Tenapanor, a gastrointestinal NHE3 inhibitor, reduces serum phosphate in patients with chronic kidney disease stage 5D and hyperphosphatemia

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Disclosures

- Geoffrey Block
  - Employment: Denver Nephrology
  - Consultancy agreements: Amgen, Ardelyx, AstraZeneca, Atara Biotherapeutics, Celgene, FMC Technologies, Keryx Biopharmaceuticals, Merck, Outset Medical, Shield Therapeutics
  - Ownership interest: Ardelyx, Atara Biotherapeutics, Nephroceuticals
  - Research funding: Amgen, Ardelyx, AstraZeneca, Keryx Biopharmaceuticals, La Jolla Pharmaceutical Company
  - Honoraria: Amgen, AstraZeneca, Celgene, Keryx Biopharmaceuticals, Merck, Mitsubishi, Outset Medical, Sanofi
  - Scientific advisor or membership: Amgen
  - Other: Medical Director with DaVita

- David Rosenbaum
  - Employment and ownership interest: Ardelyx

- Susanne Johansson
  - Employment and ownership interest: AstraZeneca

- Maria Leonsson-Zachrisson, Magnus Åstrand, Mikael Knutsson and Anna Maria Langkilde
  - Employment: AstraZeneca

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Tenapanor acts locally to reduce sodium absorption from the gut

- Tenapanor (RDX5791, AZD1722), a small molecule with minimal systemic availability, is a specific inhibitor of the sodium/hydrogen exchanger isoform 3 (NHE3)
- Intestinal NHE3 plays an important role in sodium/fluid homeostasis
- Studies in healthy volunteers show that tenapanor reduces absorption of dietary sodium over 7 days, with concomitant reductions in urinary sodium excretion

Data in the chart are mean + standard error (tenapanor administered as HCl tablet); HCl, hydrochloride; q.d., once daily.
Tenapanor reduces phosphate absorption from the gut

- Phase 1 studies show that tenapanor increases stool phosphorus levels over 4 days, with concomitant reductions in urinary phosphorus levels.\(^1\)
- Preclinical data show tenapanor reduces serum phosphorus levels and protects against vascular calcification.\(^2\)

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\(^{a}\)Tenapanor formulation study (D5611C00002): includes mean of day −1, with data for tenapanor (15 mg b.i.d. HCl tablet) as mean + standard deviation of treatment days 1–4.

\(^{b}\)Republished with permission of American Society of Nephrology from Labonté ED et al.\(^2\) with permission conveyed through Copyright Clearance Center, Inc.; data are presented as mean + standard error; ***p ≤ 0.001 (tenapanor vs vehicle).

A phase 2, double-blind, multicenter, dose-finding study on the effect of tenapanor on serum phosphate levels

- Patients with CKD stage 5D who are undergoing hemodialysis and have hyperphosphatemia (baseline serum phosphate level 6.0–<10.0 mg/dL and ≥ 1.5 mg/dL increase from pre-washout levels; NCT02081534)

- Blood samples were collected weekly

**Randomization**

**Screening**

N = 597

**Washout**

Cessation of existing phosphate binders

1 week

1–3 weeks

4 weeks

**Follow-up**

Resumption of pre-study phosphate binders

2 weeks

- Tenapanor 1 mg b.i.d. (n = 23)
- Tenapanor 3 mg b.i.d. (n = 21)
- Tenapanor 10 mg b.i.d. (n = 23)
- Tenapanor 30 mg b.i.d. (n = 26)
- Tenapanor 3 mg q.d. (n = 22)
- Tenapanor 30 mg q.d. (n = 21)
- Placebo (n = 26)

**Week 4 endpoints**

- Change in serum phosphate level (primary)
- Serum phosphate dose–response analysis
- Serum PTH levels
- Plasma FGF-23 levels (exploratory)

b.i.d., twice daily; FGF, fibroblast growth factor; PTH, parathyroid hormone; q.d., once daily.
Patient demographics and baseline characteristics were balanced across groups

<table>
<thead>
<tr>
<th></th>
<th>Tenapanor</th>
<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>1 mg b.i.d. (n = 23)</td>
<td>3 mg b.i.d. (n = 21)</td>
</tr>
<tr>
<td>Age, years</td>
<td>57.9 ± 14.8</td>
<td>61.5 ± 11.2</td>
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<tr>
<td>Body weight, kg</td>
<td>85.9 ± 22.7</td>
<td>84.3 ± 19.2</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>16 (70)</td>
<td>15 (71)</td>
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<tr>
<td>Race, n (%)</td>
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<tr>
<td>White</td>
<td>17 (74)</td>
<td>12 (57)</td>
</tr>
<tr>
<td>African–American</td>
<td>2 (9)</td>
<td>8 (38)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (4)</td>
<td>0</td>
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<tr>
<td>Patient disposition</td>
<td></td>
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<tr>
<td>Completed study, n (%)</td>
<td>18 (78)</td>
<td>13 (62)</td>
</tr>
</tbody>
</table>

Unless otherwise stated, data are mean ± standard deviation. b.i.d., twice daily; q.d., once daily.
Tenapanor reduced serum phosphate levels from baseline at 4 weeks

A dose–response relationship was evident

- b.i.d. dosing showed improved efficacy over q.d. dosing

In the figure, data are shown at EOT/ET, and are shown as LS mean with error bars depicting the lower limit of 95% confidence intervals. 

*mean ± standard deviation of last washout value; bLS mean (95% confidence interval).

ANCOVA, analysis of covariance; b.i.d., twice daily; ET, early termination; EOT, end of treatment; LS, least-squares; q.d., once daily.
Tenapanor reduced serum FGF-23 levels from baseline at 4 weeks

- Mean changes in serum parathyroid hormone levels from baseline did not differ significantly between treatment groups (ANCOVA: \( p = 0.305 \))

- No clinically significant changes in serum electrolytes
  - Serum calcium, potassium, sodium and bicarbonate

In the figure, data are shown at EOT/ET, and are shown as geometric LS mean (%) with numbers in brackets indicating the 95% confidence interval. \( a \)Numbers in brackets indicate the range.

ANCOVA, analysis of covariance; b.i.d., twice daily; ET, early termination; EOT, end of treatment; FGF-23, fibroblast growth factor 23; q.d., once daily.
Diarrhea was the most common treatment-related AE reported with tenapanor treatment

<table>
<thead>
<tr>
<th></th>
<th>Tenapanor</th>
<th>Placebo</th>
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<tbody>
<tr>
<td></td>
<td>1 mg b.i.d. (n = 23)</td>
<td>3 mg b.i.d. (n = 21)</td>
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<tr>
<td>Any AE</td>
<td>10 (43)</td>
<td>12 (57)</td>
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<tr>
<td>Deaths</td>
<td>1 (4)</td>
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<tr>
<td>Serious AEs</td>
<td>2 (9)</td>
<td>2 (10)</td>
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<tr>
<td>Treatment-related AEs(a)</td>
<td>7 (30)</td>
<td>7 (33)</td>
</tr>
<tr>
<td>Diarrhea(c)</td>
<td>6 (26)</td>
<td>6 (29)</td>
</tr>
<tr>
<td>Hyperphosphatemia</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>AEs leading to discontinuation of study drug(d)</td>
<td>3 (13)</td>
<td>3 (14)</td>
</tr>
<tr>
<td>Diarrhea(c)</td>
<td>2 (9)</td>
<td>3 (14)</td>
</tr>
<tr>
<td>Hyperphosphatemia</td>
<td>1 (4)</td>
<td>0</td>
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</tbody>
</table>

- Other than diarrhea, the incidence of investigator-judged treatment-related AEs was low and balanced between groups
  - No treatment-related AEs were considered serious
- One reported death was not judged treatment-related

Data are number of patients (%); unless otherwise stated, data are shown for any AE irrespective of relationship to study drug.
\(^a\)Includes 1 patient with fatal serious AE (cardiac failure); \(^b\)as judged by investigator and shown for \(\geq 2\) patients in any treatment group; \(^c\)including fecal incontinence; \(^d\)data shown for \(\geq 2\) patients who experienced an AE leading to discontinuation in any treatment group. AE, adverse event; b.i.d., twice daily; q.d., once daily.
## Occurrence of AEs

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<td>3 mg b.i.d. (n = 21)</td>
<td>10 mg b.i.d. (n = 23)</td>
<td>30 mg b.i.d. (n = 25)</td>
<td>3 mg q.d. (n = 22)</td>
<td>30 mg q.d. (n = 21)</td>
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<td>1 (5)</td>
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<td>0</td>
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<td>2 (8)</td>
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<td>GI disorders</td>
<td>7 (30)</td>
<td>9 (43)</td>
<td>15 (65)</td>
<td>19 (76)</td>
<td>5 (23)</td>
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<td>5 (19)</td>
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<tr>
<td>Diarrhea&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6 (26)</td>
<td>7 (33)</td>
<td>13 (57)</td>
<td>17 (68)</td>
<td>4 (18)</td>
<td>11 (52)</td>
<td>3 (12)</td>
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<td>1 (4)</td>
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<td>1 (4)</td>
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<td>1 (4)</td>
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<tr>
<td>Injury, poisoning and procedural complications</td>
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<td>2 (10)</td>
<td>1 (4)</td>
<td>2 (8)</td>
<td>1 (5)</td>
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<td>Metabolism and nutrition disorders</td>
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<td>1 (5)</td>
<td>2 (9)</td>
<td>1 (4)</td>
<td>1 (5)</td>
<td>1 (5)</td>
<td>2 (8)</td>
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<tr>
<td>Nervous system disorders</td>
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<td>1 (4)</td>
<td>2 (8)</td>
<td>2 (9)</td>
<td>3 (14)</td>
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<td>Respiratory, thoracic, and mediastinal disorders</td>
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<td>0</td>
<td>1 (4)</td>
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<td>2 (10)</td>
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<td>1 (4)</td>
<td>0</td>
<td>1 (5)</td>
<td>2 (8)</td>
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</table>

Data are number of patients (%); data shown for system organ class (and preferred terms for GI disorders) in which ≥ 2 patients experienced an AE across all treatment groups, irrespective of relationship of the AE to the study drug.

<sup>a</sup>Including 3 patients reporting fecal incontinence (tenapanor 3 mg b.i.d. [n = 1]; tenapanor 10 mg b.i.d. [n = 2]).

AE, adverse event; b.i.d., twice daily; GI, gastrointestinal; q.d., once daily.
Conclusions

- Tenapanor, a novel NHE3 inhibitor, taken twice daily, provided dose-dependent, clinically significant reductions in serum phosphate levels in patients with CKD stage 5D (hemodialysis) and hyperphosphatemia
  - Tenapanor showed comparable efficacy with phosphate binders\(^1\)

- Diarrhea was the most common adverse event
  - Expected due to its pharmacodynamic effect on stool sodium
  - The highest doses of tenapanor were associated with the highest rates of diarrhea
  - Rarely resulted in withdrawal from trial

- Tenapanor may offer a new treatment mechanism to reduce serum phosphate levels in patients with CKD, with the added benefit of reducing sodium/fluid absorption

Data in chart are LS mean – standard error; tenapanor (10 mg b.i.d.) data are from this study; phosphate binder data are from patients with hyperphosphatemia undergoing hemodialysis treated with lanthanum carbonate (1 g t.i.d.) or sevelamer hydrochloride (t.i.d. \([2 \times 2.4 \text{ g}] + [1 \times 1.6 \text{ g}]\)) in a two-way crossover trial.\(^1\)

b.i.d., twice daily; LS, least-squares; t.i.d., three times daily.

Tenapanor has the potential to reduce the pill burden on patients with hyperphosphatemia

**Calcium acetate**
- Common dose, 1–2 g with each meal

**Sevelamer carbonate**
- Common dose, 2–2.5 g with each meal

**Lanthanum carbonate**
- Common dose, 0.5–1.0 g with each meal

**Tenapanor hydrochloride**
- Milligram quantities, twice daily in one small tablet

Different medication images are not on a consistent scale.
A phase 2b, double-blind, randomized-withdrawal, dose regimen study of tenapanor

- Patients with CKD stage 5D who are undergoing hemodialysis and have hyperphosphatemia
- Study initiation in last quarter of 2015

**Randomization**

- Screening
  - Washout: Cessation of existing phosphate binders
    - 1–3 weeks
  - Tenapanor 3 mg b.i.d.
  - Tenapanor 10 mg b.i.d.
  - Tenapanor down-titration scheme: 30, 20, 15, 10, 3 mg b.i.d.

**Primary endpoint**

Target: \( n = 50 \)/group

- Change in serum phosphate

**Secondary endpoint**

- Placebo
- Tenapanor (same dose)

**Randomized withdrawal**

- 8 weeks
- 4 weeks

b.i.d., twice daily; EOT, end of treatment; q.d., once daily.
Acknowledgments

● The investigators acknowledge and thank the study participants, the study centers and the clinical teams

● Medical writing support was provided by Laura Schmidt (MPhil, MRes) and Steven Inglis (PhD) of Oxford PharmaGenesis, Oxford, UK, and was funded by Ardelyx Inc., Fremont, USA