Hyperkalemia/ZS-9

Discussant

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- Consultant: Relypsa, Pfizer, Bayer, Eli Lilly, Astra Zeneca, SC Pharmaceuticals, Tricida, DaVinci therapeutics, Stealth Peptides, Aura sense, Sarfez
- Stock options: Relypsa, SC Pharmaceuticals, Tricida, Aurasense
- Patent pending: site specific delivery of eplerenone to the myocardium
Hyperkalemia

• What level of serum potassium is associated with an increased risk of mortality?
• What therapies are currently available or being developed for the chronic treatment of patients with hyperkalemia?
• What have we learned from the ZS-9 study?
• What would we like to know about ZS-9?
**Adjusted Mortality* by Serum K⁺ Level, Patients 45–64 Yr and ≥65 Yr With and Without Comorbid Illness**

*Evaluated through de-identified medical records (2007-2012) of individuals with ≥2 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 diabetes, heart failure, chronic kidney disease stages 3-5, cardiovascular disease, or hypertension.

Pitt B. et al AHA 2014
# What Therapies are Available or being Developed for the Chronic Therapy of Hyperkalemia

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Structure</th>
<th>Exchange Ion</th>
<th>Primary site of Action</th>
<th>Safety</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium polystyrene sulfonate (kayexalate)</td>
<td>Cation exchange polymer -Crystal lattice</td>
<td>Na⁺</td>
<td>Large intestine</td>
<td>Sodium Retention</td>
<td>1958</td>
</tr>
<tr>
<td>ZS-9 Patiromer</td>
<td>Zironium silicate -3 dimensional crystalline lattice</td>
<td>Na⁺ and H⁺</td>
<td>throughout the GI tract</td>
<td>Intestinal necrosis and GI perforation</td>
<td>NDA submission:2015</td>
</tr>
<tr>
<td>Patiromer</td>
<td>Metal free polymer</td>
<td>Ca⁺</td>
<td>Throughout the GI tract, predominately colon</td>
<td>Hypokalemia, Hypocalcemia, Hypomagnesemia</td>
<td>NDA submission:2011</td>
</tr>
</tbody>
</table>
Hyperkalemia

What Have we Learned from the Efficacy and Safety Study of ZS-9 in Patients with Hyperkalemia?

• Doses of 5, 10, and 15 g QD appear to be effective in lowering serum potassium into the normal range.
• 84% of patients were normokalemic by 48 hrs.
• Normokalemia ($K^+ <5.1$ m Eq/L) was maintained over the 28 day study period.
• The overall safety profile appeared to be comparable to placebo except for hypokalemia and edema.
Hyperkalemia
What Would We Like to Know About ZS-9 for the Treatment of Hyperkalemia

• What is the long term (> 1 year) safety and tolerability of ZS-9 (Zirconium?)
• What is the explanation for the increase in edema, which appears to be dose related? (Na+ exchanger?)
• What type of long term monitoring of serum potassium and renal function will be required?
• What are the risk/benefit and cost/benefit implications of the long term administration ZS-9 vs. reducing the dose or discontinuing RAAS-inhibitors?
Hyperkalemia

Conclusions:

• The risk of death in patients with CKD, HF, and or DM, especially those \( \geq 65 \) years, is increased at serum potassium values above and below 4.5 meq/L.

• ZS-9 provides a potential opportunity to treat and possibly prevent hyperkalemia in high risk patients such as those with CKD, HF, DM and or those on a RAAS-inhibitor.

• Further data is however needed in regard to its long term safety and tolerability as well as its cost/benefit and health economic implications.