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

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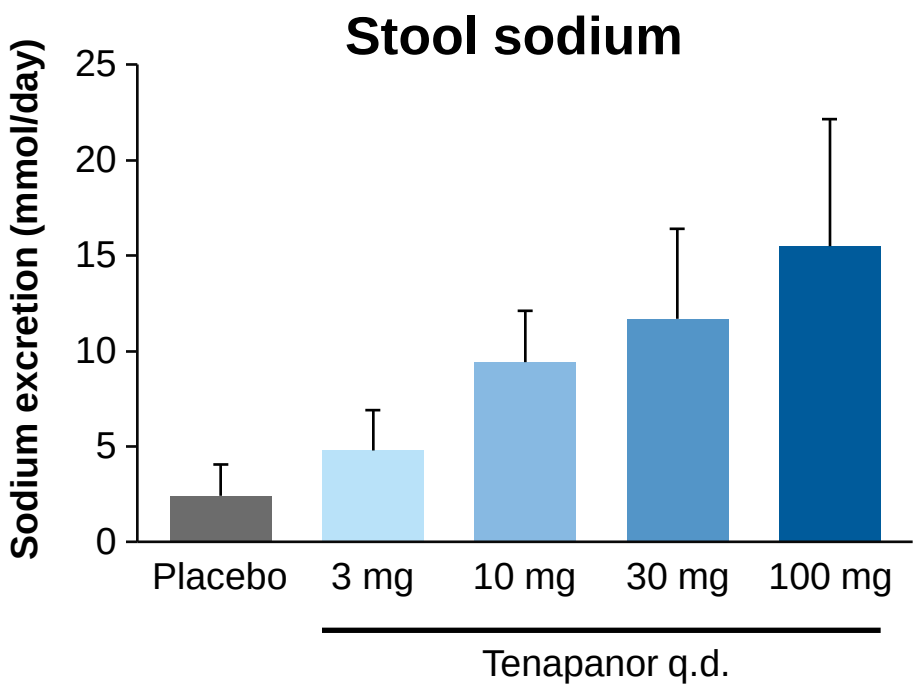
Disclosures

- 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
- These studies were funded by AstraZeneca and Ardelyx

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 studies[1] show that tenapanor reduces absorption of dietary sodium over 7 days[2]



- Preclinical data show that tenapanor reduces phosphorus absorption and protects against vascular calcification[3]

q.d., once daily

1. Study codes: RDX5791-101 and RDX5791-102; 2. Spencer AG *et al. Sci Transl Med* 2014;6:227ra36; 3. Charmot D *et al.* Oral presentation, American Society of Nephrology Kidney Week (abstract 425), 2014

Studies of tenapanor in healthy volunteers

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

- 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

Study numbers: 1. RDX5791-101; 2. RDX5791-102; 3. D5611C00002; 4. D5611C00003

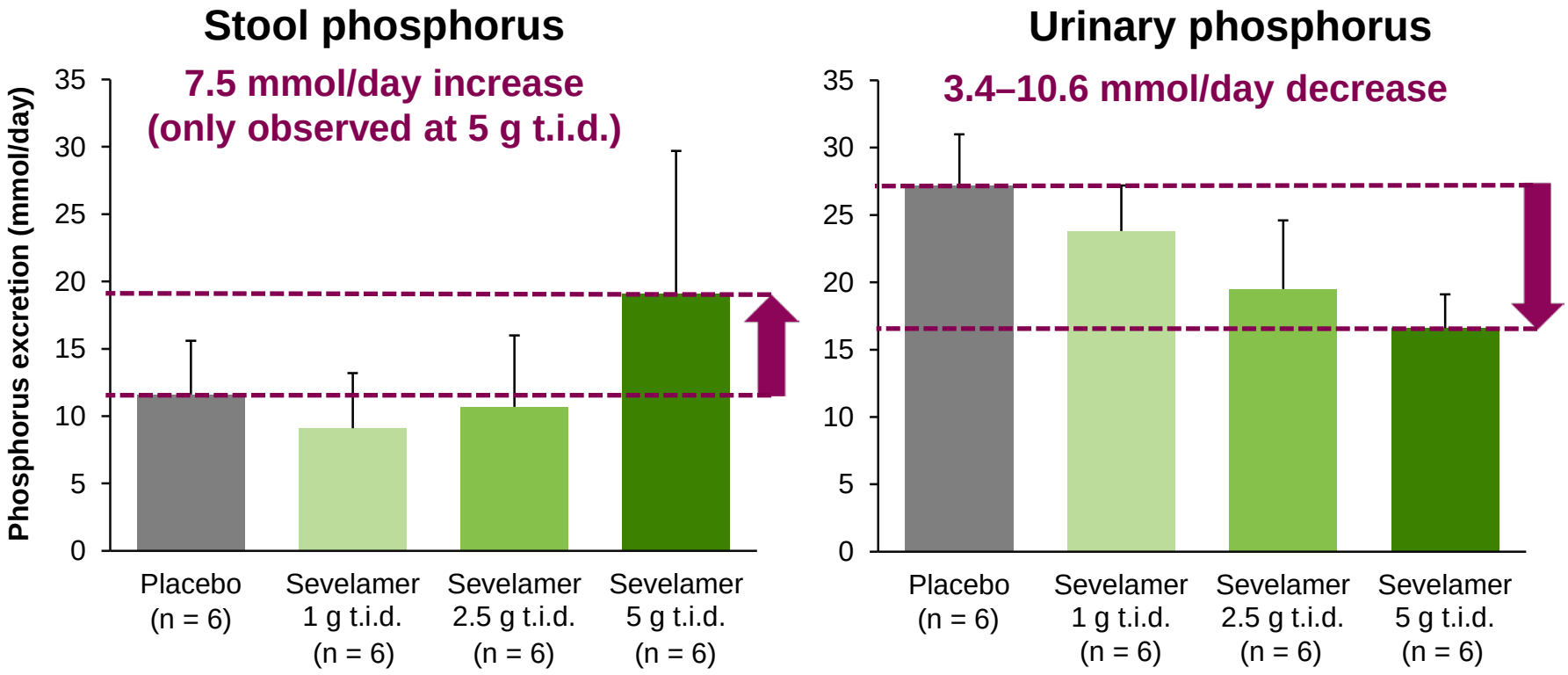
Tenapanor was generally well tolerated and minimally absorbed

- 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

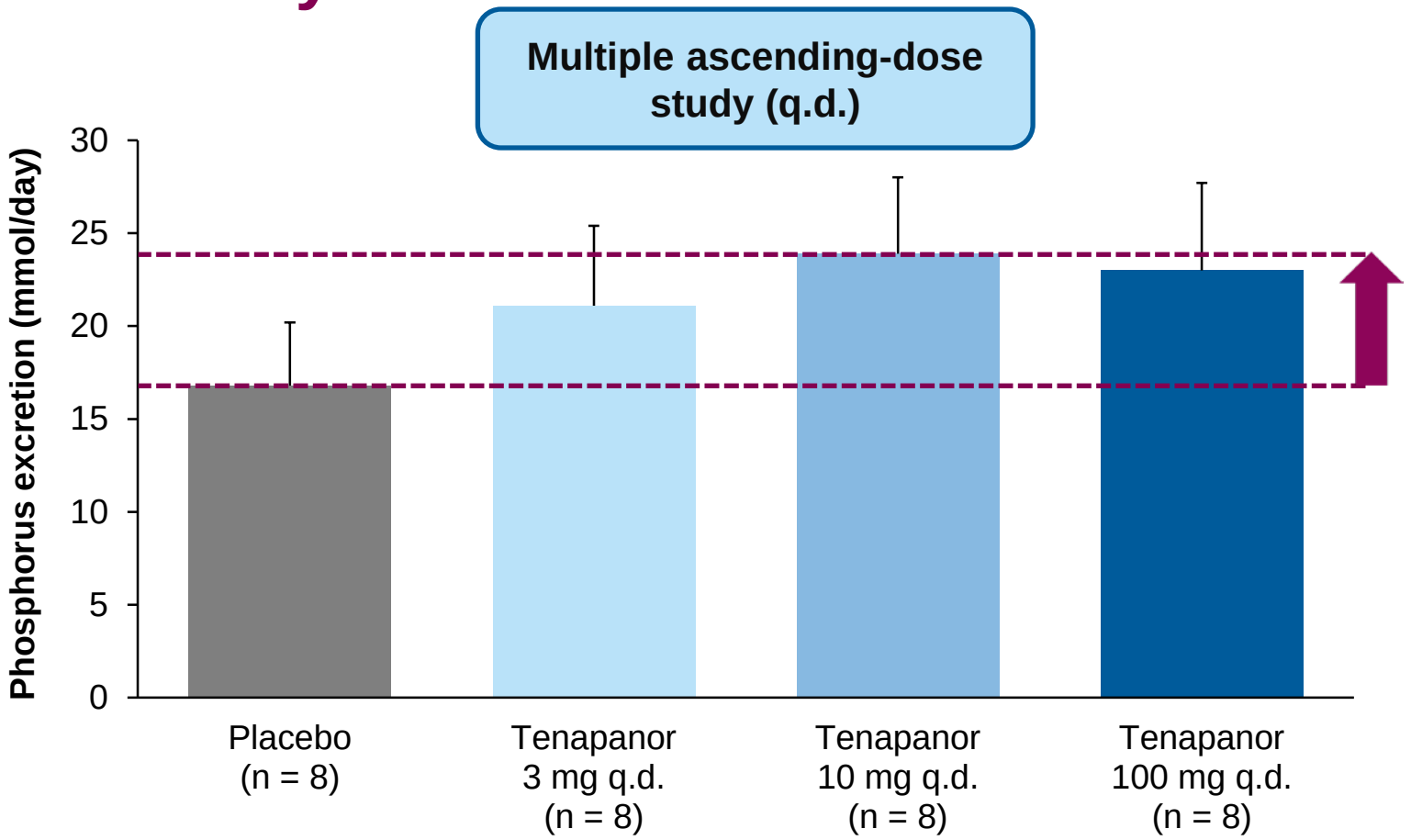
Learning from phosphate binders

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



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

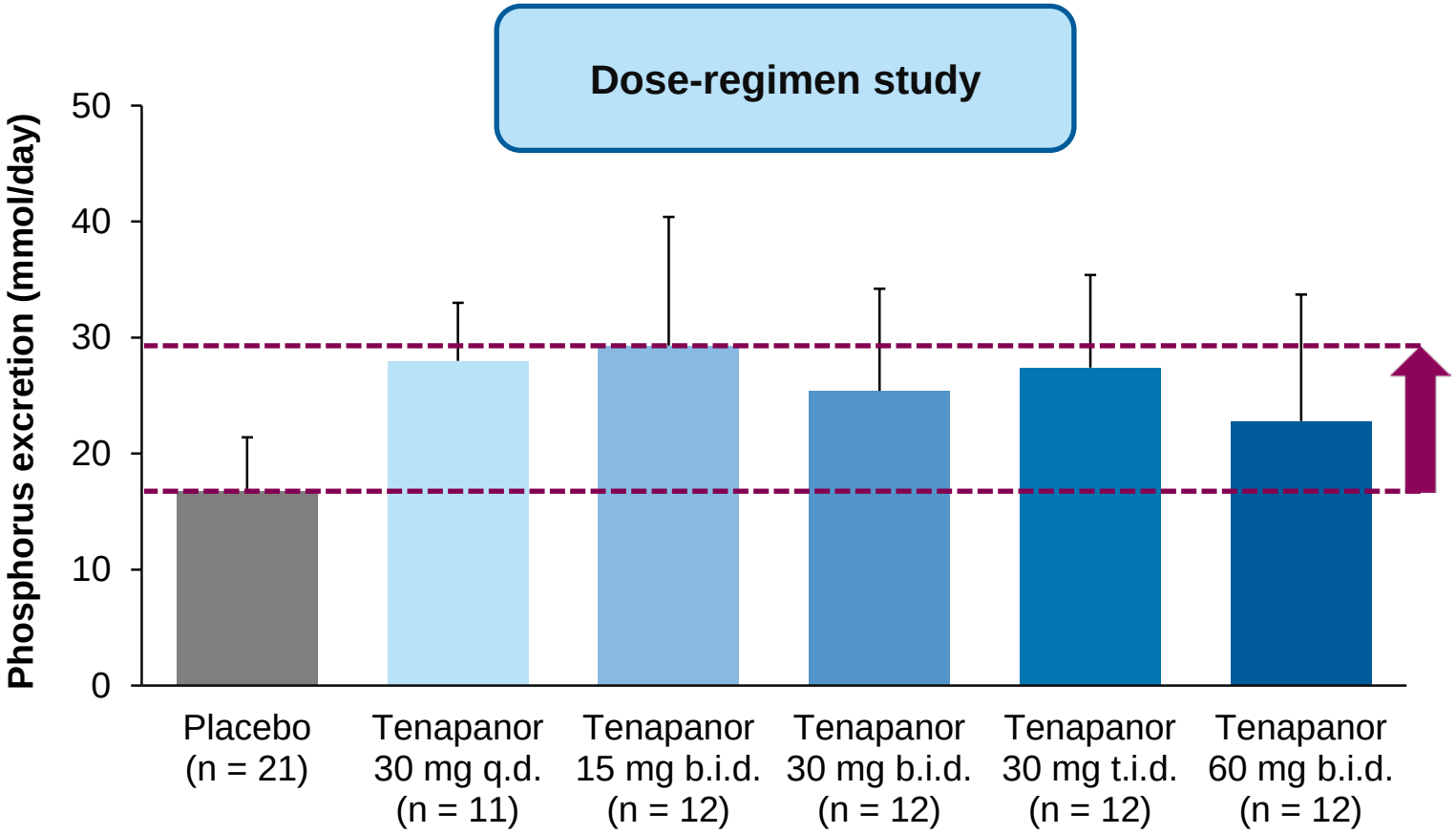
Tenapanor increased stool phosphorus over 7 days



- 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)

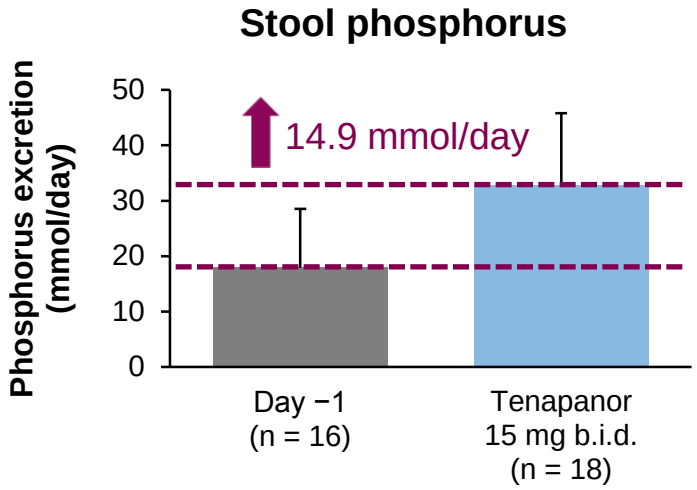


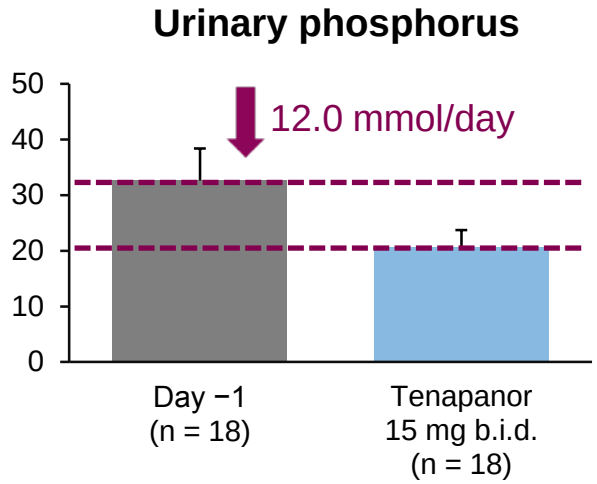
- Stool phosphorus increases of 6.0–12.5 mmol/day vs placebo (mean across all tenapanor dose regimens: 9.8 mmol/day)
  - cf. increase of 7.5 mmol/day with 5 g sevelamer t.i.d.

Data are daily means over 7 days' treatment. Error bars show one standard deviation. b.i.d., twice daily
Study RDX5791-102

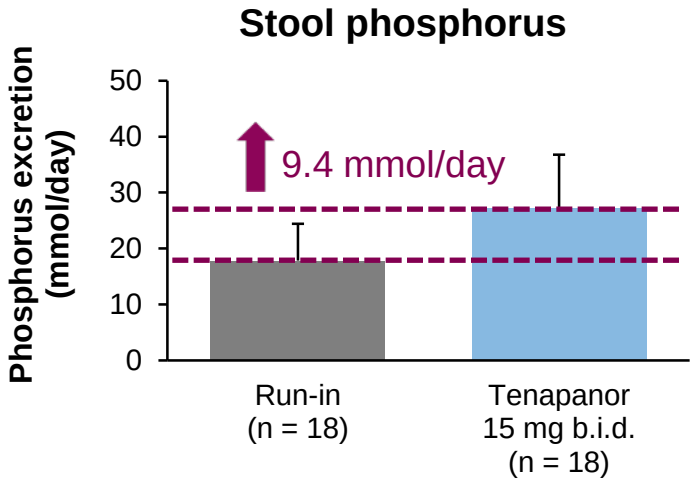
Increases in stool phosphorus were consistent with decreases in urinary phosphorus

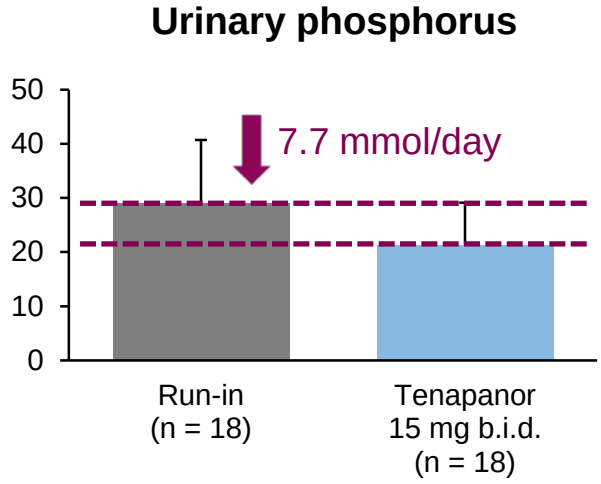
Formulation study





Food-effect study





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

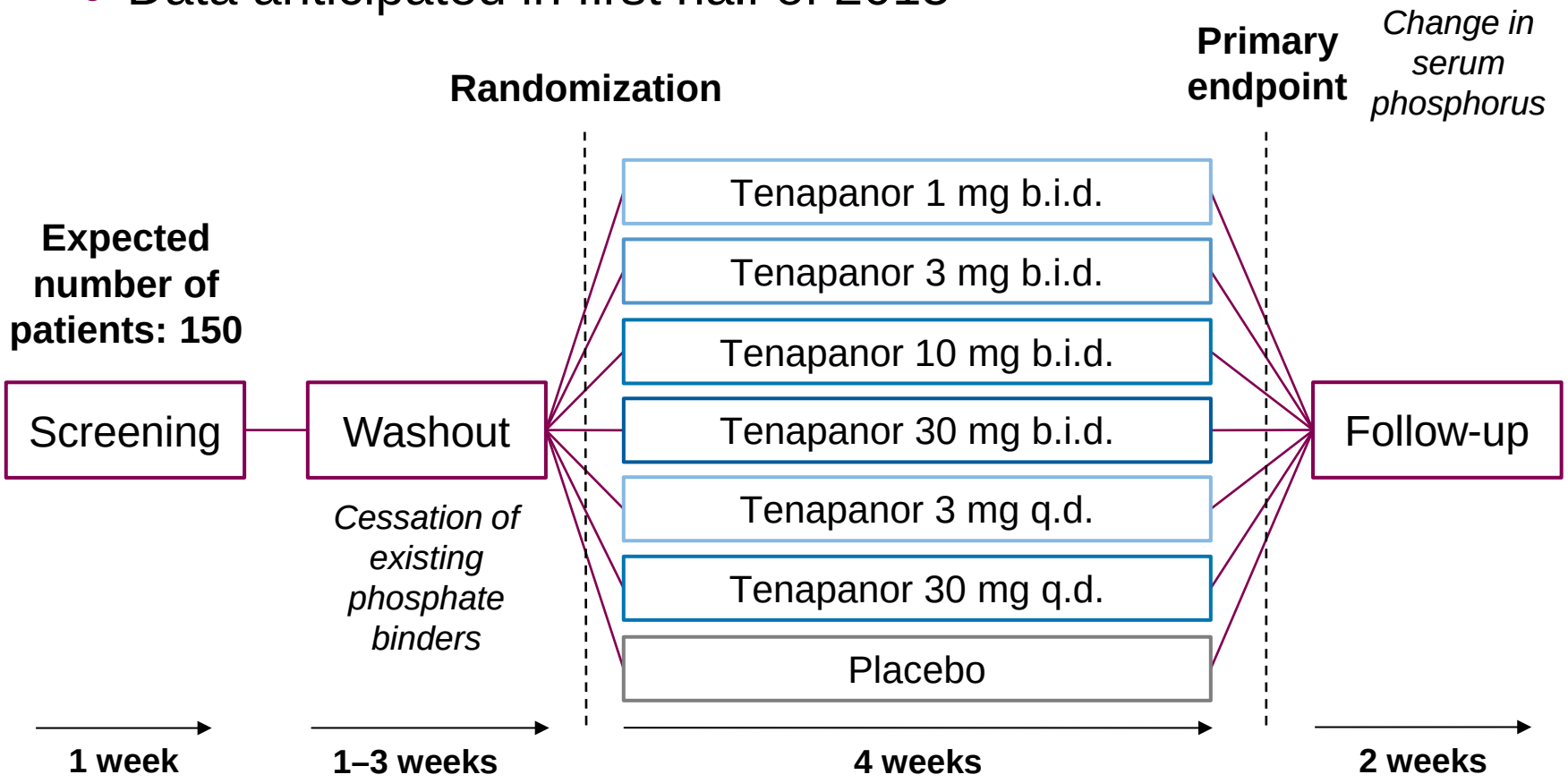
Conclusions

- 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[1]
- 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

1. Burke SK *et al. Nephrol Dial Transplant* 1997;12:1640–4

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



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