Tenapanor, a minimally absorbed NHE3 inhibitor, reduces dietary phosphorus absorption in healthy volunteers

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Disclosures

- David Rosenbaum, Andrew G Spencer, Jeffrey Jacobs and Dominique Charmot are employees of, and have ownership interest in, Ardelyx

- Susanne Johansson and Björn Carlsson are employees of, and have ownership interest in, AstraZeneca. Bergur Stefansson and Mikael Knutsson are employees of AstraZeneca

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Tenapanor reduces sodium and phosphorus absorption

- Tenapanor (AZD1722) is a first-in-class small-molecule inhibitor of the Na⁺/H⁺ exchanger isoform 3 (NHE3)
- Two healthy volunteer studies¹ show that tenapanor reduces absorption of dietary sodium over 7 days²
- Preclinical data show that tenapanor reduces phosphorus absorption and protects against vascular calcification³

q.d., once daily
Studies of tenapanor in healthy volunteers

- Phosphorus excretion measured daily
- Participants received a diet standardized for sodium content
  - In each study, all cohorts received the same meals on the same study days

Multiple ascending-dose study\(^1\)
- Once-daily tenapanor HCl 3, 10, 30 or 100 mg or placebo for 7 days

Dose-regimen study\(^2\)
- Tenapanor HCl 30 mg once daily, 15, 30 or 60 mg twice daily, 30 mg three times daily or placebo for 7 days

Formulation study\(^3\)
- Twice-daily tenapanor HCl 15 mg for 4 days

Food-effect study\(^4\)
- Twice-daily tenapanor HCl 15 mg for 4 days
Tenapanor was generally well tolerated and minimally absorbed

• No serious adverse events
• No clinically significant changes in other\(^a\) serum or urinary electrolytes
  – Serum sodium, potassium, calcium or creatinine
  – Urinary potassium or creatinine
• No significant changes in other clinical laboratory measurements, vital signs, electrocardiographic parameters or physical examinations
• Minimal to no systemic availability of tenapanor
  – Plasma concentrations of tenapanor were below the lower limit of quantification (0.5 ng/mL) in > 99% of all measured samples (1072 samples across four studies)
  – No individual had more than one measurable tenapanor plasma concentration: the highest measured concentration was 0.792 ng/mL

\(^a\)Other than pharmacodynamic variables: urinary sodium and phosphorus
Learning from phosphate binders

- Healthy volunteer studies of sevelamer hydrochloride provide a useful benchmark for developing new treatments for patients with hyperphosphatemia

**Stool phosphorus**

- 7.5 mmol/day increase (only observed at 5 g t.i.d.)

**Urinary phosphorus**

- 3.4–10.6 mmol/day decrease

Data are shown as means. Error bars show one standard deviation. Treatment period was 4 days. t.i.d, three-times daily

Adapted from Burke SK et al. Nephrol Dial Transplant 1997;12:1640-4
Tenapanor increased stool phosphorus over 7 days

- Stool phosphorus increases of 4.3–7.1 mmol/day vs placebo (mean across all tenapanor q.d. doses: 5.9 mmol/day)
  - cf. increase of 7.5 mmol/day with 5 g sevelamer t.i.d.

Data are daily means over 7 days’ treatment. Error bars show one standard deviation
Study RDX5791-101
Tenapanor increased stool phosphorus over 7 days (continued)

- Stool phosphorus increases of 6.0–12.5 mmol/day vs placebo (mean across all tenapanor dose regimens: 9.8 mmol/day)
  - cf. increase of 7.5 mmol/day with 5 g sevelamer t.i.d.

Data are daily means over 7 days’ treatment. Error bars show one standard deviation. b.i.d., twice daily Study RDX5791-102
Increases in stool phosphorus were consistent with decreases in urinary phosphorus.

**Formulation study**

- **Stool phosphorus**
  - Day −1 (n = 16)
  - Tenapanor 15 mg b.i.d. (n = 18)
  - Error bars show one standard deviation. Data for tenapanor are means of treatment days 1–4.

**Food-effect study**

- **Stool phosphorus**
  - Run-in (n = 18)
  - Tenapanor 15 mg b.i.d. (n = 18)
  - Error bars show one standard deviation. Data for tenapanor are means of treatment days 1–4.

Error bars show one standard deviation. Data for tenapanor are means of treatment days 1–4.

Formulation study (D5611C00002) includes mean of day −1. Data are for tenapanor 15 mg b.i.d. HCl tablet treatment group.

Food-effect study (D5611C00003): run-in comprised mean of days −2 and −1. Data are tenapanor 15 mg b.i.d. preprandial treatment group.
Conclusions

- Tenapanor, a small-molecule inhibitor of NHE3, was generally well tolerated and minimally absorbed in healthy volunteers
- Tenapanor reduced absorption of dietary phosphorus
  - Increases in stool phosphorus
  - Concomitant decreases in urinary phosphorus
- Increases in stool phosphorus were similar to published data for sevelamer hydrochloride in healthy volunteers

- Tenapanor may provide a new mechanism for the treatment of hyperphosphatemia in patients with chronic kidney disease, with the potential to:
  - Improve phosphate control
  - Reduce pill burden (i.e. mg vs g doses)
  - Reduce sodium overload

Tenapanor is under investigation for treating hyperphosphatemia in a phase 2 study

- Patients with chronic kidney disease on maintenance hemodialysis (NCT02081534)
- Data anticipated in first half of 2015

**Expected number of patients: 150**

**Screening**

**Washout**

*Cessation of existing phosphate binders*

1 week

1–3 weeks

**Randomization**

Tenapanor 30 mg q.d.

Tenapanor 3 mg q.d.

Tenapanor 10 mg b.i.d.

Tenapanor 30 mg b.i.d.

Tenapanor 1 mg b.i.d.

Placebo

4 weeks

**Primary endpoint**

Change in serum phosphorus

**Follow-up**

2 weeks
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