Patiromer for Hyperkalemia Treatment in Resistant Hypertensive Patients on RAASi with Diabetic Kidney Disease

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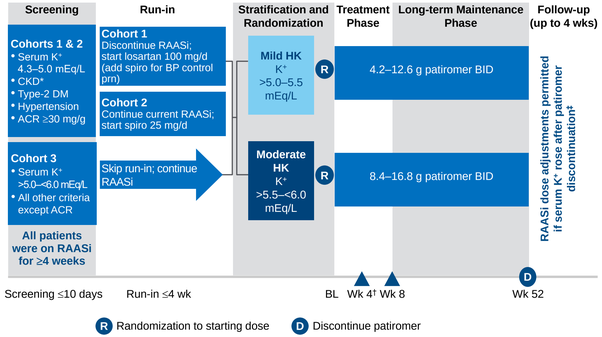
INTRODUCTION

- Resistant hypertension (RH) is common among patients with diabetic kidney disease (DKD) and is frequently associated with adverse renal and cardiovascular outcomes.[1,2]
- Renin-angiotensin-aldosterone system inhibitors (RAASi) reduce blood pressure (BP) and are known to improve clinical outcomes in patients with chronic kidney disease (CKD) and diabetes and/or hypertension,[3-5] and are therefore well-established guideline-recommended therapies for patients with DKD.
- However, RAASi use increases the risk for developing hyperkalemia (HK).[6-8]
- Patiromer is a sodium-free non-absorbed potassium (K^+)-binding polymer approved by the FDA for the treatment of HK.[9] Patiromer exchanges calcium for K^+ throughout the gastrointestinal tract but predominantly in the colon, where concentration of K^+ is high.[10]
- In the 52-week AMETHYST-DN study in HK patients with DKD, patiromer resulted in statistically significant decreases in serum K^+ from the first post-baseline visit through 52 weeks.[11] All randomized patients in AMETHYST-DN had hypertension at baseline.
- We evaluated efficacy and safety of patiromer in patients with RH in a post hoc analysis of AMETHYST-DN.

METHODS

- AMETHYST-DN was a 52-week multicenter, randomized, open-label, phase 2 study of 304 patients with CKD and type-2 diabetes (all on RAASi at baseline) (**Figure 1**). Patients with a history of hypertension were required to have an average sitting systolic blood pressure (SBP) >130 to ≤180 mmHg and average diastolic blood pressure (DBP) >80 to ≤110 mmHg at screening.
  - Patiromer starting doses were 4.2–12.6 g BID in patients with mild HK (serum K^+ >5.0–5.5 mEq/L) and 8.4–16.8 g BID in those with moderate HK (>5.5–<6.0 mEq/L).
- We identified 79 patients with RH, defined as:
  - SBP >140 mmHg at baseline.
  - On ≥4 different classes of antihypertensive medication including a diuretic.
- By protocol, RAASi could not be down-titrated or discontinued secondary to HK, although patiromer could be up-titrated using the study-defined dosing algorithm.

Figure 1. AMETHYST-DN Study Design



*eGFR 15–<60 mL/min/1.73m^2. †Primary endpoint. ‡RAASi therapy was continued after patiromer discontinuation only in patients who were normokalemic (serum K^+ ≤5.0 mEq/L) at the last on-treatment visit. ACR, albumin-to-creatinine ratio; BID, twice daily; BL, baseline; BP, blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; prn, as needed; RAASi, renin-angiotensin-aldosterone system inhibitors; spiro, spironolactone; Wk, week.

RESULTS

Patient disposition

- Of the patients with RH, 50 (63.3%) completed the study; the most common reasons (>5.0% incidence) for discontinuations were:
  - Withdrawal of consent (15.2%).
  - Adverse events (AEs; 5.1%).
  - Low serum K^+ (5.1%).
- Only 1 (1.3%) patient discontinued because of recurrent HK.

Baseline demographic and clinical characteristics

- Baseline demographic and clinical characteristics and concomitant medications are shown in **Table 1** and **Table 2**, respectively.

Table 1. Baseline Demographic and Clinical Characteristics for Patients with RH

Parameter			Patients with RH (N = 79)
Male, n (%)			40 (50.6)
Age (years), mean (SD)			66.7 (7.0)
White, n (%)			79 (100.0)
Systolic blood pressure (mmHg), mean (SD)*			156.6 (10.4)
Diastolic blood pressure (mmHg), mean (SD)*			83.3 (11.3)
Heart rate, mean (SD)			73.0 (9.9)
Serum K^+ (mEq/L), mean (SD) – mild HK stratum			5.2 (0.25)
Serum K^+ (mEq/L), mean (SD) – moderate HK stratum			5.8 (0.17)
Heart failure, n (%)			35 (44.3)
CKD stage at baseline	**3a**	**3b**	**4/5**
Number of patients (n)	20	29	23
eGFR (mL/min/1.73 m^2), mean (SD)	49.3 (3.6)	37.3 (4.1)	23.3 (4.6)
Urine ACR (mg/g)†, mean (SD)	377.7 (856.2)	1678.8 (2419.2)	1422.4 (1757.8)

*Screening value. †n = 19 for CKD Stage 3a, and n = 26 for CKD Stage 3b. ACR, albumin-to-creatinine ratio; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HK, hyperkalemia; RH, resistant hypertension; SD, standard deviation.

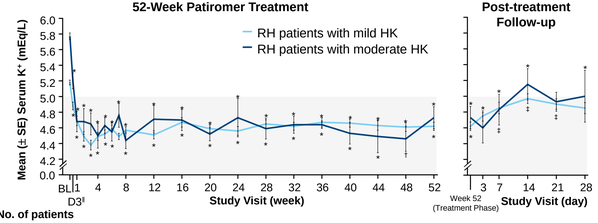
Table 2. Concomitant Medications at Baseline

No. of patients (%)	Patients with RH (N = 79)
Any concomitant medication	79 (100)
Diuretics	79 (100)
Beta blockers	66 (83.5)
Calcium channel antagonists	57 (72.2)
Other antihypertensive medications*	52 (65.8)
RAASi	79 (100)
ACE inhibitors	54 (68.4)
ARBs	43 (54.4)
MRAs	7 (8.9)
Antidiabetic medications	78 (98.7)
Insulin	33 (41.8)
Non-insulin drugs	55 (69.6)

*Includes vasodilators, alpha-2 adrenergic receptor agonists, and alpha blocking agents. ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; MRA, mineralocorticoid receptor antagonist; RAASi, renin-angiotensin-aldosterone system inhibitors; RH, resistant hypertension.

RESULTS (CONT'D)

Figure 2. Serum K^+ in Patients with RH During 52 Weeks of Treatment and 4 Weeks of Post-Treatment Follow-up



No. of patients

Mild HK:	64	62	57	52	49	47	46	47	47	45	45	44	43	42	42	42	47	47	40	39	40
Moderate HK:	15	15	14	10	11	11	11	11	11	8	7	8	8	7	7	7	9	11	8	8	8

*P <0.001 for change from baseline from a parallel lines ANCOVA model with a fixed effect for randomized starting dose and the baseline serum K^+ value as a covariate. †P = 0.002; ‡P ≤0.05 for change from the last serum K^+ value before study termination from the same model as noted above, except baseline covariate was the last serum K^+ value before study termination. †At Day 3 (D3), n = 58 for mild HK and n = 15 for moderate HK. BL, baseline; D3, day 3; HK, hyperkalemia; RAASi, renin-angiotensin-aldosterone system inhibitors; RH, resistant hypertension; SE, standard error. Note: During the follow-up period, patients with serum K^+ ≤5.0 mEq/L continued on RAASi; those with serum K^+ >5.0 mEq/L discontinued RAASi.

Serum K^+

- In patients with RH and mild and moderate HK, mean serum K^+ decreased significantly from baseline to day 3, the first post-baseline visit (**Figure 2, left panel**; P <0.001 for both).
- Mean serum K^+ 3.8–<5.0 mEq/L was achieved at day 3 (mild HK) and week 1 (moderate HK) and maintained through week 52 (**Figure 2, left panel**).
- Mean serum K^+ increased during the follow-up period after discontinuation of patiromer (**Figure 2, right panel**).

Table 3. Safety Summary Over 52 Weeks in Patients with RH

No. of patients (%)	Patients with RH (N = 79)
Patients with ≥1 AE	58 (73.4)
Treatment-related	21 (26.6)
Serious*	16 (20.3)
Two most common treatment-related AEs	
Constipation (none severe)	8 (10.1)
Hypomagnesemia (none severe)	7 (8.9)
AEs leading to study discontinuation†	10 (12.7)
Most common (>2%)	
Hypokalemia	3 (3.8)
Constipation	2 (2.5)
Chronic renal failure	2 (2.5)
Death (sudden death)*	1 (1.3)
Prespecified laboratory values of interest‡	
Serum K^+ <3.5 mEq/L	7 (8.9)
Serum Mg^{2+} <1.2 mg/dL	3 (3.8)

*None were considered related to patiromer in the judgment of the investigators. †Includes one patient withdrawn secondary to hypertensive crisis (not related to patiromer in the judgement of the investigator). ‡No patients had a serum K^+ of <3.0 mEq/L, and no patients had a serum Mg^{2+} of <1.0 mg/dL. AE, adverse event; RH, resistant hypertension. All AEs are as reported by the investigators.

Safety and tolerability

- Patiromer was generally well tolerated in patients with RH, with a low rate of discontinuations due to AEs (12.7%) over 52 weeks; constipation (10.1%; none severe) and hypomagnesemia (8.9%; none severe) were the two most common treatment-related AEs as reported by the investigators **(Table 3).**

RESULTS (CONT'D)

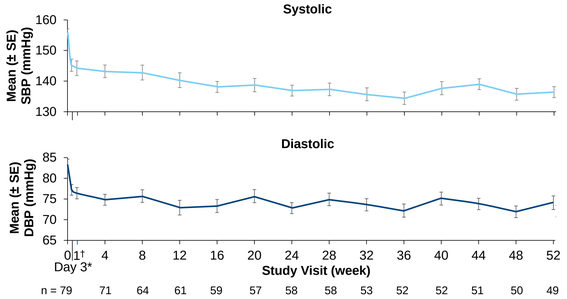
Safety and tolerability (Cont.)

- Serious AEs were reported in 16 (20.3%) RH patients (including 1 death); none were considered by the investigators to be related to patiromer (**Table 3**).
- Mean serum Ca and Mg levels remained within normal range throughout the study. The decrease in mean serum Mg occurred in the first 4 weeks of treatment and subsequent levels remained relatively constant through week 52.
- Prespecified laboratory values of serum Mg <1.2 mg/dL was reported in 3 (3.8%) patients (**Table 3**). No patient developed severe hypomagnesemia (<1.0 mg/dL), and no patient had cardiac arrhythmias or neuromuscular abnormalities that were temporally associated with hypomagnesemia.

Blood pressure

- Mean SBP/DBP decreased by −10.9/−5.6 mmHg from baseline to day 3 visit and by −18.4/−10.1 mmHg from baseline to week 52 visit (**Figure 3**).

Figure 3. Systolic and Diastolic Blood Pressure Over 52 Weeks in Patients with RH



*n = 75; †n = 78.
DBP, diastolic blood pressure; RH, resistant hypertension; SBP, systolic blood pressure; SE, standard error.

CONCLUSIONS

- A strategy focused on aggressive treatment of HK may be an important component to the management of RH in patients with DKD.
- Clinically significant reductions in mean serum K^+ were observed in patients with RH and HK as early as day 3 (first post-baseline visit), and were sustained over 52 weeks.
- Mean SBP/DBP fell by −18.4/−10.1 mmHg over 52 weeks.
- Patiromer was generally well tolerated in HK patients with RH and advanced DKD on RAASi in a post hoc analysis of AMETHYST-DN.

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Disclosures
ME: consultant for Relypsa, Bayer, and OPKO Health; **MM**, **DG**, **DJW**: employment by Relypsa. **GB**: personal fees and other from Relypsa, fees paid to university from AbbVie, Janssen, and Bayer.

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