CTST-21: A Phase 2, Randomized, Double-Blind, Multi-center Study Comparing 15 g Cross-linked Polyelectrolyte (CLP) versus Placebo in Heart Failure Patients with Chronic Kidney Disease

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Disclosures

• Maria Rosa Costanzo - Consultant to Sorbent
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• Barry M. Massie - Consultant to Sorbent
• Julie Iwashita - Sorbent Employee
• Lee Henderson - Sorbent Employee
• Merab Mamatsashvili - Investigational Grant Recipient
• Hamayak Sisakian - Investigational Grant Recipient
• Hamlet Hayrapetyan - Investigational Grant Recipient
• Philip Sager - Consultant to Sorbent
• Dirk J van Veldhuisen - Consultant to Sorbent
• Detlef Albrecht - Sorbent Employee
Background

• Fluid overload accounts for 90% of heart failure hospitalizations\(^1\)
• Diuretics rapidly relieve symptoms of congestion, but concerns exist regarding their efficacy and safety\(^2-4\)
• Alternative therapies may improve fluid overload in heart failure patients
• CLP, an acrylic polyelectrolyte absorbs electrolytes and water in the GI tract and eliminates them through the feces
• Pilot studies in normal volunteers and patients with ESRD showed that use of CLP was associated with increases in stool weight and fecal sodium and potassium excretion

Sources: \(^1\)Adams et al, AHJ, 2005; \(^2\)Brandimarte et al, JCM 2010; \(^3\)Domanski et al, JCF 2006; \(^4\)Peacock et al, Cardiology 2009
Cross Linked Polyelectrolyte (CLP) Removes Sodium and Fluid

**Key Features:**

- Orally administered
- Superabsorbent polymer
- Non-metabolized, not absorbed
- Binds cations and water
- Excreted in the stool
Design of CTST-21 Heart Failure Study

Objectives

- Evaluate in HF Patients the Effects of CLP Therapy On
  - Serum Potassium
  - Parameters of Fluid Overload
- Evaluate in HF Patients the Tolerability of CLP Therapy

Design

- Double-Blind, Placebo-Controlled, Randomized, Parallel Group Study
- 100 HF Patients with Chronic Kidney Disease (GFR <60ml/Min)
- Randomized to 15g CLP or Placebo for 8 Weeks
- Study Drug administered as 30 Capsules per Day (2 x 15)
- 24 sites in Armenia, Georgia, Moldova
Key Entry Criteria

**Potassium and Sodium/Fluid Related Eligibility Criteria**

- **Potassium related**
  - CKD Stage 3 or 4 (eGFR >15ml to < 60ml by Cockrauft Gault)
  - Serum Potassium >4.3 to <5.1 mEq/L
  - Indicated to start aldosterone antagonist therapy

- **Sodium/Fluid related**
  - Heart Failure NYHA Class 3 or 4
  - Recent hospitalization for fluid overload (>1 mo & less than 6 mo)
  - Presence of at least 2 signs of current fluid:
    - Jugular Venous Pressure (JVP) > 8cm;
    - Peripheral edema or ascites;
    - Pulmonary congestion on chest X-ray;
    - Pulmonary rales on auscultation
  - NT pro BNP >1000pg/mL
Key Exclusion Criteria

• Concomitant use of sodium bicarbonate, antacids containing magnesium or calcium, polystyrene sulfonate

• Myocardial infarction, transient ischaemic attack, stroke, or acute coronary syndrome within 1 month

• Any cardiovascular, renal, hepatic, endocrine, neurological, or other disease or condition that made the patient’s study participation unsafe

• History of clinically significant GI pathology

• Liver transaminases > 3 x the upper limit of normal (ULN); serum creatinine ≥ 3 mg/dL
Timeline of Study

8-Week Double-Blind Treatment Period

CLP 15 g/d + spironolactone 25 mg/d

Placebo + spironolactone 25 mg/d

Screening Period ≤ 4 weeks

Baseline

Study Visits

V1 V2

V3 V4 V5 V6

V7 V8 V9

3 days after V2

3 days after V6

Wk 1 Wk 2 Wk 4 Wk 5 Wk 8 (EOS)
Study Endpoints

Efficacy Endpoints
- Serum Potassium Level (primary)
- NYHA Class changes
- 6 Minute Walk Test
- Dyspnea Evaluations (7-Point Likert and Physician Determined)
- Kansas City Cardiomyopathy Questionnaire
- Body weight

Safety Endpoints
- Cations (sodium, magnesium, calcium)
- Anions (phosphorus)
- Bicarbonate
- Adverse events
- Safety laboratory
Statistical Methods

• Formal power/sample size calculations were not performed (exploratory Phase 2 study)
• The primary analyses were performed on the intent to treat (ITT) population, and end of study results for non-completers were excluded.
• Categorical data were evaluated using the chi-square test for homogeneity of proportions
• Continuous or ordinal data were analyzed with repeated measures analysis of covariance (RM-ANCOVA) using change from baseline values to compare the CLP and placebo treatments.
• Using this model, a restricted maximum likelihood approach was used to estimate and compare mean profiles between the two treatment groups, assuming an unstructured covariance matrix.
• Sensitivity analyses were performed for the primary and secondary endpoints using a last observation carried forward approach which included Week 8/End end of Study results for non-completers.
• Corrections for multiplicity were not performed and a p-value ≤ 0.05 was considered statistically significant.
• Statistical testing was not performed for any of the non-efficacy variables.
# Study Demographics

<table>
<thead>
<tr>
<th></th>
<th>CLP (N=59)</th>
<th>Placebo (N=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male</strong></td>
<td>42 (71.2%)</td>
<td>29 (55.8%)</td>
</tr>
<tr>
<td><strong>Mean Age (years)</strong></td>
<td>68.4</td>
<td>70.2</td>
</tr>
<tr>
<td><strong>Mean Weight (kg)</strong></td>
<td>75.3</td>
<td>75.1</td>
</tr>
<tr>
<td><strong>Mean BL eGFR (mL/min)</strong></td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td><strong>Study Drug Compliance (mean % capsules taken)</strong></td>
<td>96.3</td>
<td>97.1</td>
</tr>
<tr>
<td><strong>Preserved LVEF (&gt;40%)</strong></td>
<td>8 (14%)</td>
<td>5 (10%)</td>
</tr>
<tr>
<td><strong>Diabetics</strong></td>
<td>14 (24%)</td>
<td>16 (38%)</td>
</tr>
<tr>
<td><strong>NYHA Class II</strong></td>
<td>0 (0%)</td>
<td>2 (3.9%)</td>
</tr>
<tr>
<td><strong>NYHA Class III</strong></td>
<td>52 (88.1%)</td>
<td>45 (86.5%)</td>
</tr>
<tr>
<td><strong>NYHA Class IV</strong></td>
<td>7 (11.9%)</td>
<td>5 (9.6%)</td>
</tr>
</tbody>
</table>
## Frequency of Concomitant HF Medications

<table>
<thead>
<tr>
<th>Concomitant Medication</th>
<th>CLP (N=59)</th>
<th>Placebo (N=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE/ARBs</td>
<td>56 (95%)</td>
<td>49 (94%)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>49 (83%)</td>
<td>48 (92%)</td>
</tr>
<tr>
<td>Beta Blockers</td>
<td>56 (95%)</td>
<td>46 (89%)</td>
</tr>
<tr>
<td>Aldosterone Antagonist</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25mg</td>
<td>59 (100%)</td>
<td>52 (100%)</td>
</tr>
<tr>
<td>50mg</td>
<td>38 (64%)</td>
<td>38 (73%)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>18 (31%)</td>
<td>18 (35%)</td>
</tr>
</tbody>
</table>
Patient Disposition

- 113 patients enrolled
- 87 patients completed
- 26 early terminations
- 2 placebo patients never took study medication and were excluded

<table>
<thead>
<tr>
<th>Variable</th>
<th>15 g CLP (N=59)</th>
<th>Placebo (N=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients beginning treatment</td>
<td>59 (100.0%)</td>
<td>52 (96.3%)</td>
</tr>
<tr>
<td>Patients completing treatment</td>
<td>41 (69.5%)</td>
<td>46 (85.2%)</td>
</tr>
<tr>
<td>Reason for Termination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completed</td>
<td>41 (69.5%)</td>
<td>46 (85.2%)</td>
</tr>
<tr>
<td>Adverse Event</td>
<td>4 (6.8%)*</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Death</td>
<td>3 (5.1%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Discontinued due to hyperkalemia</td>
<td>6 (10.2%)</td>
<td>5 (9.3%)</td>
</tr>
<tr>
<td>Withdrawal by Subject</td>
<td>5 (8.5%)</td>
<td>3 (5.6%)</td>
</tr>
</tbody>
</table>

*One patient discontinued for a GI AE and died 6 days later secondary to worsening heart failure and multi-organ failure. In total, 4 deaths on study, all in active arm
Serum Potassium Change from Baseline by Study Week (mmol/L)
Body Weight Change by Study Visit (kg)

*P-values based on Repeated Measures Analysis of Covariance

*P<0.05

*Overall p-value 0.065
Dyspnea Evaluation

**Patient Reported (Week 8)**

<table>
<thead>
<tr>
<th>% Patients Moderately/Markedly Better</th>
<th>CLP</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>36.6</td>
<td>21.7</td>
</tr>
</tbody>
</table>

*Study End (Week 8) compared to Baseline on 7 Point Likert Scale*
## Change in NYHA from Baseline to Week 8

### ITT Population with Data at Week 8

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 8</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLP (N=41)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>0</td>
<td>(17)</td>
</tr>
<tr>
<td>III</td>
<td>38</td>
<td>(21)</td>
</tr>
<tr>
<td>IV</td>
<td>3</td>
<td>(3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 8</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo (N=46)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>1</td>
<td>(1)</td>
</tr>
<tr>
<td>III</td>
<td>41</td>
<td>(6)</td>
</tr>
<tr>
<td>IV</td>
<td>4</td>
<td>(2)</td>
</tr>
</tbody>
</table>

**Patients with One Class Improvement from Baseline:**
- **CLP = 48.8%, Placebo = 17.4%, (p = 0.0018)**
6 Minute Walk Test

~ 20 meter difference between CLP and Placebo at Week 8

*P-values based on Repeated Measures Analysis of Covariance
KCCQ Overall Summary Score

Increase in KCCQ score represents improvement in Overall Summary category (maximum score: 100)
P-values based on Repeated Measures Analysis of Covariance for Change in KCCQ Summary Scores
Serum Cation & Anion Concentrations

- No clinically relevant changes in electrolytes:
  - Serum Sodium
  - Serum Calcium
  - Serum Magnesium
  - Serum Phosphorus
  - Serum Bicarbonate
    - Temporary decrease within normal range

- No meaningful changes in:
  - Serum aldosterone
# Summary of CV and GI Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>15 g CLP (N=59)</th>
<th>Placebo (N=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Number of Patients with Adverse Events</strong></td>
<td>21 (35.6%)</td>
<td>16 (30.8%)</td>
</tr>
<tr>
<td><strong>Total Cardiac Disorders</strong></td>
<td>3 (5.1%)</td>
<td>3 (5.8%)</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders (all mild or moderate)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>14 (23.7%)</td>
<td>7 (13.5%)</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>7 (11.9%)</td>
<td>2 (3.8%)</td>
</tr>
<tr>
<td>Abdominal distention</td>
<td>3 (5.1%)</td>
<td>1 (1.9%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1 (1.7%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Abdominal pain (upper)</td>
<td>0 (0.0%)</td>
<td>1 (1.9%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>1 (1.7%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0 (0.0%)</td>
<td>1 (1.9%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (5.1%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (1.7%)</td>
<td>3 (5.8%)</td>
</tr>
</tbody>
</table>
### SAEs leading to death

<table>
<thead>
<tr>
<th>ID</th>
<th>EVENT</th>
<th>Wks on Study</th>
<th>Days from Last Dose to Death</th>
<th>HISTORY</th>
<th>EVENT EVALUATION</th>
<th>PI CAUSALITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>1102</td>
<td>Sudden Death</td>
<td>3</td>
<td>0</td>
<td>70y; male NYHA Class 4, LVEF 20-25%, Ischemic CM, Atrial Fibrillation, eGFR= 45.7</td>
<td>Stable 2 wks before event; stable labs except elevated ALT/AST; ECG unchanged</td>
<td>Definitely not related</td>
</tr>
<tr>
<td>1207</td>
<td>Acute CHF</td>
<td>~4</td>
<td>0</td>
<td>60y; male NYHA Class 3, LVEF 20%, MI, Ischemic CM, pulmonary embolism, CABG, Coronary Stent, Diabetes Mellitus, eGFR= 47.6</td>
<td>2 days before event stable with no lab abnormalities</td>
<td>Definitely not related</td>
</tr>
<tr>
<td>2801</td>
<td>CHF/Renal Failure</td>
<td>6</td>
<td>3</td>
<td>68y; male NYHA CHF Class 3, MI, Coronary Stent, eGFR= 48</td>
<td>2 wks before event: worsening kidney function, significant fluid overload. Hospitalization recommended. Patient refused. CR=3.7; eGFR=20; K=4.2</td>
<td>Definitely not related</td>
</tr>
<tr>
<td>3103</td>
<td>CHF/Multi organ failure</td>
<td>~6</td>
<td>6</td>
<td>67y; male NYHA Class 4, Dilated Cardiomyopathy, Afib, Chronic Venous Insufficiency, eGFR = 36.2</td>
<td>9 days before death patient complained of loss of appetite &amp; abdominal distension. Labs showed Bicarb= 11; K=5.2; CR= 1.7; Hospitalized 3 days bef. death with dyspnea, afib, ascites &amp; hydrothorax</td>
<td>Definitely not related</td>
</tr>
</tbody>
</table>

(all in CLP cohort)
Considerations Regarding Evaluation of Deaths

- The observed overall mortality rate of 4% was as expected in a population of patients with coexisting advanced HF and CKD\(^1\)
- None of the deaths were attributed by the attending investigator to the use of blinded study drug
- An independent analysis of all available patient data by a group of HF experts did not identify an etiology that could be attributed to CL
- In small studies not powered to detect differences in mortality, imbalances in this occurrence can be assumed to be a random event as it has been previously reported\(^2\)
- Regardless, this imbalance in mortality mandates cautious safety monitoring in the future development of CLP including the involvement of an independent safety monitoring board

In heart failure patients with fluid overload and CKD, the addition of 15 g of CLP to guideline based medical therapy was associated with:

- clinically meaningful
  - Body weight reduction
  - NYHA Class improvement
  - Dyspnea improvement
  - 6 Minute Walk Test improvement
  - Improvements in KCCQ

- No effects on serum ion concentrations

- Good overall gastrointestinal tolerability
  - Expected frequency & severity adverse events

- No obvious CLP-related mechanism for the four deaths occurring in the treatment group could be identified
Implications

• Use of CLP in the GI tract may be an effective means for removal of sodium and water in HF subjects already treated with guideline therapy including diuretics

• Such extra-renal removal of fluid appears to result in meaningful improvement in function and symptoms in these patients and warrants further investigation

• An adequately powered trial is needed to confirm efficacy and carefully evaluate safety of the compound
A double-blind, randomized, parallel, placebo-controlled study examining the effect of cross-linked polyelectrolyte in heart failure patients with chronic kidney disease

Maria Rosa Costanzo¹*, J. Thomas Heywood², Barry M. Massie³, Julie Iwashita⁴, Lee Henderson⁴, Merab Mamatsashvili⁵, Hamayak Sisakian⁶, Hamlet Hayrapetyan⁷, Philip Sager⁸, Dirk J. van Veldhuisen⁹, and Detlef Albrecht⁴

http://eurjhf.oxfordjournals.org/cgi/content/full/hfs074