Tenapanor: Non-systemic inhibition of sodium and phosphorus uptake in the gastrointestinal tract

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Disclosures

- David P. Rosenbaum and Andrew G. Spencer are employees of, and have ownership interest in, Ardelyx.
- Susanne Johansson and Anna Maria Langkilde are employees of, and have ownership interest in, AstraZeneca.
- Tenapanor is an investigational drug
- NHE3 works in concert with the anion channels DRA, AE1 to re-absorb NaCl
- By blocking the reuptake of NaCl in the intestine, RDX5791 shifts a percentage of Na⁺ excretion from the kidneys to the intestine
Properties of Tenapanor

- Inhibitor of NHE3 with minimal systemic exposure: **not a binder**
- Oral agent that reduces Na and P uptake **in the intestine**
- **Potential to treat** cardiorenal disease

Tenapanor dihydrochloride
Today’s Discussion

- Preclinical pharmacology and PK-ADME profile
- Sodium-driven model of CKD in Sprague-Dawley rats
- Phosphorus/vitamin D-driven model of CKD in Sprague-Dawley rats
- Top-level summary of clinical development program
Pharmacological activity of tenapanor

Single dose studies in normal rats

Tenapanor reduces urinary Na⁺ excretion and increases stool Na⁺

*Denotes statistical significance compared to vehicle.
Pharmacological activity of tenapanor

Repeat dosing studies in normal rats

Tenapanor reduces urinary Na⁺ excretion and increases stool Na⁺

Pharmacokinetic, ADME properties of tenapanor

Normal rats radiolabeled study (left) and PK in multiple species (right)

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Species</th>
<th>Diet Description</th>
<th>Co-Dosed Administration</th>
<th>Cmax (ng/mL)</th>
<th>AUC (ng•h/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>Rat</td>
<td>Normal; 0.49% Na-Po gavage</td>
<td>&lt;3</td>
<td>BQL</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Rat</td>
<td>Normal; 0.49% Na-Po gavage</td>
<td>BQL</td>
<td>BQL</td>
<td></td>
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<tr>
<td>1</td>
<td>Rat</td>
<td>Normal; 0.49% Na-Po gavage</td>
<td>BQL</td>
<td>BQL</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5/6th NPX Rat</td>
<td>High salt; 4.0% NaCl-Po gavage</td>
<td>&lt;1</td>
<td>BQL</td>
<td></td>
</tr>
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<td>5/6th NPX Rat</td>
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<td></td>
</tr>
<tr>
<td>1</td>
<td>Dog</td>
<td>Normal; 0.49% Na-Po gavage</td>
<td>&lt;1</td>
<td>BQL</td>
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</tr>
<tr>
<td>3 mg qd</td>
<td>Human (HV)</td>
<td>1200 mg Na+-PO capsule</td>
<td>&lt;1</td>
<td>BQL</td>
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<td>150 mg qd</td>
<td>Human (HV)</td>
<td>1500 mg Na+-PO capsule</td>
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<tr>
<td>450 mg qd</td>
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<td>Human (HV)</td>
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<td>BQL</td>
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<td></td>
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</tbody>
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BQL = below quantitative limit

Tenapanor exhibits minimal systemic availability

## Disease Model: Salt driven hypertension, nephrectomy

Nephrectomized rats, prophylactic and treatment design

<table>
<thead>
<tr>
<th>Week -3</th>
<th>Week -2</th>
<th>Week -1</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal chow</td>
<td>Normal chow</td>
<td>High Salt Chow - 4% NaCl</td>
<td>Vehicle</td>
<td>Vehicle</td>
<td>3 mpk RDX5791</td>
<td>0.3 mpk RDX5791</td>
</tr>
</tbody>
</table>

UNX Sub-total NX
Preclinical activities of tenapanor

Nephrectomized rats

Tenapanor reduces extracellular fluid volume and SBP

Preclinical activities of tenapanor

Nephrectomized rats

Tenapanor reduces albuminuria and left ventricular hypertrophy

# Disease Model: Salt driven hypertension, nephrectomy

Nephrectomized rats, combination with ACE inhibitor design

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<tr>
<th>Week -3</th>
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<tr>
<td>UNX</td>
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</tr>
<tr>
<td>Vehicle</td>
<td>Vehicle</td>
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</tr>
<tr>
<td>10 mg/kg Enalapril</td>
<td>10 mg/kg Enalapril + 1.0 mg/kg RDX5791</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1.0 mg/kg RDX5791</td>
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<td></td>
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</tr>
</tbody>
</table>
Preclinical activities of tenapanor

Nephrectomized rats

Tenapanor and ACE inhibition normalize pulse wave velocity

Tenapanor: Reduces sodium absorption

Healthy human volunteers

Tenapanor diverts 20-50 mEq Na⁺/day, up to ~3g/day of salt
Summary: Pharmacology and Na\(^+\)-CKD model

- Rodent \(^{14}\text{C} \) ADME study proved minimally systemic
- Minimal systemic availability confirmed in humans

- Reduces urinary sodium excretion
- Increases stool sodium

- Reduces expanding ECFV, LVH, albuminuria, BP
- Improves PWV in combination with an ACE inhibitor

- Increases stool Na\(^+\) by 20-50 mEq/day
- Pharmacological effect: dose & regimen dependent
Tenapanor decreases urinary Na and P in normal rats

- Male Sprague-Dawley rats \((n=6)\) were orally administered vehicle (water) or tenapanor at the indicated doses by oral gavage just before the dark phase and then placed in metabolic cages for urine collection over a 16 h period.

**Labonte et al. JASN 26 (2015)**
Vascular calcification model (Lopez, 2006)

Labonte et al. JASN 26 (2015)
Tenapanor improves uremic markers in rat CKD model

- Vascular calcification model (Lopez et al., JASN 17:795 [2006]) induced by
  - 5/6\textsuperscript{th} nephrectomy
  - 0.9\% inorganic P – 0.6\% Ca diet
  - Calcitriol injection thrice a week

- At day 27 (48 hours after the last calcitriol injection), blood was collected for plasma from the remaining rats on study and measured for P, Ca, FGF-23, creatinine, BUN, and albumin.

- Dose of tenapanor: 5 mg/kg/day

\textit{Labonte et al. JASN 26 (2015)}
Tenapanor reduces vascular calcification in CKD rats

P and Ca content were assessed in the aortic arch (A) and the stomach (B) collected from NPX rats after 28 days of calcitriol treatment.

Labonte et al. JASN 26 (2015)
Summary: Phosphate effects in Sprague-Dawley rats

Reduced P absorption
- Reduces urinary phosphate in SD rats

Ectopic Calcification
- Reduces aortic & gastric calcification in rat CKD model

Uremic Markers
- Serum P, creatinine, FGF-23 improved in SD rats
Tenapanor: Reduces phosphorus absorption

**Stool phosphorus**
- **Day -1 (n = 16)**: 14.9 mmol/day
- **Tenapanor 15 mg b.i.d. (n = 18)**: 30 mmol/day

**Urinary phosphorus**
- **Day -1 (n = 18)**: 12.0 mmol/day
- **Tenapanor 15 mg b.i.d. (n = 18)**: 20 mmol/day

*Figure 2. From Rosenbaum, et al., (2014) Tenapanor increases stool P in healthy human volunteers at 15 mg day b.i.d. Tenapanor was dosed at 15 mg b.i.d. Daily 24-hour stool and urine samples were collected. Data represent the mean results for pre-dose samples (Day -1) and the four (4) days of dosing (Tenapanor). Error bars represent one standard deviation.*
Clinical Trials

Three indications being evaluated

• Chronic Kidney Disease with Diabetic Nephropathy
  – Includes CKD-3 patients with SBP >130 mmHg
  – Primary endpoint: urinary albumin:creatinine ratio (UACR)
  – Secondary endpoint: change in systolic blood pressure (among others)
  – Clinicaltrials.gov identifier: NCT01847092

• End stage renal disease (ESRD) with hyperphosphatemia
  – Primary endpoint met: mean reduction in serum phosphorus
  – Clinicaltrials.gov identifier: NCT02081534

• Irritable bowel syndrome with constipation (IBS-C)
  – Primary endpoint met: % complete spontaneous bowel movement responders v. placebo
  – Clinicaltrials.gov identifier: NCT01923428
Tenapanor Generally Well-Tolerated

- >1,000 individuals exposed to drug
- Single dose up to 900 mg
- 3 months up to 100 mg/day
- Non-systemic: >99% of all tested serum samples had no detectable levels of tenapanor (>3,500 samples)
- Most AE’s due to exaggerated pharmacology of drug (e.g. loose stools/diarrhea)
Summary: Observations with tenapanor

- **Minimal systemic availability**
  - Minimal systemic availability confirmed in humans

- **Reduces sodium absorption**
  - Reduces urinary sodium excretion
  - Increases stool sodium

- **Active in disease models**
  - Na: Reduces ECFV, LVH, albuminuria, blood pressure
  - P: Reduces calcification, FGF-23, serum P, creatinine

- **Clinical Studies**
  - Renal: CKD with diabetic nephropathy/proteinuria
  - Renal: Hyperphosphatemia in CKD-5D/ESRD
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