Hyperkalemia in Heart Failure Patients – New Approaches for Therapy

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Los Angeles, California
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, enalapril 10 mg/d, spironolactone 25 mg/d
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%.
What would you do?

• 1. Stop spironolactone
• 2. Stop enalapril.
• 3. Stop both.
• 4. Stop spironolactone and switch enalapril to Entresto?
CHAMP-HF (Change the Management of Patients with Heart Failure) Registry

• CHAMP-HF: prospective, observational, nonrandomized study designed to characterize patterns and factors associated with use and dose of HFrEF medications in current practice
  
  – 3,518 patients from 150 primary care and cardiology practices in the US
  
  • Characteristics: Mean age was 66 ± 13 years; 29% female, 71% male; Mean EF was 29 ± 8%
  
  • Chronic HFrEF (≤ 40%) and were receiving at least 1 oral medication for management of HF
    
    – Including diuretics, ACEI, ARB, ARNI, β-blockers, MRA, antihypertensives, vasoactive/inotropic agents, or other cardiovascular medications

• Key exclusion criteria: included current or anticipated participation in a clinical trial, currently receiving comfort care or enrolled in hospice, life expectancy <1 year, or history of or plan for heart transplantation, left ventricular assist device, or dialysis

• Characterized by baseline use and dose of medication

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticoid receptor antagonist.
Prevalence of Hyperkalemia Increases in Clinical Trials Employing RAASi

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
Hyperkalemia Event Rates in Patients with Heart Failure by Ejection Fraction, 1-Year Follow-Up, N = 5,848

- K+ > 5.0 mEq/L
  - Overall: 24.4%
  - HFrEF: 24.7%
  - HFmrEF: 22.2%
  - HFpEF: 25.8%

- K+ > 5.5 mEq/L
  - Overall: 10.2%
  - HFrEF: 9.6%
  - HFmrEF: 10.6%
  - HFpEF: 11.4%

HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced 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\(^1\)

- **1st HK Event**: 12,340 (39%)
  - 0.52 yrs

- **2nd HK Event**: 5,326 (43.2%)
  - 0.44 yrs

- **3rd HK Event**: 2,891 (54.3%)
  - 0.38 yrs

- **4th HK Event**: 1,738 (60.1%)
  - 0.38 yrs

Hyperkalemia risk factors: DM, CKD and spironolactone

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

Recurrent events were common and at successively shorter intervals


HF = heart failure; HK = hyperkalemia.
• To prevent complications.
• To allow the use of RASS inhibitors.
Adjusted Mortality* by Serum K⁺ Level in Patients 45 to 64 Years and ≥65 Years With and Without Comorbid Illness

**Normal Range**

**Increases in mortality remained after adjustments for demographic characteristics and comorbidities**

**Baseline Serum Potassium Level, mEq/L**


*Evaluated through de-identified medical records (2007-2012) of individuals with ≥2 mEq/L serum K⁺ readings (Humedica, Cambridge, MA). Spline analyses were performed to assess mortality at 0.1 mEq/L increments of serum K⁺ after adjusting for covariates and interactions. Comorbid patients are those with diabetes, heart failure, CKD stages 3-5, cardiovascular disease, or hypertension.


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MRC-US-MED-00313
# 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>Therapy</th>
<th>Treated</th>
<th>Without Contraindication but Not Treated</th>
<th>With Contraindication</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI/ARB</td>
<td>59.9%</td>
<td>35.8%</td>
<td>13.2%</td>
</tr>
<tr>
<td>ARNI</td>
<td>39.1%</td>
<td>86.1%</td>
<td>12.8%</td>
</tr>
<tr>
<td>ACEI/ARB/ARNI</td>
<td>26.2%</td>
<td>72.1%</td>
<td>7.2%</td>
</tr>
<tr>
<td>β-blocker</td>
<td>66.8%</td>
<td>30.4%</td>
<td>17.9%</td>
</tr>
<tr>
<td>MRA</td>
<td>65.9%</td>
<td>33.1%</td>
<td>7.1%</td>
</tr>
</tbody>
</table>

**Frequency (%)**

- **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.

2,588 US outpatients with chronic HFrEF in the CHAMP-HF registry with complete medication data and no contraindications to medical therapy

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.

RAASi Discontinuation Due to Hyperkalemia: A Retrospective Analysis with HF, CKD or Diabetes

**Change in RAASi Dose Subsequent to Hyperkalemia Events Among Patients on Maximum RAASi Dose**

- **Mild hyperkalemia (Potassium 5.1-5.4 mEq/L)**: 23,556 events
  - Maintained dose: 52%
  - Down-titrated dose: 16%
  - Discontinued: 32%

- **Moderate-to-Severe Hyperkalemia (Potassium ≥5.5 mEq/L)**: 11,608 events
  - Maintained dose: 41%
  - Down-titrated dose: 21%
  - Discontinued: 38%

**Change in RAASi Dose Subsequent to Hyperkalemia Events Among Patients on Submaximum RAASi Dose**

- **Mild hyperkalemia (Potassium 5.1-5.4 mEq/L)**: 85,567 events
  - Maintained dose: 61%
  - Down-titrated dose: 24%
  - Discontinued: 15%

- **Moderate-to-Severe Hyperkalemia (Potassium ≥5.5 mEq/L)**: 43,170 events
  - Maintained dose: 55%
  - Down-titrated dose: 27%
  - Discontinued: 18%

“Maximum,” defined as the labeled dose; “submaximum,” defined as any RAAS inhibitor dose lower than the labeled dose; or “discontinued,” defined as the absence of RAASi prescriptions for >390 days subsequent to prior Rx.

HF = heart failure; CKD = chronic kidney disease; RAASi = renin-angiotensin-aldosterone system inhibitor.

Percent Mortality by Prior RAASi Dose: A Retrospective Analysis

Mortality Rate according to RAASi Dosage

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

(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%).

BIOlogy Study to TAilored Treatment in Chronic Heart Failure (BIOSTAT-CHF)

- 2516 patients with worsening signs and/or symptoms of heart failure from 11 European countries, who were considered to be on suboptimal medical treatment
  - Median follow up: 21 months

- 22% achieved recommended treatment dose for ACEI/ARB

- Reaching 50-99% of the recommended ACEI/ARB and/or β-blocker dose had comparable risk of death and/or heart failure hospitalization to those reaching ≥100%

- Reaching <50% of recommended ACEI/ARB and beta-blocker dose was associated with an increased risk of death and/or heart failure hospitalization

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker.
• 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure²
  
  – ACEI/ARB should be given with caution to patients with elevated serum potassium (>5.0 mEq/L)
  
  – With regard to the use of MRAs, creatinine should be <2.5 mg/dL in men or <2.0 mg/dL in women (or estimated glomerular filtration rate >30 mL/min) and potassium should be <5.0 mEq/L. Careful monitoring of potassium, renal function, and diuretic dosing represents best practices at initiation and during follow-up thereafter to minimize risk of hyperkalemia and worsening renal function
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>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⁺ levels of 4.5–5.0 mEq/L not on maximal tolerated, guideline-recommended target dose of RAASi</td>
<td>Initiate/up-titre RAASi therapy and closely monitor K⁺ levels. If K⁺ levels rise above 5.0 mEq/L, initiate an approved K⁺-lowering agent</td>
</tr>
</tbody>
</table>

CVD: cardiovascular disease; HK: hyperkalemia; K⁺: potassium; RAASi: renin-angiotensin-aldosterone system inhibitors.

Treatment Patterns in Patients with HFrEF and Worsening HF

Study of 11,064 patients with incident HFrEF from the National Cardiovascular Data Registry PINNACLE (linked to pharmacy, private practitioner, and hospital claims databases). Worsening HF, defined as ≥90 days of stable HF with subsequent worsening requiring intravenous diuretic agents.

Use of standard-of-care therapies both before and after the onset of worsening HF is low.

β-blockers

ACEI/ARB

MRA

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

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## Characteristics of New Potassium Binding Agents

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patiromer</th>
<th>Zirconium Cyclosilicate</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>
<tr>
<td>Onset of [K]p lowering</td>
<td>7 hours</td>
<td>2 hours</td>
</tr>
</tbody>
</table>

*Note: SPSS stands for Standard Physiological Solution.*
Patrolmen: A Non-absorbed Crosslinked Polymer

- Patiromer for oral suspension is a non-absorbed polymer, designed to bind and remove K⁺ from the body.
- Patiromer binds to K⁺ in exchange for Ca²⁺, predominantly in the colon where K⁺ concentration is the highest.
- Ca²⁺ is used instead of Na⁺ as the counterion to avoid potential Na⁺ adverse events in patients with heart failure, severe hypertension, or marked edema, all of which are common in patients with CKD.

Ca²⁺: calcium; CKD: chronic kidney disease; K⁺: potassium; Na⁺: sodium.
Indication and Usage

• VELTASSA® is indicated for the treatment of hyperkalemia

• Limitation of Use:
  o VELTASSA® should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action

Monitor serum potassium and adjust the dose of VELTASSA® as necessary to obtain the desired serum potassium range
### Patiromer Clinical Development to Date

<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>
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<td>2009</td>
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<td>2010</td>
<td></td>
<td></td>
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<tr>
<td>2011</td>
<td></td>
<td>AMETHYST 205</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td></td>
<td>(52-week safety &amp; efficacy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td></td>
<td>HK, CKD, T2DM, HTN</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>104-116</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2016</td>
<td></td>
<td>(DDI)</td>
<td></td>
<td></td>
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<tr>
<td>2017</td>
<td></td>
<td>Healthy volunteers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2018</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2019</td>
<td></td>
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</tr>
</tbody>
</table>

#### AMETHYST 205
- (52-week safety & efficacy)
- HK, CKD, T2DM, HTN

#### PEARL-HF 202
- HF with/without CKD

#### P.O.C.
- 101 Healthy volunteers

#### Prevention
- 204 CKD with HF

#### Treatment
- OPAL-HK 301
  - (Phase 3 pivotal)
  - HK with CKD
- 103 (onset)
  - HK with CKD
- 104-116
  - (DDI)
  - Healthy volunteers

#### Post-US Approval
- TOURMALINE 401
  - (food effect)
  - HK with CKD
- DIAMOND (RAASi)
  - HK with HF

---

**Phase 1**
- 101 Healthy volunteers
- PEARL-HF 202
  - HF with/without CKD
- 204 CKD with HF
- 201 Hemodialysis subjects

**Phase 2**
- AMETHYST 205
  - (52-week safety & efficacy)
  - HK, CKD, T2DM, HTN
- 104-116
  - (DDI)
  - Healthy volunteers

**Phase 3**
- OPAL-HK 301
  - (Phase 3 pivotal)
  - HK with CKD
- 103 (onset)
  - HK with CKD

**Phase 4**
- TOURMALINE 401
  - (food effect)
  - HK with CKD
- DIAMOND (RAASi)
  - HK with HF

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**Key:***
- CKD: chronic kidney disease
- DDI: drug-drug interaction
- HTN: hypertension
- HF: heart failure
- HK: hyperkalemia
- rHTN: resistant hypertension
- T2DM: type 2 diabetes mellitus

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**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)

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*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.
## OPAL-HK (301): Part A Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mild HK N=92</th>
<th>Mod—Severe HK N=151</th>
<th>Total N=243</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>49 (53%)</td>
<td>91 (60%)</td>
<td>140 (58%)</td>
</tr>
<tr>
<td>Age (yr), mean (SD)</td>
<td>64.6 (11.0)</td>
<td>63.9 (10.2)</td>
<td>64.2 (10.5)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>90 (98%)</td>
<td>146 (97%)</td>
<td>236 (97%)</td>
</tr>
<tr>
<td>Type 2 diabetes, n (%)</td>
<td>52 (57%)</td>
<td>87 (58%)</td>
<td>139 (57%)</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²), n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 to ≤90 (Stage 2)</td>
<td>6 (7%)</td>
<td>16 (11%)</td>
<td>22 (9%)</td>
</tr>
<tr>
<td>45 to &lt;60 (Stage 3a)</td>
<td>22 (24%)</td>
<td>27 (18%)</td>
<td>49 (20%)</td>
</tr>
<tr>
<td>30 to &lt;45 (Stage 3b)</td>
<td>24 (26%)</td>
<td>39 (26%)</td>
<td>63 (26%)</td>
</tr>
<tr>
<td>&lt; 30 (Stage 4/5)</td>
<td>40 (43%)</td>
<td>69 (46%)</td>
<td>109 (45%)</td>
</tr>
<tr>
<td>Heart Failure, n (%)</td>
<td>39 (42%)</td>
<td>63 (42%)</td>
<td>102 (42%)</td>
</tr>
<tr>
<td>NYHA Class I, n (%)</td>
<td>7 (18%)</td>
<td>12 (19%)</td>
<td>19 (19%)</td>
</tr>
<tr>
<td>NYHA Class II, n (%)</td>
<td>25 (64%)</td>
<td>41 (65%)</td>
<td>66 (65%)</td>
</tr>
<tr>
<td>NYHA Class III, n (%)</td>
<td>7 (18%)</td>
<td>10 (16%)</td>
<td>17 (17%)</td>
</tr>
</tbody>
</table>

eGFR: estimated glomerular filtration rate; NYHA: New York Heart Association; SD: Standard deviation.

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

Base-line Mean Serum K⁺ (mEq/L)

HK: Hyperkalemia; K⁺: potassium.

Primary Endpoint:

Median change in serum potassium from Part B baseline*

\[ \Delta = 0.72 \text{ mEq/L} \]

\[ p < 0.001 \]

Exploratory Endpoints:

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Placebo</th>
<th>Patiromer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Requiring any adjustment of RAAS inhibitor (i.e., down-titration or discontinuation) or patiromer titration due to hyperkalemia</td>
<td>62%</td>
<td>16%</td>
</tr>
<tr>
<td>Receiving any dose of a RAAS inhibitor at the end of Part B*</td>
<td>44%</td>
<td>94%</td>
</tr>
</tbody>
</table>
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></td>
<td></td>
</tr>
</tbody>
</table>
**OPAL-HK: Withdrawal Phase**

Pre-specified Exploratory Analysis in the HF Subpopulation

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**Time to recurrence of hyperkalemia**

**Proportion of patients discontinuing RAASi**

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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 ≥ 1 ACEI or ARB or βB; OR

2. Documented Hx hyperK⁺ < 6 mo* that led to discontinuation of AA, ACEI or ARB or βB

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

* Leading to d/c of RAASi or βB.

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)

### Baseline Demographic and Clinical Characteristics

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


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

K⁺: potassium.

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

- eGFR: estimated glomerular filtration rate; K+: potassium.
**PEARL-HF (202): Proportion of Subjects Able to Increase Spironolactone Dose to 50 mg/day**

<table>
<thead>
<tr>
<th></th>
<th>Patiromer (n=55)</th>
<th>Placebo (n=49)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects able to titrate up spironolactone dose</td>
<td>50 (91%)</td>
<td>36 (74%)</td>
<td>0.019</td>
</tr>
</tbody>
</table>

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.

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

*GFR 15-60 ml/min/1.73m²
Mean (95% CI) Serum Potassium Over Time

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

Significant (p<.001) reductions in mean serum K⁺ level 48 hours after patiromer initiation.
A Multicenter, Double-blind, Placebo-controlled, Randomized Withdrawal, Parallel Group Study of Patiromer for the Management of Hyperkalemia in Subjects Receiving Renin-Angiotensin-Aldosterone System Inhibitor (RAASi) Medications for the Treatment of Heart Failure Phase 3b study
DIAMOND - Rationale

- We hypothesize that patiromer can be used to treat hyperkalemia that develops in high-risk HFREF patients while receiving treatment with RAAS inhibitors.

- This is expected to result in improved adherence to guideline RAASI treatment, and we expect reductions in CV mortality and hospitalizations for CV events compared with current standard of care to manage hyperkalemia in these patients, which includes RAASI dose reduction or discontinuation.

- The selection criteria for the present study will provide a cohort of subjects who have risk factors for hyperkalemia (e.g., CKD, diabetes mellitus, older age), who have demonstrated hyperkalemia and who pose the greatest therapeutic dilemma to clinicians, since they have the highest risk of developing hyperkalemia but stand to benefit most from these RAASI therapies.
DIAMOND - Objective

- To determine if patiromer treatment of subjects who developed hyperkalemia while receiving RAASi medications will result in continued use of RAASi medications in accordance with heart failure (HF) treatment guidelines and thereby decrease the occurrence of the combined endpoint of cardiovascular (CV) death and CV hospitalization events compared with placebo treatment.
DIAMOND Study Design

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

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

Subjects also have:
- HF refeeds (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  Week 1  Week 2$^‡$  Week 6$^‡$  Week 18$^‡$

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)$^§$

$^*$ = Start at 8.4 g/day and up-titrate 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. $^†$ = Initiate selected MRA; up-titrate to 50 mg/day. $^‡$ = 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.

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### AMETHYST-DN (205): Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Mild HK N=220</th>
<th>Moderate HK N=84</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, %</td>
<td>63%</td>
<td>63%</td>
</tr>
<tr>
<td>Age, mean (SD), yr</td>
<td>66.5 (8.8)</td>
<td>65.8 (8.2)</td>
</tr>
<tr>
<td>White, %</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Screening eGFR, mean ml/min/1.73m² (SD)</td>
<td>42 (15)</td>
<td>36 (16)</td>
</tr>
<tr>
<td><strong>CKD Stage, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3a</td>
<td>68 (31%)</td>
<td>17 (20%)</td>
</tr>
<tr>
<td>3b</td>
<td>84 (38%)</td>
<td>27 (32%)</td>
</tr>
<tr>
<td>4</td>
<td>39 (18%)</td>
<td>27 (32%)</td>
</tr>
<tr>
<td>5</td>
<td>2 (1%)</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>Urine Albumin, mean (SD), mg/g</td>
<td>1,124 (1901)</td>
<td>1,217 (1666)</td>
</tr>
<tr>
<td>Heart Failure, n (%)</td>
<td>77 (35%)</td>
<td>28 (33%)</td>
</tr>
<tr>
<td>Serum K⁺, mean (SD), mEq/L,</td>
<td>5.2 (0.25)</td>
<td>5.7 (0.36)</td>
</tr>
<tr>
<td>Sitting BP, mean (SD), mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>155.1 (11.2)</td>
<td>156.5 (13.8)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>84.4 (10.9)</td>
<td>82.9 (12.5)</td>
</tr>
</tbody>
</table>

ACR: albumin creatinine ratio; BP: blood pressure; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; HK: hyperkalemia; K⁺: potassium; SD: standard deviation

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 1. Adverse Reactions Reported in ≥2% of Patients

<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.
LOKELMA™ Is an Innovative, Highly Selective Potassium Binder That Works Differently¹,²

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.
ZS-9 is thought to begin working immediately in the small intestine, selectively trapping potassium.

SOURCE: Stavros et al. PLOS ONE 2014
Lokelma pre approval programs N=1700 patients

**STUDY 1** (Packham et al)1,2 N=753
- Large, two-part, dose-finding, double-blind, randomized, controlled withdrawal trial
  - Key Endpoints:
    - 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

**STUDY 2** (HARMONIZE)1,3 N=258
- Two-part, open-label, initial phase, double-blind, randomized, placebo-controlled withdrawal trial
  - Key Endpoint:
    - Mean serum K+ levels among patients taking LOKELMA vs placebo during Days 8 through 29 of the randomized phase

**STUDY 3** (Fishbane et al)1,4 N=751
- Open-label, single-arm, maintenance trial
  - Key Endpoint:
    - Proportion of patients who achieved normokalemia* during the acute phase and those who maintained it† over months 3-12

**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 Trial

- **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.1

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 lactulose.2

*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.*
Mean Serum Potassium Levels Over 48 Hours With ZS-9

![Graph A](image)

10-g Zirconium cyclosilicate, 6 doses

![Graph B](image)

- 0 hours
- 48 hours

<table>
<thead>
<tr>
<th>Baseline Potassium Level, mEq/L</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5.5</td>
<td>119</td>
</tr>
<tr>
<td>5.5-&lt;6.0</td>
<td>100</td>
</tr>
<tr>
<td>≥6.0</td>
<td>39</td>
</tr>
</tbody>
</table>

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MRC-US-MED-00313
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}

\textsuperscript{1}Relypsa, Inc. 2019. Confidential. For Relypsa advisory board use only. Not for external use or distribution.
Mean Serum K⁺ Over 48 Hours in Patients With Severe Hyperkalemia on LOKELMA*

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

- Patients with higher starting potassium levels had a greater response to LOKELMA²
- Mean baseline serum K⁺ level of 6.27 mEq/L¹
- Median time to K⁺ <6 mEq/L and <5.5 mEq/L was 1.1 and 4 hours, respectively¹
- 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.¹

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

Study 2: 11-month Open-Label Extension Phase – Mean Serum Potassium

- The treatment effect on serum potassium was maintained during continued therapy in the open-label extension phase for up to 11 months.

LOKELMA should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action.³

Note: Normal serum potassium: 3.5-5.0 mEq/L.

*Severe HK: K⁺ ≥5.0 mEq/L. P<0.0001.⁴

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Retrospective Analysis of the Changes in RAASi Use During the Maintenance Phase in Study 3\(^1\)

Study 3: Long-Term Efficacy of LOKELMA in a 12-Month, Open-Label, Phase 3 Study

- The mean baseline potassium level in this study was 5.6 mEq/L\(^1,2\).
- Following the initial phase treatment of LOKELMA 10 g 3 times a day, patients who achieved normokalemia within 72 hours (n=746; 99%) entered the maintenance phase\(^3\).
- For maintenance treatment, the initial dosage of LOKELMA was 5 g once daily and was adjusted to a minimum of 5 g every other day up to a maximum of 15 g once daily, based on serum potassium level\(^3\).
- The treatment effect on serum potassium was maintained during continued therapy\(^3\).

The recommended starting dose is 10 g 3 times a day for up to 48 hours. 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.\(^2\)

*Excluded 5 patients who discontinued RAASi therapy prior to first dose of study drug.\(^1\)

\(^1\)Patients were counted more than once if they required more than 1 RAASi adjustment, so total percentage across all 4 categories may exceed 100%.\(^1\)
**Adverse Effects**

**ZS-9 (Lokelma)**
- Edema 8% - 11%
- Each 5 g dose of **LOKELMA** contains approximately 400 mg of **sodium**.
- Hypokalemia 4%.

**Patiromer (Veltassa)**
- Constipation 7%
- Diarrhea 5%
- Nausea 2%
- Abdominal discomfort 2%
- Hypokalemia 5%
- Hypomagneseemia 9%
• Patiromer and ZS-9 may be considered in patients with HF with or without CKD to manage hyperkalaemia. In selected patients these therapies may enable use of MRAs and other renin–angiotensin–aldosterone system inhibitors (RAASi) in more patients and at higher doses, but it is not known whether this will improve patient outcomes.

• Patiromer and ZS-9 may be considered in selected patients with HF with or without CKD in order to enable up-titration of MRA while avoiding hyperkalaemia.

CKD = chronic kidney disease; ESC = European Society of Cardiology; HF = heart failure; MRA = mineralocorticoid receptor antagonist.
Guidelines Recommend Spironolactone in Patients with Resistant Hypertension

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

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

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

eGFR $\geq 45$ mL/min 1.73m$^2$

And plasma potassium $K^+ \leq 4.5$ mmol/L$^2$

*eGFR = estimated glomerular filtration rate; $K^+$ = potassium; MRA = mineralocorticoid receptor antagonist.*

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 RAAS inhibitors.

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

• Both drugs may be used to allow initiation or prevent discontinuation of life saving RAASi.