NEW AND EMERGING THERAPIES FOR ANEMIA OF CKD

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DISCLOSURES

• **Consultancy:**
  Co-chair of the global executive steering committee of Akebia
  (phase 3 program for vadadustat)

• **Lecture fees:**
  Bayer, Vifor

• **Grant support:**
  Amgen, Astra Zeneca, Bayer, FMC, Genzyme, Vifor
5 main causes of renal anemia
- Inappropriately low EPO production
- Inhibitors of erythropoiesis
- Blood (and iron) loss
- Decreased iron reabsorption and release from macrophages
- Increased production and decreased clearance of hepcidin

Therapeutic approaches
- EPO (ESA) administration
- Stimulation of endogenous EPO
- Iron administration
- Inhibition of hepcidin
- Inhibition of inflammation
- (RBC transfusions)
NOVEL AND EMERGING THERAPIES FOR ANEMIA OF CKD

• Prolyl Hydroxylase Inhibitors (HIF stabilizers)

• Hepcidin antagonists

• Antiinflammatory therapies

• Novel iron compounds
1. HIF-dependent gene expression is iron-dependent
   - PHDs are iron-dependent
     → iron chelators (iron deficiency) stabilize HIF
   - IRE in the HIF-2 gene

2. Iron-absorbing genes are HIF target genes

3. FPN stabilizes HIF-2 in enterocytes

EFFECT OF ROXADUSTAT IN DD CKD PATIENTS

open label RCT - N=305; prevalent HD/PD patients (89:11%)
randomized 2:1 to roxadustat or epoetin alfa; i.v. iron as rescue only

- change in Hgb: roxadustat non-inferior
- roxadustat: decline in hepcidin

Chen et al. *NEJM* 2019 311; 1011-1022
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  – Stimulation of endogenous EPO → enhanced erythropoiesis
  – Additional effects; benefit / risk relationship?
  – Synergic effects on iron reabsorption and iron metabolism; clinical relevance?

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HEPCIDIN ANTAGONISTS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tocilizumab (mc IL-6 rec Ab)</td>
<td>IL-6 receptor</td>
<td>Song et al. 2010</td>
</tr>
<tr>
<td>Situximab (mc IL-6 Ab)</td>
<td>IL-6</td>
<td>Casper et al. 2015</td>
</tr>
<tr>
<td>AG490 (small molecule)</td>
<td>JAK2</td>
<td>Zhang et al. 2011</td>
</tr>
<tr>
<td>Highly sulfated heparins</td>
<td>BMPs</td>
<td>Pli et al. 2014</td>
</tr>
<tr>
<td>Monoklonal HJV Ab</td>
<td>HJV</td>
<td>Abbvie (<a href="http://www.abbvie.com">www.abbvie.com</a>)</td>
</tr>
<tr>
<td>PRS-808 (pegylated anticalin)</td>
<td>Hepcidin</td>
<td>Pieris Pharmaceuticals (<a href="http://www.pieris.com">www.pieris.com</a>)</td>
</tr>
<tr>
<td>TP-0184</td>
<td>ALK2</td>
<td>Tolero Pharmaceuticals (<a href="http://www.toleropharma.com">www.toleropharma.com</a>)</td>
</tr>
<tr>
<td>LDN-193189 (small molecule)</td>
<td>Type I BMPRs</td>
<td>Steinbicker et al. 2011</td>
</tr>
<tr>
<td>NOX-H94 (pegylated Spiegelmer)</td>
<td>Hepcidin</td>
<td>Schwoebel et al. 2013</td>
</tr>
<tr>
<td>LY2787106 (mc hepcidin Ab)</td>
<td>Hepcidin</td>
<td>Sheetz et al. 2019</td>
</tr>
<tr>
<td>LY2928057 (mc FPN Ab)</td>
<td>Ferroportin</td>
<td>Witcher et al. 2013</td>
</tr>
</tbody>
</table>

Sebastini, *Front Pharmacol* 2016
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  – Hepcidin inhibitors or antibodies
  – Ferroportin antibodies

• Antiinflammatory therapies

• Novel iron compounds
Study Description

Brief Summary:
Patients with chronic kidney disease, who have evidence of systemic inflammation with increased cardiovascular risk, will be enrolled into this trial. The purpose of this trial is to determine a dose to select for a potential cardiovascular outcome trial with Zillivekimab. Doses to be tested will be 7.5 mg, 15 mg and 30 mg subcutaneous monthly compared to placebo for six months.

<table>
<thead>
<tr>
<th>Condition or disease</th>
<th>Intervention/treatment</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Kidney Diseases</td>
<td>Biological: Zillivekimab</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Inflammation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Study Design

- **Study Type**: Interventional (Clinical Trial)
- **Estimated Enrollment**: 240 participants
- **Allocation**: Randomized
- **Intervention Model**: Parallel Assignment
- **Masking**: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
- **Masking Description**: Matching placebo
- **Primary Purpose**: Treatment
- **Official Title**: A Phase 2b, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate Reduction in IL-6 Mediated IL-6 Inhibition
- **Actual Study Start Date**: June 3, 2019
- **Estimated Primary Completion Date**: September 2020
- **Estimated Study Completion Date**: September 2020

Corvidia Therapeutics to Present New Data at ASN Kidney Week 2019

WALTHAM, Mass., Nov. 6, 2019 /PRNewswire/ -- Corvidia Therapeutics, a clinical stage company focused on the research, development and commercialization of transformative therapies in cardio-renal disease, will deliver two key presentations at the American Society of Nephrology's annual meeting in Washington D.C. Both presentations will release new data on Corvidia's lead asset, zillivekimab™, being developed to be the first therapy to reduce inflammation for the purpose of reducing major cardiovascular events in CKD patients.

**SESSION DETAILS:**
- **Anemia and Iron Metabolism: Clinical Research (OR020-2):**
  - November 7, 2019
  - Presentation time: 5:18pm - 5:30pm EST
  - Location: Session Room 150, Walter E. Washington Convention Center
  - Abstract Publication Number: TH-OR025
  - **Description**: Session will detail Corvidia's latest data on investigational therapy zillivekimab (COR-001) for targeting inflammation and its potential effect on anemia and ESA resistance in chronic kidney disease patients on dialysis.
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• Antiinflammatory therapies
  – Anti-IL 1
  – Anti-IL 6

• Novel iron compounds
**Novel Iron Compounds — Ferric Citrate**

Mixture of ferric citrate coordination complexes (Auryxia®, Fexeric®, Riona®, Nephoxil®)
- Binds phosphate
- Releases iron

Ganz et al., *Drugs* 2019

N=203; eGFR ≤ 20ml/min x 1.73m² single center, open label (!) trial, 2:1 ferric citrate vs usual care (!)

To be interpreted with caution; placebo controlled ph3 trial warranted

Block et al., *JASN* 2019
NOVEL IRON COMPOUNDS – FERRIC MALTOSE

Preparation of ferric pyrophosphate protected by y phospholipid bilayer membrane
- Increased tolerability / compliance in inflammatory bowel disease

Pergola et al., Am J Chron Kid Dis 2019

Longterm extension of 3 placebo controlled phase 3 trials in patients with IBD that showed efficacy and high tolerability

Schmidt et al., Aliment Pharmacol Ther 2016
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  – Hepcidin antibodies and antagonists
  – Ferroportin antibodies

• Antiinflammatory therapies
  – Anti-IL 1
  – Anti-IL 6

• Novel iron compounds
  – Oral iron compounds
  – IV iron compounds

• And last, but not least …. 
EXCITING NEW CLASS OF “ANTI-ANEMIC” DRUGS

- Completely new MOA
  - primarily volume contraction
- Raises hematocrit
  - contributes ~ 50% to
- Improves hard outcomes
- Does not work in patients on dialysis

$\Delta \sim 0.8 \text{ g/dL Hgb}$

Inzucchi et al., Diab Care 2018
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- **Hepcidin antagonists**
  - BMP6 antibodies
  - Ferroportin antibodies

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  - Anti-IL 6

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  - Oral iron compounds
  - IV iron compounds

- **And last, but not least**
  - Sglt 2 inhibitors (in NDD patients)

How does this all matter to the patient?

Diagram showing the role of hepcidin in iron regulation and erythropoiesis.