Effect of Patiromer in Patients 75 Years or Older with Diabetic Kidney Disease and Hyperkalemia Receiving a RAAS Inhibitor

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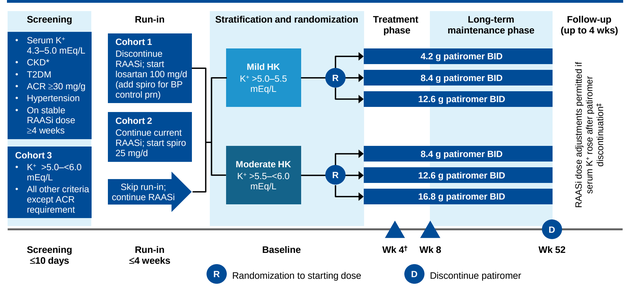
BACKGROUND

- The prevalence of hyperkalemia (HK) in the general population has been estimated at 2% to 3%,[3] and elderly patients are particularly susceptible to this electrolyte disturbance.[1,4]
- In older patients, a combination of age-associated reductions in glomerular filtration rate (GFR), diabetes, heart failure, and disturbances in the renin-angiotensin-aldosterone system (RAAS) lead to this predisposition.[2-5]
- Guideline-recommended RAAS inhibitors (RAASi) are indicated to slow the progression of diabetic kidney disease (DKD) regardless of age; however, patients with DKD are at a higher risk of developing HK, which may prevent the use of these life-saving medications.[5-6]
- Patiromer is a sodium-free, non-absorbed, potassium (K^+)-binding polymer approved for the treatment of HK including in the United States,[7] the European Union,[8] Switzerland,[9] and Australia,[10] among others.
- Here we report the results of a subgroup, post hoc analysis of 60 patients aged 75 years or older.[11]

METHODS

- AMETHYST-DN was a multicenter, open-label trial of 306 randomized patients aged 30–80 years with chronic kidney disease (CKD), type 2 diabetes mellitus (T2DM), and hypertension.[11]
- Patients who were normokalemic (serum K^+ 4.3–5.0 mEq/L) at screening entered a run-in period (up to 4 weeks) and either switched from their current RAASi to maximum-labeled dose RAASi (100 mg/day losartan and/or up to 50 mg/day spironolactone [**cohort 1**]) or continued their current RAASi and added spironolactone (**cohort 2**).
  - Patients who developed mild HK (serum K^+ >5.0–≤5.5 mEq/L) or moderate HK (serum K^+ >5.5–<6.0 mEq/L) during run-in were eligible to be randomized to three separate patiromer starting dose cohorts (**Figure 1**).
- Patients with preexisting HK (serum K^+ >5.0–<6.0 mEq/L) at screening **(cohort 3)** were directly eligible to be randomized to the treatment phase and one of three patiromer dosing cohorts (**Figure 1**).
- All patients were on a RAASi during the treatment and maintenance phases.

FIGURE 1. AMETHYST-DN STUDY DESIGN



*eGFR 15 to <60 mL/min/1.73m^2. †Primary endpoints. ‡RAASi therapy was continued after patiromer discontinuation only in patients who were normokalemic (serum K^+ ≤5.0 mEq/L) at the end of the maintenance phase.
ACR, albumin-to-creatinine ratio; BID, twice daily; BP, blood pressure; CKD, chronic kidney disease; d, day; eGFR, estimated glomerular filtration rate; PRN, as needed; spiro, spironolactone; T2DM, type 2 diabetes mellitus; Wk, week.

RESULTS

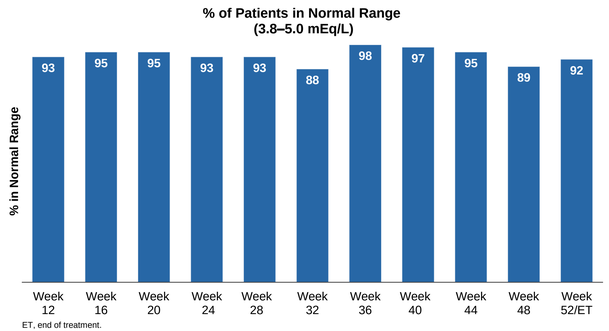
TABLE 1. BASELINE DEMOGRAPHICS

Patient Characteristics	Patients with CKD, T2DM, and ≥75 years of age (n=60)
Mean age, years	77
Male, n (%)	30 (50)
Caucasian, n (%)	60 (100)
eGFR at screening, mL/min/1.73m^2, mean ± SD	41.6 ± 14.3
Urine ACR, mg/g, mean ± SD	789 ± 1554
Heart failure (NYHA I/II), n (%)	22 (37)
Cohort 1, n (%)	12 (20)
Cohort 2, n (%)	0 (0)
Cohort 3, n (%)	48 (80)

NYHA, New York Heart Association; SD, standard deviation.

- Mean age of 77 years, 50% male population, mean eGFR ~42 mL/min/1.73m^2, and ~40% with NYHA class I or II heart failure (**Table 1).**
- 20% of patients were in cohort 1 and received an optimal dose of losartan ± spironolactone for blood pressure control and the remainder were in cohort 3 and continued their current RAASi (**Table 1**).

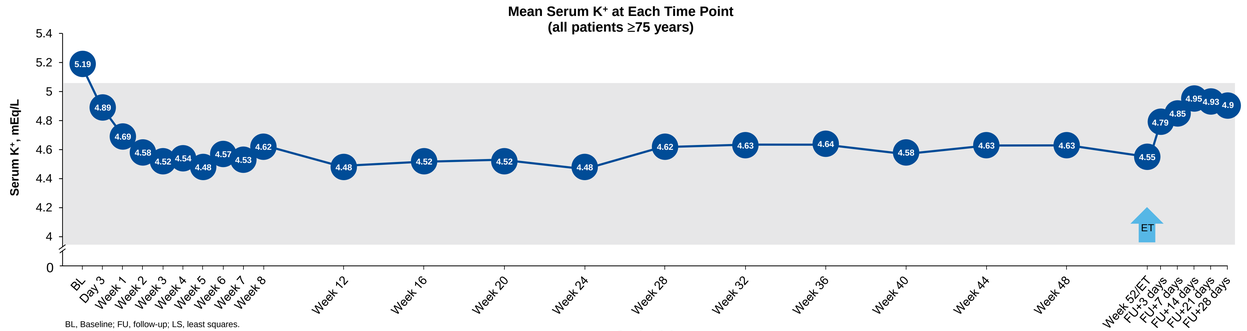
FIGURE 2. ACHIEVEMENT OF NORMOKALEMIA



ET, end of treatment.

- Proportion of patients with a measured serum K^+ between 3.8–5.0 mEq/L (normokalemia) at each time point (**Figure 2**).
- Mean serum K^+ at each time point from Baseline through Week 52 and up to 4 weeks of follow-up (**Figure 3**).

FIGURE 3. LS MEAN SERUM K^+ OVER 52 WEEKS



BL, Baseline; FU, follow-up; LS, least squares.

- Optimal RAASi dosing (**cohort 1**) over 52 weeks.
  - 12 patients completed the cohort 1 run-in period and entered the 8-week treatment phase receiving losartan 100 mg/day ± spironolactone.
  - 10/12 patients completed the treatment phase and entered the long-term maintenance phase.
    - 90% (n=9) of patients entering the long-term maintenance phase completed the full 52 weeks of treatment receiving losartan 100 mg.
- The most common treatment-emergent adverse events were gastrointestinal related (**Table 2**).

TABLE 2. TREATMENT-EMERGENT ADVERSE EVENTS RELATED TO PATIROMER WITH ONSET OVER THE ENTIRE TREATMENT PERIOD

	Patients ≥75 years, n (%)
Constipation	2 (3.3)
Abdominal discomfort	1 (1.7)
Gastroesophageal reflux disease	1 (1.7)
Vomiting	1 (1.7)
Hypomagnesemia*	4 (6.6)

*1 patient receiving 8.4 g/day; 1 patient receiving 16.8 g/day; 2 patients receiving 25.2 g/day.

TABLE 3. SERUM CALCIUM AND MAGNESIUM OVER 52 WEEKS

	Serum Calcium		Serum Magnesium	
mg/dL, mean ± SD	Mild HK (K^+ >5.0 to ≤5.5)	Mod HK (K^+ >5.5 to <6.0)	Mild HK (K^+ >5.0 to ≤5.5)	Mod HK (K^+ >5.5 to <6.0)
BL	9.41 ± 0.59*	9.13 ± 0.56¶	1.96 ± 0.24*	2.09 ± 0.27¶
Week 4	9.52 ± 0.45†	9.0 ± 0.38#	1.87 ± 0.28†	1.94 ± 0.14#
Change from BL	0.12 ± 0.58	–0.05	–0.09	–0.13
Week 24	9.48 ± 0.52‡	9.38 ± 0.56**	1.9 ± 0.32‡	2.09 ± 0.21**
Change from BL	–0.01	0.3 ± 0.45	–0.05	0.04 ± 0.27
Week 52/ET	9.48 ± 0.51§	9.5 ± 0.19**	1.88 ± 0.20§	1.94 ± 0.13**
Change from BL	0.0 ± 0.59	0.28 ± 0.36	–0.06	–0.08
FU+28 days	9.5 ± 0.56‖	9.4 ± 0.38††	1.91 ± 0.27‖	2.12 ± 0.20††
Change from BL	0.06 ± 0.65	0.15 ± 0.39	–0.04	0.12 ± 0.14

*n=49; †n=46; ‡n=36; §n=34; ‖n=25; ¶n=10; #n=9; **n=5; ††n=4.

- Mean serum calcium remained in the normal range throughout the study (**Table 3**).
- Mean serum magnesium decreased slightly at 4 weeks, and remained stable through 52 weeks (**Table 3**).

LIMITATIONS

- There was a lack of blinding, which may have affected data reporting through observer bias.
- There was a lack of a comparator, which raises the possibility of regression to the mean.

CONCLUSIONS

- Patiromer reduced and maintained serum K^+ to ≤5.0 mEq/L in most elderly (>75 years) diabetic CKD patients with HK.
- The majority of patients starting the guideline-recommended dose of losartan (cohort 1) were maintained at that dose through 52 weeks.
- Patiromer was well tolerated with a low rate of adverse events.
- Mean serum calcium and magnesium remained within normal limits through 52 weeks of the study.

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DISCLOSURES

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