)
Week 4[a]	1.95 (0.27)	1.88 (0.27)
Change from baseline to Week 4	−0.19 (0.28)	−0.12 (0.21)
Mean (SD) phosphate, mg/dL		
Baseline[a]	3.97 (0.73)	3.58 (0.60)
Week 4[a]	3.76 (0.87)	3.48 (0.66)
Change from baseline to Week 4	−0.19 (0.80)	−0.11 (0.74)

[a]Not all patients had baseline or post-baseline measurements available.

Ca^{2+}, calcium; CKD, chronic kidney disease; Mg^{2+}, magnesium; SD, standard deviation.

Supplemental Table 5. Mean (SD) eGFR and spot urine ACR at baseline, Week 4 and change from baseline to Week 4 (safety population; N=632)

	Patients with Stage 3b–5 CKD (n=421)	**Patients with Stage 1–3a CKD (n=211)**
Mean (SD) eGFR, mL/min/1.73m^2		
Baseline[a]	27.9 (8.9)	58.1 (12.7)
Week 4[a]	31.0 (13.4)	59.4 (16.2)
Change from baseline to Week 4	+2.6 (10.0)	+0.9 (13.6)
Mean (SD) spot urine ACR (mg/g)		
Baseline[a]	1249.9 (1913.4)	599.8 (1235.9)
Week 4[a]	887.9 (1416.9)	634.9 (1375.1)
Change from baseline to Week 4	−213.6 (1118.65)	+4.4 (905.08)

[a]Not all patients had baseline or post-baseline measurements available.

ACR, albumin–creatinine ratio; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SD, standard deviation.