Long-Term Effect of Patiromer for Hyperkalemia Treatment in Patients With HFmrEF and Diabetic Nephropathy on RAAS Inhibitors

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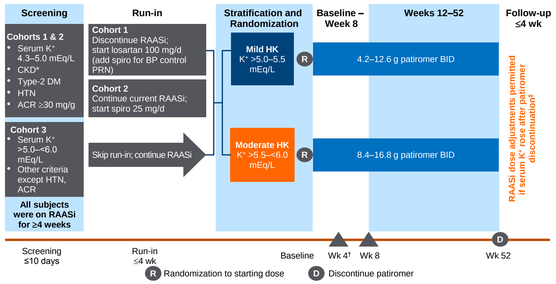
INTRODUCTION

- Heart failure (HF) with mid-range ejection fraction (HFmrEF, 40–49%) has not been studied to the same extent as HF with reduced or preserved ejection fraction (HFrEF and HFpEF, respectively) and knowledge is limited regarding effective therapies for this population of HF patients.[1]
- In HFmrEF, renin-angiotensin-aldosterone system inhibitors (RAASi) have not been shown to reduce mortality but are often used to manage coexisting conditions, such as hypertension, diabetes mellitus (DM), and chronic kidney disease (CKD), or to provide symptom relief and potentially reduce hospitalizations.
- The CHARM-Preserved trial demonstrated a reduction in recurrent hospitalizations in patients with left ventricular ejection fraction (LVEF) >40% treated with candesartan.[2]
- A state-of-the-art review provided a level IIb recommendation for RAASi.[1]
  - However, as patients with HFmrEF may have comorbid DM and CKD, RAASi can be poorly tolerated due to increases in serum potassium (K^+).
- Patiromer is a sodium-free, non-absorbed, K^+-binding polymer that is approved for the treatment of hyperkalemia (HK) in the United States,[3] the European Union,[4] Switzerland,[5] and Australia.[6] Patiromer exchanges calcium for K^+ throughout the gastrointestinal tract, but mainly in the colon where K^+ concentrations are high.[7]
- Patiromer was previously shown to lower serum K^+ concentrations through 52 weeks in patients with HK and diabetic nephropathy on RAASi,[8] including in patients with a clinical diagnosis of HF (AMETHYST-DN).[9]
- We conducted a post hoc analysis of AMETHYST-DN to examine the effects of patiromer on serum K^+ concentrations in the subset of HK patients with HFmrEF.

METHODS

- AMETHYST-DN was a 52-week multicenter, randomized, open-label, phase 2 study of patients with CKD and type 2 diabetes who were receiving RAASi (**Figure 1**).
- Patients with a history of hypertension were required to have an average sitting systolic blood pressure (SBP) >130–≤180 mmHg and average diastolic blood pressure (DBP) >80–≤110 mmHg at screening.

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; BP, blood pressure; CKD, chronic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HK, hyperkalemia; HTN, hypertension; K^+, potassium; PRN, as needed; RAASi, renin-angiotensin-aldosterone system inhibitors; spiro, spironolactone; Wk, week.

- Starting doses of patiromer were 4.2–12.6 g twice daily (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 (serum K^+ >5.5–<6.0 mEq/L).
- The study protocol specified that the RAASi dosage could not be down-titrated or discontinued due to HK, although patiromer could be up-titrated according to the study-defined dosing algorithm.
- The dosing algorithm was designed to maintain serum K^+ in the target range of 4.0–5.0 mEq/L from baseline to week 8 and 3.8–5.0 mEq/L from week 12 to week 52.
- Withdrawal criteria for high serum K^+ were ≥6.2 mEq/L during the first 8 weeks and ≥6.5 mEq/L from week 12 to week 52.
- Withdrawal criteria for low serum K^+ were <3.5 mEq/L during the first 8 weeks and <3.5 mEq/L that did not respond to patiromer down-titration from week 12 to week 52.

METHODS (CONT'D)

Subset With HFmrEF

- Of the 304 patients who were randomized and received ≥1 patiromer dose, 105 were assessed as having HF. Among these patients, 81 had ejection fraction (EF) measurement at baseline, with 46 patients having EF 40–49%. These patients comprise the subset with HFmrEF.
- Data were analyzed for all 46 patients combined and were not analyzed separately for patients with mild versus moderate HK.

RESULTS

Patient Disposition

- Thirty-two of 46 patients (69.6%) with HFmrEF completed the 52-week study.
- The two most common reasons for early withdrawal were death (n=4; 8.7%) and withdrawal of consent (n=3; 6.5%). Two (4.3%) patients withdrew due to low serum K^+ values. There were no early withdrawals due to recurrent HK.

Baseline Demographics and Clinical Characteristics

- The subset with HFmrEF had a mean age of 69.2 years; all but 3 patients had New York Heart Association (NYHA) class II heart failure (**Table 1**). Mean (SD) EF was 44.2% (2.9).
- At baseline, all patients were on RAASi therapy; 58.7% of patients were on an ACE inhibitor and 32.6% were on an ARB alone. Overall, 29 patients were on diuretic therapy (**Table 2**). All patients were receiving treatment for DM.
- Mean screening sitting SBP/DBP was 154.2/84.2 mmHg.

Table 1. Baseline demographic and clinical characteristics of patients with HFmrEF

Characteristic	Patients with HFmrEF (N=46)
Age at screening (years), mean (SD)	69.2 (8.2)
Male, n (%)	34 (73.9)
White, n (%)	46 (100)
Serum K^+ (mEq/L), mean (SD)*	5.21 (0.4)
Kidney function	
eGFR (mL/min/1.73m^2), mean (SD)*	42.0 (14.4)
CKD stage ≥3b, n (%)*	25 (56.8)
Urine albumin-to-creatinine ratio (mg/g), mean (SD)†	1080.7 (1829.0)
Ejection fraction (%), mean (SD)	44.2 (2.9)
Heart failure, NYHA class II, n (%)‡	43 (93.5)
Hypertension, n (%)	46 (100)
Sitting blood pressure at screening (mmHg), mean (SD)	
Systolic	154.2 (10.1)
Diastolic	84.2 (11.7)

*2 patients did not have a central laboratory serum K^+ at baseline; †n=45; ‡3 patients had NYHA class I; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HFmrEF, heart failure with mid-range ejection fraction; K^+, potassium; NYHA, New York Heart Association; SD, standard deviation.

Table 2. Concomitant medications for heart failure at baseline

Medication, n (%)	Patients with HFmrEF (N=46)
RAASi medication	46 (100)
ACE inhibitors only	27 (58.7)
ARBs only	15 (32.6)
ACE inhibitor plus ARB	3 (6.5)
MRA (alone or in combination)	0 (0)
Loop or thiazide diuretic	29 (63.0)
Digitalis/digoxin	8 (17.4)
Beta-blockers	26 (56.5)

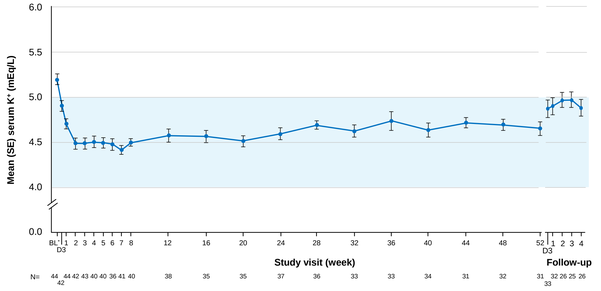
ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; HFmrEF, heart failure with mid-range ejection fraction; MRA, mineralocorticoid receptor antagonist; RAASi, renin-angiotensin-aldosterone system inhibitor.

Serum K^+

- In patients with HFmrEF, mean serum K^+ was reduced below 5.0 mEq/L at the first post-baseline visit on day 3 (ie, 48 hours after starting patiromer); from a mean (SE) value at baseline of 5.21 (0.06), the mean (SE) change from baseline on day 3 was –0.32 (0.06) mEq/L (**Figure 2**).
- Mean serum K^+ was then maintained below 5.0 mEq/L through week 52; the mean (SE) change from baseline in serum K^+ at week 52 was –0.58 (0.1) mEq/L.
- From week 12 to week 52, ≥85% of patients had serum K^+ in the target range of 3.8 to 5.0 mEq/L at monthly visits.
- Mean serum K^+ increased during the 4-week follow-up period after patiromer was discontinued.

RESULTS (CONT'D)

Figure 2. Serum K^+ in patients with HFmrEF during treatment for 52 weeks and 4 weeks of post-treatment follow-up



*Two patients did not have a central laboratory serum K^+ at baseline and are not included in the analysis. BL, baseline; D, day; HFmrEF, heart failure with mid-range ejection fraction; K^+, potassium.

Safety and Tolerability

- Overall, 33 patients with HFmrEF had 1 or more adverse events (AEs) during the 52-week treatment period, with 3 discontinuing due to AEs; 3 patients had AEs that were considered related to patiromer in the opinion of the investigator (**Table 3**).
- The 2 most common AEs, regardless of causality, were influenza and worsening of CKD, occurring in 5 patients each; none severe (**Table 4**). There were no reported events of sustained ventricular arrhythmias. Two patients had mild AEs of worsening hypertension. There were no reported AEs of edema and no clinically relevant changes in mean weight.
- One patient with HFmrEF had an AE of worsening of cardiac failure. There were no other AEs within the category of cardiac failure events (cardiac failure, worsening of cardiac failure, chronic heart failure, left ventricular failure, or acute left ventricular failure) in the HFmrEF subgroup. The AE of worsening of cardiac failure was not serious and not considered by the investigator to be related to patiromer treatment.
- Eight patients had serious AEs during study treatment, which resulted in death in 6 patients. Causes of death were sudden death (n=2), sudden cardiac death (n=1), endotoxic shock (n=1), septic shock (n=1), and unknown (n=1). None of the serious AEs or deaths were reported as related to patiromer by the investigator, and none of the deaths were considered by the independent safety review board to be related to hyperkalemia or hypokalemia.
- Two patients met prespecified discontinuation criteria for low serum K^+; the lowest serum K^+ values in these patients were 3.3 mEq/L and 3.4 mEq/L, respectively; the last recorded values were 3.7 mEq/L and 5.4 mEq/L, respectively. No patient met prespecified discontinuation criteria for high serum K^+ and there were no reported AEs of hyperkalemia or hypokalemia.
- The mean (SE) change in serum magnesium (Mg^{2+}) from baseline to week 52 was –0.10 (0.07) mg/dL. Over the entire study, 7 patients (15.2%) had a reported serum Mg^{2+} <1.4 mg/dL; 1 patient (2.2%) had serum Mg^{2+} <1.2 mg/dL. In 4 patients with serum Mg^{2+} <1.4 mg/dL, AEs of hypomagnesemia were reported (serum Mg^{2+} levels of 1.29–1.53 mg/dL; none severe and no symptoms). No patient with serum Mg^{2+} <1.4 mg/dL or <1.2 mg/dL had cardiac arrhythmias temporally associated with low serum Mg^{2+} values, or neuromuscular abnormalities.
- In these patients with HFmrEF, mean BP was 152.4/84.3 mmHg at baseline; 38 (82.6%) patients had baseline SBP ≥140 mmHg. Mean BP was reduced from baseline to week 52 by 21.1/9.5 mmHg in the HFmrEF patients (**Table 5**). There were no AEs of hypotension and few reported episodes of symptoms potentially associated with hypotension; mild dizziness was reported in 1 (2.2%) patient and syncope was reported in no patients. Of 11 patients with SBP <110 mmHg at any time during the study, none reported AEs that would appear to be related to hypotension.
- There were no clinically meaningful alterations in the mean estimated glomerular filtration rate (eGFR); mean (SD) eGFR change from baseline to week 52 was +5.2 mL/min/1.73m^2, (19.6) (**Table 5**). During the study 5 patients (10.9%) had AEs of worsening renal function (acute renal failure or CKD), 5 patients (10.9%) had a 50% decrease in eGFR, and 3 patients (8.3%) had a 100% increase in serum creatinine.

RESULTS (CONT'D)

Table 3. Safety summary over 52 weeks in patients with HFmrEF

Patients, n (%)	Patients with HFmrEF (N=46)
Patients with ≥1 AE	33 (71.7)
Patients with ≥1 treatment-related AEs*	3 (6.5)
Patients with serious AEs†	8 (17.4)
AEs leading to patiromer discontinuation‡	3 (6.5)
Deaths	6 (13.0)
Prespecified laboratory values of interest	
Serum K^+ <3.5 mEq/L	2 (4.3)
Serum K^+ >5.5 mEq/L	8 (17.4)
Serum Mg^{2+} <1.2 mg/dL	1 (2.2)
Serum Mg^{2+} <1.4 mg/dL	7 (15.2)

*Four treatment-related AEs as reported by investigators were observed in 3 patients: abdominal discomfort (n=1) and hypomagnesemia (n=3); †None of the serious AEs were related to patiromer in the opinion of the investigator. ‡AEs leading to patiromer discontinuation were chronic renal failure (n=2) and diabetic vascular disorder (n=1); none were related to patiromer in the opinion of the investigator. AE, adverse event; HFmrEF, heart failure with mid-range ejection fraction; K^+, potassium; Mg^{2+}, magnesium.

Table 4. Most common adverse events in patients with HFmrEF*

Preferred term,† n (%)	Patients with HFmrEF (N=46)
Influenza	5 (10.9)
Worsening of CKD	5 (10.9)
Hypomagnesemia	4 (8.7)
Diarrhea	3 (6.5)
Sudden death	3 (6.5)
Hypoglycemia	3 (6.5)

*AEs occurring in 3 or more patients regardless of causality to study treatment. †AEs were coded by preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), version 12.0. AE, adverse event; CKD, chronic kidney disease; HFmrEF, heart failure with mid-range ejection fraction.

Table 5. Change in blood pressure and eGFR in patients with HFmrEF from baseline to Week 4 and to Week 52

Parameter	Baseline	Change from baseline to Week 4	Change from baseline to Week 52
Blood pressure, n	n=46	n=42	n=32
Systolic (mmHg), mean (SD)	152.4 (10.7)	–15.6 (18.7)	–21.1 (19.2)
Diastolic (mmHg), mean (SD)	84.3 (12.2)	–8.0 (12.6)	–9.5 (11.7)
eGFR, n	n=44	n=38	n=30
eGFR (mL/min/1.73m^2), mean (SD)	42.1 (16.9)	+5.3 (15.7)	+5.2 (19.6)

eGFR, estimated glomerular filtration rate; HFmrEF, heart failure with mid-range ejection fraction; SD, standard deviation.

CONCLUSIONS

- This post hoc analysis of the AMETHYST-DN study suggests that patiromer allows control of HK in HFmrEF patients who are receiving RAASi therapy.
- Clinically relevant reductions in mean serum K^+ were observed as early as the first post-baseline visit on day 3 and were maintained over the 52-week treatment period in these HFmrEF patients with HK.
- Patiromer was generally well tolerated.
- Further prospective evaluation of clinical outcomes in patients with HK and HFmrEF maintained on RAASi is warranted.

Declaration of Interest

BP reports serving as a consultant to Sanofi, Relypsa Inc. a Vifor Pharma Group Company, Merck, Bayer, AstraZeneca, scPharmaceuticals, Tricida, KBP Biosciences, Stealth Peptides, Sarfez and AuraSense. He has stock options in scPharmaceuticals,Tricida, KBP Biosciences, Sarfez and AuraSense. He serves on data safety monitoring committees for and receives personal fees from Johnson & Johnson. In addition, he has a pending patent EFS ID 14916043, application number licensed to the University of Michigan School of Medicine; **MM, DG,** and **SA** report employment by Relypsa Inc., a Vifor Pharma Group Company; **ML** reports personal fees from Relypsa, Inc., a Vifor Pharma Group Company and other from Relypsa, Inc., a Vifor Pharma Group during the conduct of the study; and personal fees from Novartis, Relypsa, Inc., a Vifor Pharma Group, and Pfizer outside the submitted work

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