Consistency of Serum Potassium Effects in Patiromer Clinical Trials

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1. INTRODUCTION

- Patiromer is a sodium-free, nonabsorbed potassium (K^+)-binding polymer[1,2] that uses calcium (Ca^{2+}) as the counterion for exchange with K^+.[1,2]
- It is approved for treatment of hyperkalemia (HK) in the United States,[1] the European Union,[3] Switzerland,[4] and Australia.[5]
- In clinical trials[6-8] patiromer has been shown to:
  - Lower elevated serum K^+, with equivalent efficacy when taken without or with food.
  - Allow continuation of renin-angiotensin-aldosterone-system (RAAS) inhibitors.
  - Maintain mean serum K^+ in the normal range for up to 52 weeks.
- To date, more than 45,000 patients have been treated with patiromer in the clinical practice setting, and no new safety risk has been identified.[9]

2. OBJECTIVES

- Patiromer has been rigorously evaluated in the clinical trial setting, with 3 randomized trials in patients with HK: AMETHYST-DN, OPAL-HK, and TOURMALINE.[6-8]
- We therefore examined the consistency of serum K^+-lowering in these trials of patiromer for HK treatment.

3. STUDY DESIGNS AND PARTICIPANTS

- OPAL-HK[6] was a 12-week, 2-part single-blind study (n=243).
  - Part A: 4-week, treatment phase; Part B: 8-week, randomized, withdrawal phase.
- AMETHYST-DN[7] was a 52-week, randomized, open-label study (n=304).
- TOURMALINE[8] was a 4-week, randomized, open-label study (n=114) comparing administration of patiromer without and with food.
- For OPAL-HK and AMETHYST-DN, study participants had to have estimated glomerular filtration rate (eGFR) 15–59 mL/min/1.73m^2 by local lab at screening and be on ≥1 RAAS inhibitor at baseline. In addition, in AMETHYST-DN all patients had to have type 2 diabetes mellitus.
- Entry serum K^+ was 5.1–<6.5 mEq/L (OPAL-HK), >5.0–<6.0 mEq/L (AMETHYST-DN), and >5.0 mEq/L (TOURMALINE).
- In OPAL-HK and AMETHYST-DN, patiromer total daily starting doses were 8.4–16.8 g and 8.4–33.6 g, respectively, given divided twice daily. In TOURMALINE, the starting dose was 8.4 g once daily.
- Patiromer doses were titrated to achieve and maintain serum K^+ levels in the range of 4.0–5.0 mEq/L (AMETHYST-DN, first 8 weeks) or 3.8–5.0 mEq/L (OPAL-HK, AMETHYST-DN after 8 weeks, and TOURMALINE).

4. METHODS

- Study participants who took at least one dose of patiromer and had at least one post-baseline serum K^+ measurement are included in the analyses.
- Mean serum K^+ results over the first 4 weeks of each study are shown by baseline serum K^+ stratum (mild HK: <5.5 mEq/L; moderate-to-severe HK: ≥5.5 mEq/L) by study.
- In addition, data were analyzed for change from baseline in serum K^+ to Week 4 (primary endpoint in OPAL-HK and AMETHYST-DN; secondary endpoint in TOURMALINE) and the proportion of patients achieving serum K^+ between 3.8–5.0 mEq/L, by study and pooled across all 3 studies.
- Efficacy data are also presented for the subgroup of study participants who initiated patiromer at 8.4 g/day (the recommended starting dose in the United States and European Medicines Agency prescribing information[1,3]).
- Safety in the first 4 weeks was assessed by reports of adverse events (AEs) and laboratory abnormalities, and is reported for study participants pooled across all 3 studies.

5. RESULTS

- Overall, 653 study participants were evaluable for efficacy and safety in this analysis (AMETHYST-DN, n=304; OPAL-HK, n=237; TOURMALINE, n=112).
- The majority of study participants were male (62%) and White (96%); mean (SD) age was 66 (10) years and 98% had hypertension **(Table 1)**.
- 65% of study participants had chronic kidney disease (CKD) stage 3b or higher; 42% had serum K^+ ≥5.5 mEq/L at baseline.

Table 1. Baseline demographics and clinical characteristics

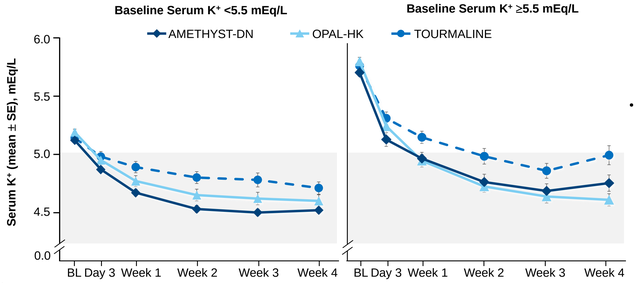
Characteristic	All patients (n=653)
Male, n (%)	402 (62%)
Age (years), mean (SD)	66 (10)
White, n (%)	629 (96%)
Hypertension, n (%)	639 (98%)
Type 2 diabetes mellitus, n (%)	534 (82%)
Heart failure, n (%)	214 (33%)
NYHA Class I, n (%)	50 (8%)
NYHA Class II, n (%)	146 (22%)
NYHA Class III*, n (%)	18 (3%)
CKD, n (%)	626 (96%)
Stage 3b or higher; eGFR 30–<15 mL/min/1.73 m^2, n (%)	418/647 (65%)†
eGFR (mL/min/1.73 m^2), mean (SD)	39 (19)†
Serum K^+; mEq/L, mean (SD)	5.4 (0.4)
Baseline serum K^+ ≥5.5 mEq/L, n (%)	273 (42%)
RAAS inhibitor use at baseline, n (%)	606 (93%)

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; K^+, potassium; NYHA, New York Heart Association; RAAS, renin-angiotensin-aldosterone-system.
*Patients with NYHA Class IV heart failure were excluded from the studies. †Six patients in AMETHYST-DN did not have serum creatinine values at baseline, so their baseline eGFR could not be calculated.

Efficacy

- Patiromer reduced mean serum K^+ to <5.0 mEq/L by Day 3 in those with mild HK at baseline (serum K^+ <5.5 mEq/L). In those with moderate-to-severe HK at baseline (serum K^+ ≥5.5 mEq/L), patiromer reduced mean serum K^+ to <5.0 mEq/L by Week 1 or 2 **(Figure 1)**.
- In participants with mild HK at baseline, the least square mean (SE) change in serum K^+ from baseline to Week 4 was –0.60 ± 0.03 (AMETHYST-DN), –0.57 ± 0.05 (OPAL-HK), and –0.41 ± 0.05 mEq/L (TOURMALINE). For those with moderate-to-severe HK at baseline, the changes were –1.01 ± 0.07, –1.29 ± 0.06, and –0.81 ± 0.09 mEq/L, respectively.
- The least square mean (SE) change in serum K^+ from baseline to Week 4 in the subgroup of study participants who started on patiromer 8.4 g/day (n=275) is shown in **Figure 2**.

Figure 1. Changes in serum K^+ over the first 4 weeks of three patiromer HK studies by baseline HK stratum



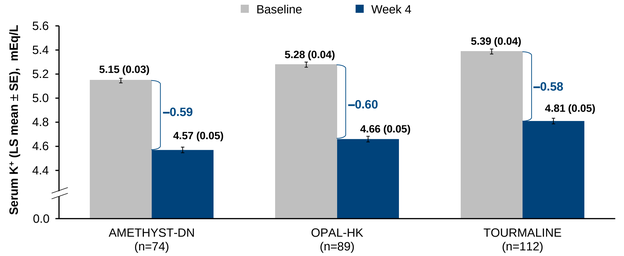
N:										
AMETHYST-DN	216	205	209	204	201	194	88	86	87	84	82	80
OPAL-HK	98	95	98	95	90	88	139	139	138	130	125	124
TOURMALINE	66	61	62	61	59	58	46	44	44	44	44	42

BL, baseline.

5. RESULTS (CONT'D)

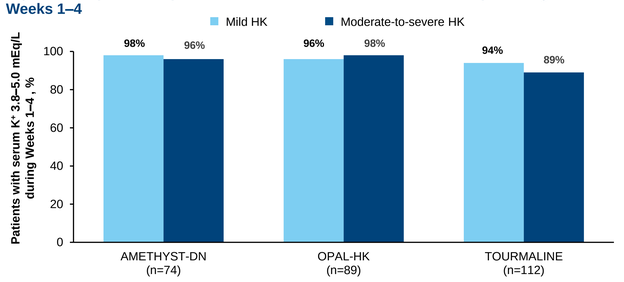
Efficacy (cont'd)

Figure 2. Mean (SE) change in serum K^+ from baseline to Week 4 in subgroup started on patiromer 8.4 g/day



- Overall, 629 (96%) of study participants achieved serum K^+ between 3.8–5.0 mEq/L during the first 4 weeks of the studies.
- In the subgroup of study participants who started on patiromer 8.4 g/day (n=275), 262 (95%) achieved serum K^+ between 3.8–5.0 mEq/L during the first 4 weeks of the studies.
- As shown in **Figure 3**, the percentage of study participants in this range was similar in those with mild or moderate-to-severe HK at baseline, and generally consistent across studies.

Figure 3. Proportion of patients with serum K^+ between 3.8–5.0 mEq/L during Weeks 1–4



- Median daily dose during the first 4 weeks of the studies:
  - For study participants with mild HK at baseline, the median daily dose across all 3 studies was 16.1 g/day (for AMETHYST-DN, 16.5 g/day; for OPAL-HK, 15.7 g/day; and for TOURMALINE, 8.4 g/day).
  - For those with moderate-to-severe HK at baseline, the median daily dose across all 3 studies was 17.7 g/day (for AMETHYST-DN, 24.7 g/day; for OPAL-HK, 16.8 g/day; and for TOURMALINE, 12.5 g/day).
  - For those started on patiromer 8.4 g/day, the median daily dose across all 3 studies was 8.4 g/day (for AMETHYST-DN, 8.3 g/day; for OPAL-HK, 10.4 g/day; and for TOURMALINE, 8.4 g/day).

Safety and Tolerability During Weeks 1–4

- Patiromer was well tolerated, with 209 (32%) study participants reporting 1 or more AE during the first 4 weeks of the studies. Most AEs were mild or moderate in severity, with severe AEs reported in 11 (2%) participants **(Table 2)**.
- In addition to the 13 (2%) patients with AEs of hypomagnesemia, 4 (0.6%) participants had AEs of decreased blood magnesium; serum magnesium (Mg^{2+}) was <1.8 mg/dL (LLN) at baseline in 6 of these 17 patients.
- AEs that were considered by the investigator to be related to patiromer were reported in 88 (14%) participants.
- 3 patients died during the first 4 weeks of the studies; none of the serious AEs, including the 3 leading to death, were considered related to patiromer in the opinion of the investigator.
- Laboratory values of K^+ <3.5 mEq/L occurred in 10 (2%) participants.
- Serum Mg^{2+} <1.4 mg/dL occurred in 30 (5%) participants; in 21 of these patients serum Mg^{2+} was <1.8 mg/dL (LLN) at baseline (including in the single patient with serum Mg^{2+} <1.2 mg/dL).

Table 2. Summary of safety through Week 4

No. of patients (%)	All patients (n=653)
≥1 AE	209 (32%)
Most common AEs (all mild or moderate)*	
Constipation	39 (6%)
Diarrhea	19 (3%)
Hypomagnesemia	13 (2%)
Patiromer-related AE	88 (14%)
≥1 serious AE†	17 (3%)
AEs leading to discontinuation of patiromer	24 (4%)
Prespecified laboratory values of interest	
Serum K^+ <3.5 mEq/L	10 (2%)
Serum Mg^{2+} <1.4 mg/dL	30 (5%)‡
Serum Mg^{2+} <1.2 mg/dL	1 (0.2%)

*AEs occurring in ≥2% of study participants pooled across all 3 studies. †None of the serious AEs were considered related to patiromer in the opinion of the investigator, including those that led to death in 3 patients. ‡In all but 9 (1%) participants, serum Mg was below the lower limit of normal (1.8 mg/dL) at baseline.

6. DISCUSSION AND CONCLUSION

- The serum K^+-lowering effect of patiromer was consistent across 3 clinical trials of the treatment of HK.
- Patiromer reduced mean serum K^+ to <5.0 mEq/L by Day 3 in those with mild HK at baseline (serum K^+ <5.5 mEq/L) and by Week 1 or 2 in those with moderate-to-severe HK at baseline (serum K^+ ≥5.5 mEq/L).
- 96% of study participants pooled across all 3 studies achieved serum K^+ between 3.8–5.0 mEq/L during the first 4 weeks (95% of participants initiated on the 8.4 g/day starting dose).
- Patiromer was well tolerated, with gastrointestinal AEs (constipation, 6%; diarrhea, 3%; all mild to moderate) being the most common AEs.
- In conclusion, the consistency of clinical effect of patiromer has been shown in 3 trials of the treatment of HK, predominantly in participants with CKD and diabetes on RAAS inhibitor therapy.

References

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