Hyperkalemia in Heart Failure Patients – New Approaches for Therapy

Uri Elkayam, MD
Professor of Medicine / Cardiology
University of Southern California
Los Angeles, California
Prevalence of Hyperkalemia Increases in Clinical Trials Employing RAASi

<table>
<thead>
<tr>
<th>Clinical Trials</th>
<th>EMPHASIS-HF(^1)</th>
<th>RALES(^2)</th>
<th>PARADIGM-HF(^3)</th>
<th>SOLVD(^4)</th>
<th>CHARM-Added(^5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum K+ Level</td>
<td>&gt; 5.5 mEq/L</td>
<td>&gt; 5.5 mEq/L</td>
<td>&gt; 5.5 mEq/L</td>
<td>&gt; 5.5 mEq/L</td>
<td>&gt; 6.0 mEq/L</td>
</tr>
<tr>
<td>Patient Population</td>
<td>HF with reduced EF</td>
<td>HF with EF of 35% or less</td>
<td>HF with EF of 40% or less</td>
<td>HF with EF of 35% or less</td>
<td>Pts with HF and EF of 40% or less and were treated with ACEI</td>
</tr>
</tbody>
</table>

RAASi = renin-angiotensin-aldosterone system inhibitor; HF = heart failure; EF = ejection fraction; ACEI = angiotensin-converting enzyme inhibitor; pts = patients.

Hyperkalemia in Patients with Heart Failure

SwedeHF (Swedish Heart Failure) Registry from 2006 to 2011
1-Year Follow-Up
N = 5,848

<table>
<thead>
<tr>
<th>K+ &gt;5.0 mEq/L</th>
<th>Overall</th>
<th>HFrEF</th>
<th>HFmrEF</th>
<th>HFpEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>K+ &gt;5.0 mEq/L</td>
<td>24.4%</td>
<td>24.7%</td>
<td>22.2%</td>
<td>25.8%</td>
</tr>
<tr>
<td>K+ &gt;5.5 mEq/L</td>
<td>10.2%</td>
<td>9.6%</td>
<td>10.6%</td>
<td>11.4%</td>
</tr>
</tbody>
</table>

HFrEF = heart failure with reduced ejection fraction; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; K+ = potassium.

Recurrent Hyperkalemia (>5.0 mEq/L) in Patients with HF

31,649 patients with HF in primary or hospital care were assessed in a population-based cohort\(^1\)

- **12,340** patients (1st HK Event, 39%) after 0.52 years
- **5,326** patients (2nd HK Event, 43.2%) after 0.44 years
- **2,891** patients (3rd HK Event, 54.3%) after 0.38 years
- **1,738** patients (4th HK Event, 60.1%) after 0.38 years

Approximately half of the patients experience a second, third, and fourth HK event

Recurrent events were common and at successively shorter intervals

Hyperkalemia risk factors: DM, CKD and spironolactone

HF = heart failure; HK = hyperkalemia.

Two main reasons to treat Hyperkalemia in HF

• To prevent complications.
• To allow the use of RASS inhibitors.
PARADIGM-HF: Patients with K level of > 5.2 mEq were excluded at screening
Guidelines Recommend Spironolactone in Patients with Resistant Hypertension

Adding an MRA is a key step in the recommended algorithm to manage resistant hypertension\textsuperscript{1,2}

...the use of spironolactone for resistant hypertension should usually be restricted to patients at low-risk for hyperkalemia\textsuperscript{1,2};

As such, the use of spironolactone should be restricted to patients with:

\[
eGFR \geq 45 \text{mL/min} \times 1.73m^2
\]

And plasma potassium K\textsuperscript{+} \leq 4.5 \text{mmol/L}\textsuperscript{2}

\textit{eGFR} = estimated glomerular filtration rate; K\textsuperscript{+} = potassium; MRA = mineralocorticoid receptor antagonist.

## CHAMP-HF Registry: When Prescribed, Majority of Patients on Subtarget GDMT Doses

### Use and Dosing of Guideline Directed Medical Therapy

**US Patients with Chronic HFrEF (N=3,518)**

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Treated</th>
<th>Without Contraindication but Not Treated</th>
<th>With Contraindication</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI/ARB</td>
<td>39.1%</td>
<td>12.8%</td>
<td>59.9%</td>
</tr>
<tr>
<td>ARNI</td>
<td>86.1%</td>
<td>1.8%</td>
<td>1.1%</td>
</tr>
<tr>
<td>ACEI/ARB/ARNI</td>
<td>26.2%</td>
<td>72.1%</td>
<td>35.8%</td>
</tr>
<tr>
<td>β-blocker</td>
<td>66.8%</td>
<td>30.4%</td>
<td>32.9%</td>
</tr>
<tr>
<td>MRA</td>
<td>65.9%</td>
<td>100%</td>
<td>1.1%</td>
</tr>
</tbody>
</table>

**Documented percentage of target dose prescribed**

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; GDMT = guideline-directed medical therapy; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticoid receptor antagonist.

Elevated K⁺ Is one of the Principal Reasons for Reducing or Stopping RAASi Therapy

**~50% of CKD and HF patients are treated at the target dose**

- **Mild hyperkalemia** (potassium 5.1–5.4 mEq/L)
  - Maintained dose: 52%
  - Down-titrated: 38%
  - Discontinued: 22%

- **Moderate-to-severe hyperkalaemia** (potassium ≥5.5 mEq/L)
  - Maintained dose: 41%
  - Down-titrated: 47%
  - Discontinued: 26%

(23,556 hyperkalemic events experienced across doses) (11,608 hyperkalemic events experienced across doses)

Patients with CKD at Stages 3–5 were enlisted within the study. Only those patients who were on maximum RAASi dose were included within this part of the study (which is why the total numbers do not equal 100%).

Percent Mortality by Prior RAASi Dose: A Retrospective Analysis

Mortality Rate according to RAASi Dosage

- **CKD Stage 3-4**: 9.8% (Maxium Dose), 20.3% (Submaximum Dose), 22.4% (Discontinued)
- **Heart Failure**: 13.7% (Maxium Dose), 27.7% (Submaximum Dose), 30.1% (Discontinued)
- **Diabetes**: 5% (Maxium Dose), 10.1% (Submaximum Dose), 13.1% (Discontinued)
- **Total Population**: 4.1% (Maxium Dose), 8.2% (Submaximum Dose), 11% (Discontinued)

- **RAAS** = Renin-angiotensin-aldosterone system; **CKD** = chronic kidney disease.
Case Presentation

- 65 YO Caucasian male.
- History of hypertension for last 10 years.
- CKD stage 3A.
- Extensive anterior MI 2 years ago.
- ICD for primary prevention 1 year ago, EF 25%.
Case Presentation

• VS: HR 76 bpm, BP 122/82 mmHg.
• Functional class II, no signs of volume overload.
• Labs: Na 140, K 5.5, Scr 1.4, GFR 52 mL/min/1.73 m²
• Meds: ASA 81 mg/d, Carvedilol 25 mg bid, furosemide 40 mg bid, lisinopril 5 mg/d (reduced from 10 mg/d B/O hyperkalemia)
• Plan to D/C enalapril and start hydralazine/ISDN
Effect of RAASi on all cause mortality

- Enalapril vs placebo 16% (SOLVD study)
- Eplerenone vs placebo added to ACEi 24% (EMPHASIS)
- Secubitril / Valsartan replacing enalapril 16% (PARADIGM-HF)
Expert consensus document on the management of hyperkalaemia in patients with cardiovascular disease treated with renin angiotensin aldosterone system inhibitors: coordinated by the Working Group on Cardiovascular Pharmacotherapy of the European Society of Cardiology

Giuseppe M.C. Rosano\textsuperscript{1,2*}, Juan Tamargo\textsuperscript{3}, Keld P. Kjeldsen\textsuperscript{4,5,6}, Mitja Lainscak\textsuperscript{7}, Stefan Agewall\textsuperscript{8,9}, Stefan D. Anker\textsuperscript{10,11}, Claudio Ceconi\textsuperscript{12}, Andrew J.S. Coats\textsuperscript{1}, Heinz Drexel\textsuperscript{13,14,15}, Gerasimos Filippatos\textsuperscript{16}, Juan Carlos Kaski\textsuperscript{1}, Lars Lund\textsuperscript{17}, Alexander Niessner\textsuperscript{18}, Piotr Ponikowski\textsuperscript{19}, Gianluigi Savarese\textsuperscript{17}, Thomas A. Schmidt\textsuperscript{20,21}, Petar Seferovic\textsuperscript{22}, Sven Wassmann\textsuperscript{23,24}, Thomas Walther\textsuperscript{25,26}, and Basil S. Lewis\textsuperscript{27,28}
# 2018 Expert Consensus on the Management of HK in Patients with CVD Treated with RAASi – European Society of Cardiology

<table>
<thead>
<tr>
<th>Patients</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic or recurrent hyperkalaemia on RAASi therapy</td>
<td>An approved K(^+)-lowering agent may be initiated as soon as K(^+) levels are confirmed as (&gt;5.0) mEq/L. Closely monitor K(^+) levels. Maintain treatment unless alternative treatable aetiology is identified</td>
</tr>
<tr>
<td>K(&gt;5.0) mEq/L</td>
<td></td>
</tr>
<tr>
<td>Chronic or recurrent hyperkalaemia not on maximal tolerated guideline-recommended target dose of RAASi</td>
<td>RAASi should be optimised and an approved K(^+)-lowering agent may be initiated as soon as confirmed K(^+) levels are (&gt;5.0) mEq/L. Closely monitor K(^+) levels. Maintain treatment unless alternative treatable aetiology is identified</td>
</tr>
<tr>
<td>K(&gt;5.0) mEq/L</td>
<td></td>
</tr>
<tr>
<td>K(^+) levels of 4.5–5.0 mEq/L not on maximal tolerated, guideline-recommended target dose of RAASi therapy</td>
<td>Initiate/up-titrated RAASi therapy and closely monitor K(^+) levels. If K(^+) levels rise above 5.0 mEq/L, initiate an approved K(^+)-lowering agent</td>
</tr>
<tr>
<td>K(^+) levels of (&gt;5.0)–(&lt;6.5) mEq/L not on maximal tolerated, guideline-recommended target dose of RAASi therapy</td>
<td>Initiate an approved K(^+)-lowering agent. If levels (&lt;5.0) mEq/L are detected, up-titrated RAASi - K(^+) level should be closely monitored and K(^+) lowering treatment should be maintained unless another aetiology for hyperkalaemia is identified</td>
</tr>
</tbody>
</table>
# New Potassium Binders

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patiromer-Veltassa</th>
<th>ZS-9 (Zirconium Cyclosilicate)-Lokelma</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI Absorption</td>
<td>Non-reabsorbable</td>
<td>Non-absorbable</td>
</tr>
<tr>
<td>Molecular structure</td>
<td>Organic polymer</td>
<td>crystalline inorganic cation exchange compound</td>
</tr>
<tr>
<td>Mechanism of Action</td>
<td>Ca-K exchange</td>
<td>Na-K exchange</td>
</tr>
<tr>
<td>Relative K Affinity</td>
<td>-</td>
<td>25-fold &gt; Na</td>
</tr>
<tr>
<td>Site of Action</td>
<td>Colon</td>
<td>Upper/Lower GI tract</td>
</tr>
<tr>
<td>K selectivity relative to SPSS</td>
<td>-</td>
<td>120-fold</td>
</tr>
</tbody>
</table>
Potassium Binders

Indication and Usage

• Both VELTASSA and LOKELMA are indicated for the treatment of hyperkalemia

• Limitation of Use:
  o Both should not be used as an emergency treatment for life-threatening hyperkalemia because of their delayed onset of action
Patiromer Clinical Development Prog

<table>
<thead>
<tr>
<th>Start Year</th>
<th>P.o.C.</th>
<th>Prevention</th>
<th>Treatment</th>
<th>Post-US Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2014</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2016</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2017</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2018</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2019</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **101**: Healthy volunteers
- **102**: Healthy volunteers
- **104**: CKD with HF
- **201**: Hemodialysis subjects
- **204**: CKD with HF
- **AMETHYST 205**: (52-week safety & efficacy) HK, CKD, T2DM, HTN
- **OPAL-HK 301**: (Phase 3 pivotal) HK with CKD
- **104-116**: (DDI) Healthy volunteers
- **TOURMALINE 401**: (food effect) HK with CKD
- **PEARL-HF 202**: HF with/without CKD
- **DIAMOND**: (RAASi) HK with HF
- **AMBER 207**: (rHTN) HK with CKD
- **EMERALD 206p**: (Age 2-17) HK with CKD

**CKD**: chronic kidney disease; **DDI**: drug-drug interaction; **HTN**: hypertension; **HF**: heart failure; **HK**: hyperkalemia; **rHTN**: resistant hypertension; **T2DM**: type 2 diabetes mellitus.
Patiromer 12-week Study OPAL-HK (301): Trial Design

Part A: 4-week Treatment Phase (Single-Blind)

- Subjects with CKD* on RAASi (n=243)
  - Patiromer 4.2g BID starting dose (n=92)
    - Baseline serum K+ 5.1 to <5.5 mEq/L
  - Patiromer 8.4g BID starting dose (n=151)
    - Baseline serum K+ 5.5 to <6.5 mEq/L

Part B: 8-week Randomized Withdrawal Phase (Single-Blind)

- Randomization

  - Patiromer †, continued RAASi (n=55)
  - Placebo, continued RAASi (n=52)

Subjects with Part A baseline K+ 5.5 to < 6.5 and who completed Part A and:
- Serum K+ 3.8 to <5.1 mEq/L at Part A Week 4
- Still on RAASi (n=107)

*Estimated glomerular filtration rate 15 to <60 per minute per 1.73 m² of body-surface area.
†Patiromer dosage was adjusted as needed by treating physician.
BID: twice daily; CKD: chronic kidney disease; K+: potassium; RAASi: renin-angiotensin-aldosterone system inhibitor.
Primary and Secondary Efficacy Endpoints

Serum Potassium Levels over Time During the Initial Treatment Phase

- 8.4g BID starting dose (n=151)
- 4.2g BID starting dose (n=92)

76% of subjects had serum K+ in the target range (3.8 to <5.1 mEq/L) at week 4

Mean Serum K+ (mEq/L)

- Mild hyperkalemia
- Moderate-to-severe hyperkalemia

Primary Efficacy Endpoint: Mean Change from Baseline to Week 4 (All Subjects)

Secondary Efficacy Endpoint: 76% of subjects had serum K+ in the target range (3.8 to <5.1 mEq/L) at week 4

HK: Hyperkalemia; K+: potassium.

OPAL-HK (301) Part B: Effect of Discontinuing Patiromer

**Primary Endpoint:**

Median change in serum potassium from Part B baseline*

\[ \Delta = 0.72 \text{ mEq/L} \quad p < 0.001 \]

**Exploratory Endpoints:**

- Requiring any adjustment of RAAS inhibitor (i.e., down-titration or discontinuation) or patiromer titration due to hyperkalemia
  - Placebo: 62%
  - Patiromer: 16%

- Receiving any dose of a RAAS inhibitor at the end of Part B*
  - Placebo: 44%
Opal-HK Pre-Specified Subgroup Analysis in Patients with and Without Heart Failure on RAAS Inhibitors

Pre-specified subgroup analysis of the primary endpoint of OPAL-HK Part A

Mean Serum Change from Baseline K⁺ Levels

This analysis also found that there was no difference in the efficacy of patiromer between heart failure and non-heart failure patients. In both populations, patiromer was able to lower serum potassium by -1.1 and -1.0 mEq/L after 4 weeks.

<table>
<thead>
<tr>
<th></th>
<th>HF</th>
<th>Non-HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>-0.5 ±0.05</td>
<td>-0.5 ±0.04</td>
</tr>
<tr>
<td>Day 3</td>
<td>-0.8 ±0.05</td>
<td>-0.7 ±0.04</td>
</tr>
<tr>
<td>Week 1</td>
<td>-0.9 ±0.05</td>
<td>-0.9 ±0.04</td>
</tr>
<tr>
<td>Week 2</td>
<td>-1.1 ±0.05</td>
<td>-1.0 ±0.04</td>
</tr>
<tr>
<td>Week 3</td>
<td>-1.1 ±0.05</td>
<td>-1.0 ±0.04</td>
</tr>
<tr>
<td>Week 4</td>
<td>-1.1 ±0.05</td>
<td>-1.0 ±0.04</td>
</tr>
</tbody>
</table>
OPAL-HK: Withdrawl Phase
Pre-specified Exploratory Analysis in the HF Subpopulation

Time to recurrence of hyperkalemia

Proportion of patients discontinuing RAASi

Figure 3 Time to first recurrence of hyperkalemia [(a) K⁺ ≥5.1 mEq/L; (b) K⁺ ≥5.5 mEq/L] in patients with HF during the randomized withdrawal phase. Circles indicate censored observations. BL, baseline; HF, heart failure; K⁺, potassium; Wk, week.

Figure 4 Proportion of patients discontinuing RAASi therapy during the randomized withdrawal phase. (a) HF patients; (b) non-HF patients. BL, baseline of withdrawal; HF, heart failure; RAASi, renin-angiotensin-aldosterone system inhibitor; Wk, week.

RAASi = renin-angiotensin-aldosterone system inhibitor.

Subjects with a history of chronic HF, aged 18 or older, clinically indicated to receive spironolactone with a serum $K^+$ at screening between 4.3 – 5.1 mEq/L and:

1. CKD (eGFR <60 mL/min) and on $\geq$ 1 ACEI or ARB or $\beta$B; OR
2. Documented Hx hyper$K^+$ < 6 mo* that led to discontinuation of AA, ACEI or ARB or $\beta$B

* Leading to d/c of RAASi or $\beta$B.

**Endpoints**

1°: Mean change in serum $K^+$ from BL at Day 28

2°: % of patients with serum $K^+$ >5.5 mEq/L at any time

% of patients eligible for dose titration to Spiro 50 mg

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; $\beta$B: beta blocker; AA: aldosterone antagonist; Hx: history; Spiro: spironolactone.

Note: In the publication, 15 g BID (30 g total) is reported which refers to dosing calculation that incorporates the weight of the exchange ion and sorbitol complex;Current dosing reflects the active moiety only where 15 g BID = 12.6 g BID (25.2 g total)

### PEARL-HF (202): Prevention Study in Heart Failure With/Without CKD

<table>
<thead>
<tr>
<th>Baseline Demographic and Clinical Characteristics</th>
<th>Patiromer (n=55)</th>
<th>Placebo (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68 ± 9</td>
<td>68 ± 11</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>29 (53%)</td>
<td>34 (69%)</td>
</tr>
<tr>
<td>HF duration (years)</td>
<td>5 ± 5</td>
<td>4 ± 3</td>
</tr>
<tr>
<td>NT-proBNP (pg/ml)</td>
<td>1,395 ± 1,955</td>
<td>2,339 ± 5,432</td>
</tr>
<tr>
<td>Median NT-proBNP (pg/ml)</td>
<td>824</td>
<td>756</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>40 ± 12</td>
<td>41 ± 12</td>
</tr>
<tr>
<td>NYHA Class, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>2 (4%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>II</td>
<td>29 (53%)</td>
<td>28 (57%)</td>
</tr>
<tr>
<td>III</td>
<td>24 (44%)</td>
<td>20 (41%)</td>
</tr>
<tr>
<td>IV</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>CKD with eGFR &lt; 60 mL/min</td>
<td>27 (50%)</td>
<td>30 (63%)</td>
</tr>
<tr>
<td>History of hyperkalemia</td>
<td>22 (41%)</td>
<td>15 (31%)</td>
</tr>
</tbody>
</table>

PEARL-HF (202): Measurement of Serum $K^+$ During Treatment Course

Spironolactone initiated at 25 mg/day on day 1

Spironolactone increased to 50 mg/day on day 15

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Placebo (n=49)</th>
<th>Patiromer (n=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4.73 (4.52-4.94)</td>
<td>4.47 (4.26-4.68)</td>
</tr>
<tr>
<td>3</td>
<td>4.70 (4.49-4.91)</td>
<td>4.44 (4.23-4.65)</td>
</tr>
<tr>
<td>7</td>
<td>4.67 (4.46-4.88)</td>
<td>4.41 (4.20-4.62)</td>
</tr>
<tr>
<td>14</td>
<td>4.64 (4.43-4.85)</td>
<td>4.38 (4.17-4.59)</td>
</tr>
<tr>
<td>17</td>
<td>4.61 (4.40-4.82)</td>
<td>4.35 (4.14-4.56)</td>
</tr>
<tr>
<td>21</td>
<td>4.58 (4.37-4.79)</td>
<td>4.32 (4.11-4.53)</td>
</tr>
<tr>
<td>28</td>
<td>4.55 (4.34-4.76)</td>
<td>4.29 (4.08-4.49)</td>
</tr>
</tbody>
</table>

*K*: potassium.

PEARL-HF (202) Secondary Efficacy Endpoint: Proportion of Subjects With Serum K+ > 5.5 mEq/L by Baseline eGFR

- **Mean eGFR**
  - **Placebo**
    - n=104
    - 25% (7%)
    - **P=0.015**
  - **Patiromer**
    - n=76
    - 19% (8%)
    - **P=0.125**

- **Mean eGFR ≥60mL/min**
  - **Placebo**
    - n=76
    - 39% (7%)
    - **P=0.041**
  - **Patiromer**
    - n=28
    - 7% (0%)

- **Mean eGFR <60mL/min**
  - **Placebo**
    - n=16
    - 56% (0%)

- **Mean eGFR <45mL/min**
  - **Placebo**
    - 0% (0%)
  - **Patiromer**
    - 7% (0%)

- **P=0.017**

---

eGFR: estimated glomerular filtration rate; K+: potassium.
Long-Term Efficacy Study: AMETHYST-DN (205) Study Design

Subjects with CKD* and T2DM on stable RAASi dose (enrolled n=324)

79 normokalemic patients who had uncontrolled blood pressure were entered into the run-in period (used to identify patients without hyperkalemia who could potentially benefit from initiation or optimization of RAAS therapy).

245 patients with serum potassium levels greater than 5.0 to less than 6.0 mEq/L at screening continued use of prescribed ACE inhibitor, ARBs, or both, skipped the run-in, and were randomized directly into treatment phase.

1 Year, Open-Label Study

Subjects randomized to 1 of 3 starting dose groups in each stratum and titrated to the target serum K⁺ goal:

- Mild HK (K⁺ >5.0–5.5) n=220
  - 4.2, 8.4, or 12.6 g patiromer, given BID

- Moderate HK (K⁺ >5.5–<6.0) n=84
  - 8.4, 12.6, or 16.8 g patiromer, given BID

Screening ≤10 days
Run-in ≤4 week
Baseline
Week 4†
Week 8
Week 52

*Mild HK (K⁺ >5.0–5.5)
Moderate HK (K⁺ >5.5–<6.0)

†Randomization
Discontinuation

* eGFR 15-60 ml/min/1.73m²
AMETHYST-DN (205): 52-Week Study: Long-term Control of Hyperkalemia in Patients with CKD and T2D on RAASi

Mean (95% CI) Serum Potassium Over Time

Significant (p<.001) reductions in mean serum K⁺ level 48 hours after patiromer initiation

Up to 95% of patients who had moderate hyperkalemia obtained serum K⁺ within target range

CKD: chronic kidney disease; K⁺: potassium; RAASi = renin angiotensin aldosterone inhibitors; T2D: type 2 diabetes.

Mild 5.0-5.5 mEq N=218
Moderate 5.6-6.0 mEq N=83

Phase 3b study
DIAMOND - Objective

Effect of patiromer treatment of subjects with hyperkalemia while receiving RAASi on:

• 1. Continued use of RAASi medications in accordance to guidelines and

• 2. Decrease the combined endpoint of cardiovascular (CV) death and CV hospitalizations.
**DIAMOND Study Design**

### Hyperkalemia (HK)
- $k^+ > 5.0 \text{ mEq/L}$
- On RAASi

### History of HK
- $k^+ \leq 5.0 \text{ mEq/L}$
- History of hyperkalemia in the past 12 months leading to reduction or discontinuation of RAASi

### Subjects also have:
- HFrEF (LVEF < 40%)
- eGFR ≥ 30 mL/min/1.73 m²
- Hospitalization for HF (or equivalent) within 12 months

---

### Run-in Phase (single blinded, up to 12 weeks)
- Initiate patiromer$
•$
- Optimize ACEI/ARB/ARNi
- Initiate/optimize MRA$
†$

### Treatment Phase (double blinded)
- Patiromer Continued
- Placebo (withdraw patiromer)

---

### Day 1/Day 3
- Randomization

### Week 1

### Week 2$
‡$

### Week 6$
‡$

### Week 18$
‡$

---

### EoS Visit
- Event Driven
- Every 3-Month Visits
- Potassium Assessment Visit (within 2 weeks of patiromer/placebo discontinuation) and/or Follow-up Phone Call (at least 2 weeks after the EOS visit)$§$

---

*$\ast$ Start at 8.4 g/day and up-titrated as necessary up to 25.2 g/day. Subject must return within 1 week ($\pm$ 3 days) after patiromer initiation or dose adjustment to assess potassium levels.

$\dagger$ Initiate selected MRA; up-titrated to 50 mg/day.

$\ddagger$ If there are changes to ACEI, ARB, ARNi and/or MRA dose or serum potassium varies outside the intended range, unscheduled weekly or monthly visits should occur until stability returns.

$§$ If the potassium Assessment Visit is at 2 weeks after the EOS Visit, then follow-up Phone call is not required.
6.1 Clinical Trials Experience

• Table 1 provides a summary of the most common adverse reactions (occurring in ≥2% of patients) in patients treated with Veltassa in these clinical trials. Most adverse reactions were mild to moderate. Constipation generally resolved during the course of treatment.

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Patients treated with Veltassa (N=666)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>7.2%</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>5.3%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4.8%</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.3%</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>2.0%</td>
</tr>
<tr>
<td>Flatulence</td>
<td>2.0%</td>
</tr>
</tbody>
</table>
6.1 Clinical Trials Experience (cont’d)

• During the clinical studies, the most commonly reported adverse reactions leading to discontinuation of Veltassa were gastrointestinal adverse reactions (2.7%), including vomiting (0.8%), diarrhea (0.6%), constipation (0.5%) and flatulence (0.5%).

• Mild to moderate hypersensitivity reactions were reported in 0.3% of patients treated with Veltassa in clinical trials. Reactions have included edema of the lips.

Laboratory Abnormalities

• Approximately 4.7% of patients in clinical trials developed hypokalemia with a serum potassium value <3.5 mEq/L.

• Approximately 9% of patients in clinical trials developed hypomagnesemia with a serum magnesium value <1.4 mg/dL.
Sodium Zirconium Cyclosilicate (Lokelma)

Non absorbable crystalline. Works in the small and large GI tract resulting in early capture of K. Highly selective for K capture in exchange for hydrogen and sodium.
Lokelma pre approval programs N=1700 patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Key Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1 (Packham et al)</td>
<td>Large, two-part, dose-finding, double-blind, randomized, controlled withdrawal trial</td>
<td>Exponential rate of change in mean serum K⁺ levels at 48 hours; Exponential rate of change in serum K⁺ levels over the 12-day treatment interval</td>
</tr>
<tr>
<td>Study 2 (HARMONIZE)</td>
<td>Two-part, open-label, initial phase, double-blind, randomized, placebo-controlled withdrawal trial</td>
<td>Mean serum K⁺ levels among patients taking LOKELMA vs placebo during Days 8 through 29 of the randomized phase</td>
</tr>
<tr>
<td>Study 3 (Fishbane et al)</td>
<td>Open-label, single-arm, maintenance trial</td>
<td>Proportion of patients who achieved normokalemia* during the acute phase and those who maintained it† over months 3-12</td>
</tr>
</tbody>
</table>

Study 12:
- 48-hour initial phase
- 12-day randomized withdrawal phase

Study 21,3:
- 48-hour initial phase
- 1-month randomized withdrawal phase
- 11-month extension phase

Study 34:
- Up to 72-hour initial phase
- 12-month extended dosing phase

Safety and tolerability were assessed in each trial.

*Serum K⁺ ≥3.5-≤5.0 and ≥3.5-≤5.5 mEq/L. †Mean serum K⁺ ≤5.1 and ≤5.5 mEq/L.

LOKELMA Was Studied in a Second Two-part, Double-blind, Placebo-controlled, Phase 3 Trial¹

The HARMONIZE Randomized Clinical Trial
JAMA. 2014;312(21):2223-2233.

251 patients were treated with LOKELMA (10 g TID with meals)

237 patients* randomized

82 received placebo

45 received LOKELMA 5 g QD

50 received LOKELMA 10 g QD

54 received LOKELMA 15 g QD

Optional 11-month extension study
(n=123)

Open-label acute phase
(48 hrs)

Month-long, randomized, double-blind, placebo-controlled withdrawal phase

The recommended dose for continued treatment is 10 g once daily with a recommended maintenance dose ranging from 5 g every other day to 15 g once daily based on desired serum potassium target range.²

Adult ambulatory patients with a history or laboratory evidence of hyperkalemia were recruited and to be eligible, patients needed documented hyperkalemia (2 consecutive potassium values, 1 hour apart, both ≥5.1 mEq/L). Patients were excluded if they were pseudohyperkalemic, required dialysis, had diabetic ketoacidosis, had cardiac arrhythmias requiring immediate treatment, or had active treatment with sodium polystyrene sulfonate or furosamide.

*Normalized patients who achieved normokalemia (potassium 3.5-5.0 mEq/L) in the open-label phase entered the double-blind, randomized phase to receive 3 different doses of LOKELMA (5, 10, or 15 g) or placebo for 28 days.
LOKELMA Helped 92% of Patients Achieve Normokalemia Within 48 Hours\textsuperscript{1,2}

Study 2: Mean Serum Potassium Level Over Time in Patients Treated With LOKELMA During the Initial Open-Label Phase (48 hours)

- Average K\textsuperscript{+} levels decreased from 5.6 mEq/L to 4.5 mEq/L with LOKELMA 10 g TID for 48 hours with meals\textsuperscript{1}
- 66\% of patients had serum K\textsuperscript{+} levels between 3.5-5.0 mEq/L at 24 hours\textsuperscript{3}
- 92\% of patients achieved normokalemia within 48 hours\textsuperscript{1}
- Patients with higher starting potassium levels had a greater response to LOKELMA\textsuperscript{1}
Greater response in severe hyperkalemia and sustained effect

45 patients with baseline serum K+ >6.0 mEq/ml

Mean Serum K⁺ Over 48 Hours in Patients With Severe Hyperkalemia on LOKELMA®

<table>
<thead>
<tr>
<th>Study 1 and 2: Post-hoc Pooled Analysis of 45 Patients With Baseline Serum K⁺ ≥6.0 mEq/L Who Received 10 g TID for 48 Hours¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Patients with higher starting potassium levels had a greater response to LOKELMA²</td>
</tr>
<tr>
<td>• Mean baseline serum K⁺ level of 6.27 mEq/L¹</td>
</tr>
<tr>
<td>• Median time to K⁺ &lt;6 mEq/L and &lt;5.5 mEq/L was 1.1 and 4 hours, respectively³</td>
</tr>
<tr>
<td>• Serum K⁺ levels at 1, 2, 4, 24, and 48 hours were -0.4, -0.6, -0.7, -0.9 and -1.5 mEq/L, respectively</td>
</tr>
</tbody>
</table>

This data analysis was for initial phase only. There is limited experience in 45 patients with serum K⁺ concentrations ≥6.0 mEq/L.

LOKELMA should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action.⁴

Note: Normal serum potassium: 3.5–5.5 mEq/L.

*Severe HK: K⁺ ≥6.0 mEq/L, P<0.001.⁵

LOKELMA Helped Patients Achieve and Sustain Normokalemia for Up to 1 Year

<table>
<thead>
<tr>
<th>Study 2: 11-month Open-Label Extension Phase – Mean Serum Potassium</th>
</tr>
</thead>
<tbody>
<tr>
<td>• The treatment effect on serum potassium was maintained during continued therapy in the open-label extension phase for up to 11 months</td>
</tr>
</tbody>
</table>

K⁺ levels increased in patients not continuing LOKELMA

APSL: Baseline; EPFL: Extension phase baseline; EDD: End of study 7–11 day after last dose; EDD-end within 1 day of last dose.

LOKELMA 10 g TID

45 pts with K⁺ ≥ 6.0
## Adverse Effects

<table>
<thead>
<tr>
<th>ZS-9 (Lokelma)</th>
<th>Patiromer (Veltassa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Edema 8% - 11%</td>
<td>• Constipation 7%</td>
</tr>
<tr>
<td>• Each 5 g dose</td>
<td>• Diarrhea 5%</td>
</tr>
<tr>
<td>of LOKELMA contains</td>
<td>• Nausea 2%</td>
</tr>
<tr>
<td>approximately 400 mg</td>
<td>• Abdominal discomfort 2%</td>
</tr>
<tr>
<td>of sodium.</td>
<td>• Hypokalemia 5%</td>
</tr>
<tr>
<td>• Hypokalemia 4%.</td>
<td>• Hypomagnesemia 9%</td>
</tr>
</tbody>
</table>
summary

• Hyperkalemia is common in patients with HF, CKD and/or diabetes and can be fatal.

• High levels of potassium may lead to dose reduction or discontinuation of life saving RAAS inhibitors.

• Both Patiromer and Lokelma have been shown to be effective and relatively safe in preventing and treating hyperkalemia.
summary

• Side effects profile is different mainly GI symptoms and hypomagnesemia with Patiromer and leg edema with Lokelma.

• Hypokalemia may develop in a small number of patients with both drugs and needs to be monitored.