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

Geoffrey A Block,[1] David P Rosenbaum,[2] Maria Leonsson-Zachrisson,[3] Magnus Åstrand,[3] Susanne Johansson,[3] Mikael Knutsson,[3] Anna Maria Langkilde[3]

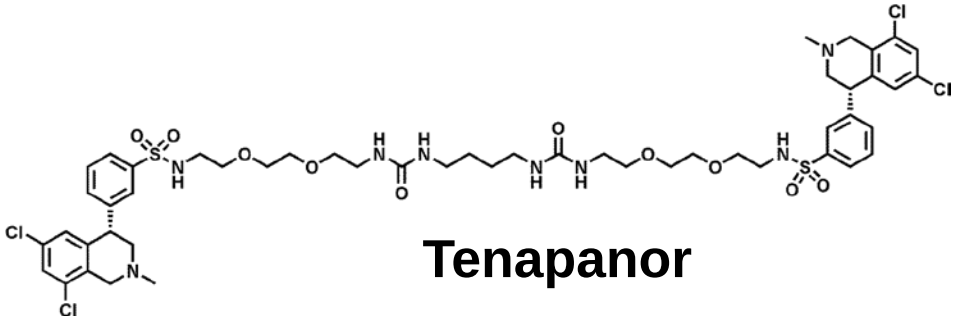
[1]Denver Nephrology, Denver, CO, USA; [2]Ardelyx Inc., Fremont, CA, USA; [3]AstraZeneca Gothenburg, Mölndal, Sweden

Disclosures

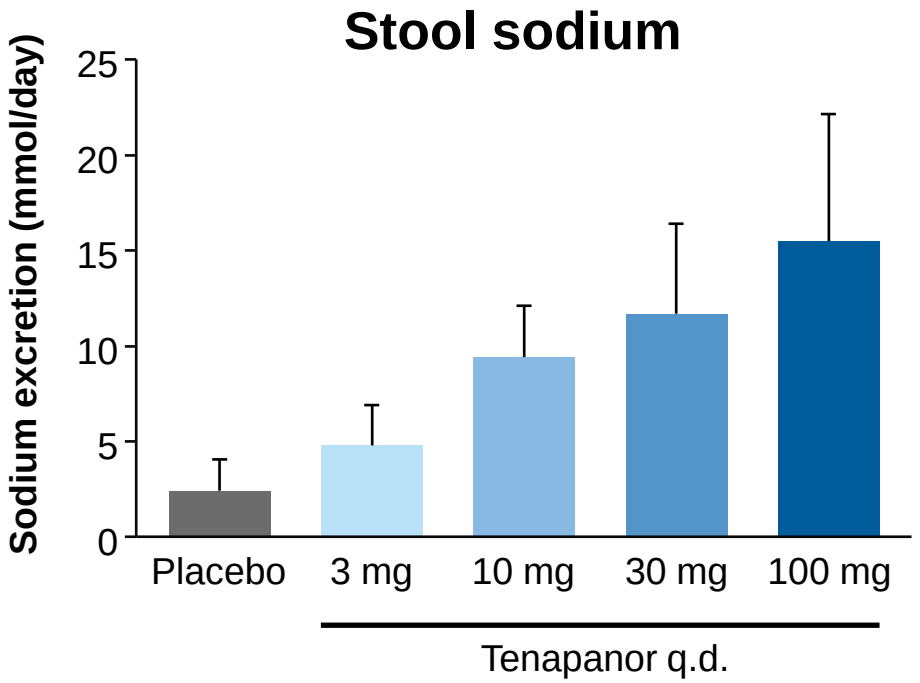
- Geoffrey Block
  - Employment: Denver Nephrology
  - Consultancy agreements: Amgen, Ardelyx, AstraZeneca, Atara Biotherapeutics, Celgene, FMC Technologies, Keryx Biopharmaceuticals, Merck, Outset Medical, Shield Therapeutics
  - Ownership interest: Ardelyx, Atara Biotherapeutics, Nephroceuticals
  - 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
- This study was funded by AstraZeneca

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,[1,2] with concomitant reductions in urinary sodium excretion[2]



Tenapanor

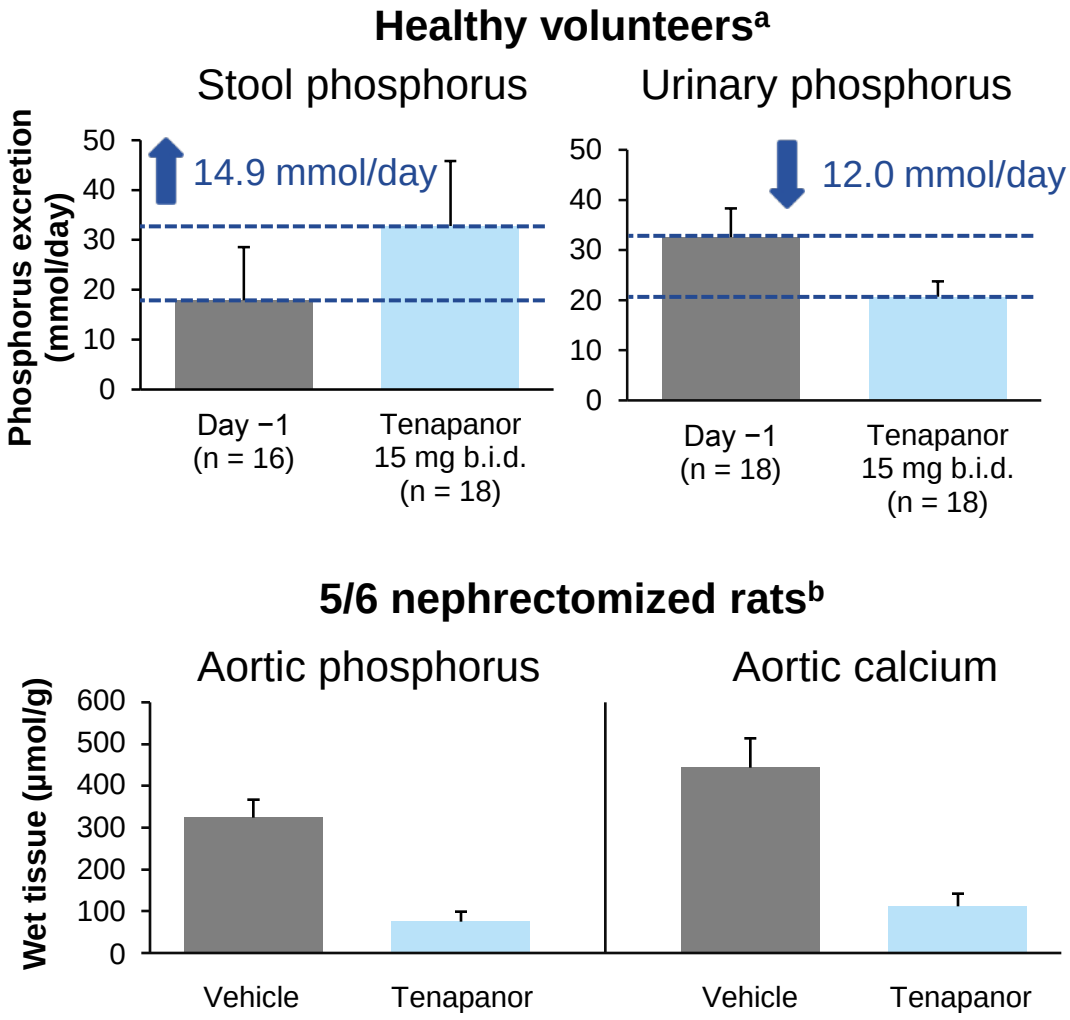


Data in the chart are mean + standard error (tenapanor administered as HCl tablet); HCl, hydrochloride; q.d., once daily.

1. Spencer AG *et al*. *Sci Transl Med* 2014;6:227ra36; 2. Johansson S *et al*. *J Am Soc Nephrol* 2014;25:593A (presentation FR-PO965).

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]



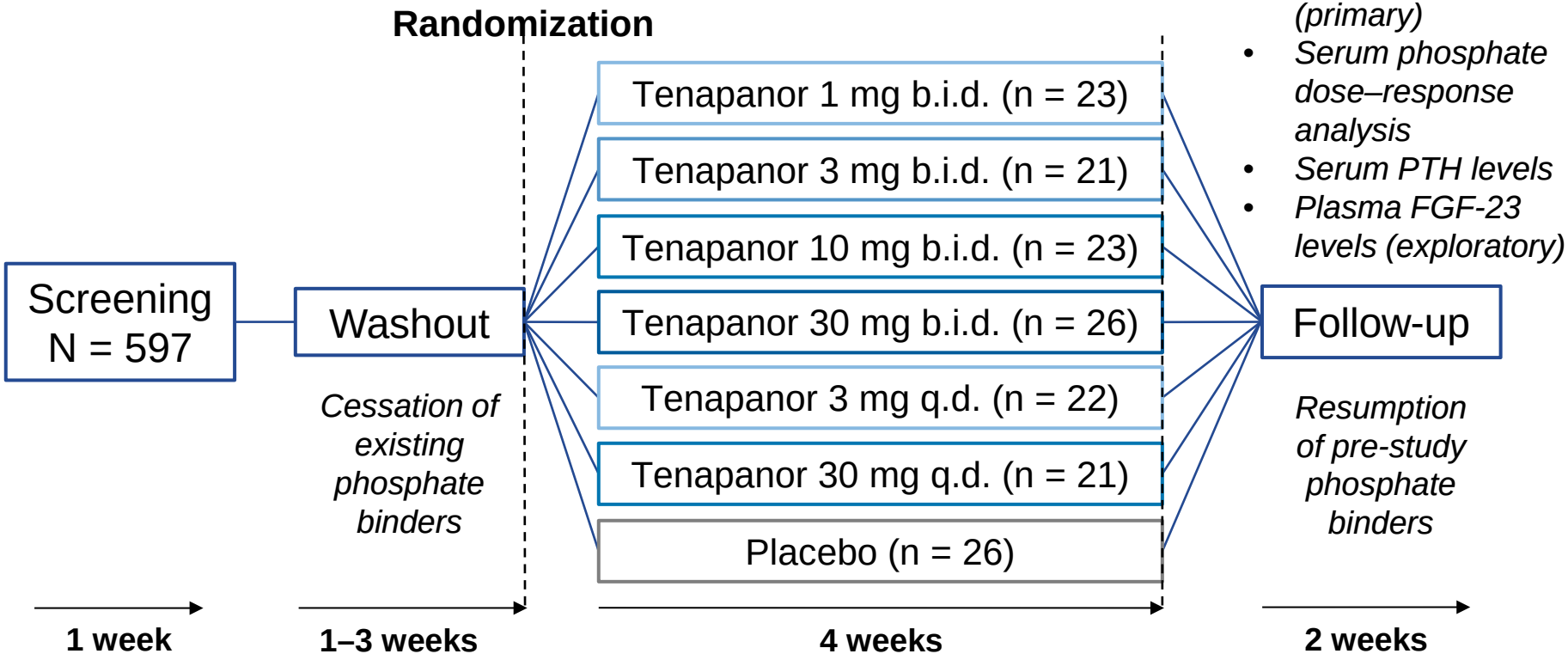
[a]Tenapanor formulation study (D5611C00002): includes mean of day −1, with data for tenapanor (15 mg b.i.d. HCl tablet) as mean + standard deviation of treatment days 1–4.
[b]Republished with permission of American Society of Nephrology from Labonté ED *et al.*[2] with permission conveyed through Copyright Clearance Center, Inc.; data are presented as mean + standard error; ***$p \leq 0.001$ (tenapanor vs vehicle).
b.i.d., twice daily; HCl, hydrochloride.
1. Rosenbaum DP *et al. J Am Soc Nephrol* 2014;25:72A (presentation FR-OR112); 2. Labonté ED *et al. J Am Soc Nephrol* 2015;26:1138–49.

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

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.

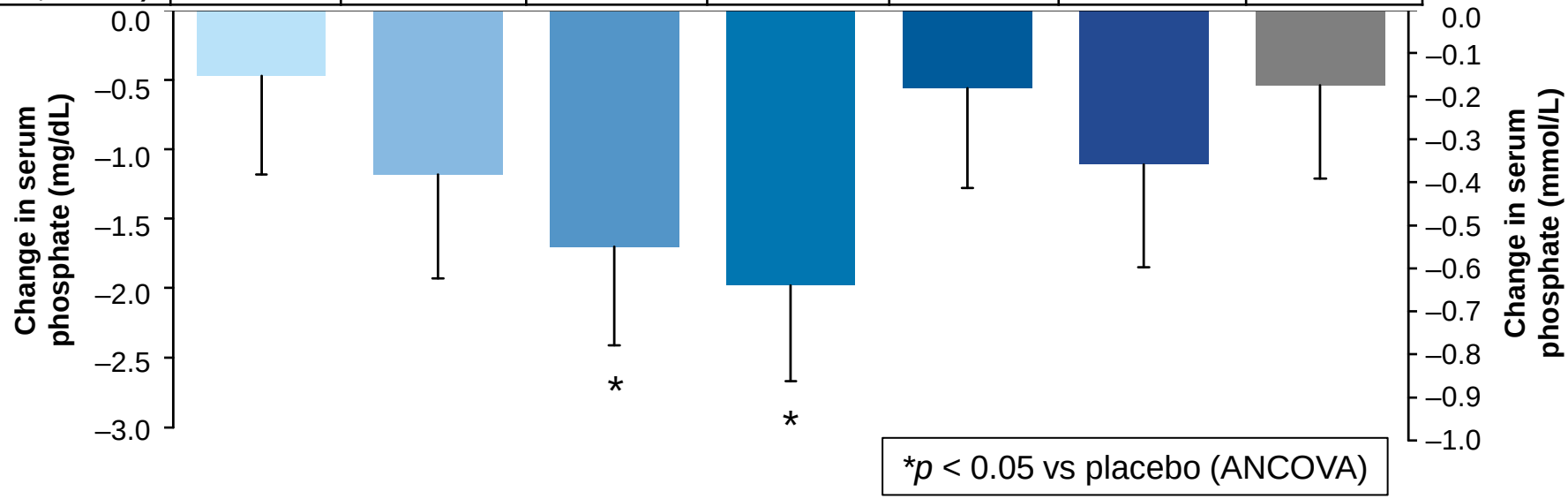
Patient demographics and baseline characteristics were balanced across groups

	Tenapanor						Placebo
	1 mg b.i.d. (n = 23)	3 mg b.i.d. (n = 21)	10 mg b.i.d. (n = 23)	30 mg b.i.d. (n = 26)	3 mg q.d. (n = 22)	30 mg q.d. (n = 21)	(n = 26)
Age, years	57.9 ± 14.8	61.5 ± 11.2	62.7 ± 12.5	59.7 ± 13.0	57.6 ± 15.8	58.2 ± 15.8	56.1 ± 13.1
Body weight, kg	85.9 ± 22.7	84.3 ± 19.2	84.8 ± 18.9	88.6 ± 24.6	76.6 ± 18.9	79.6 ± 18.8	83.3 ± 18.4
Men, n (%)	16 (70)	15 (71)	15 (65)	17 (65)	12 (55)	13 (62)	16 (62)
Race, n (%)							
White	17 (74)	12 (57)	16 (70)	15 (58)	13 (59)	16 (76)	17 (65)
African–American	2 (9)	8 (38)	3 (13)	9 (35)	6 (27)	3 (14)	4 (15)
Asian	1 (4)	0	3 (13)	1 (4)	1 (5)	0	3 (12)
Patient disposition							
Completed study, n (%)	18 (78)	13 (62)	19 (83)	13 (50)	18 (82)	12 (57)	22 (85)

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

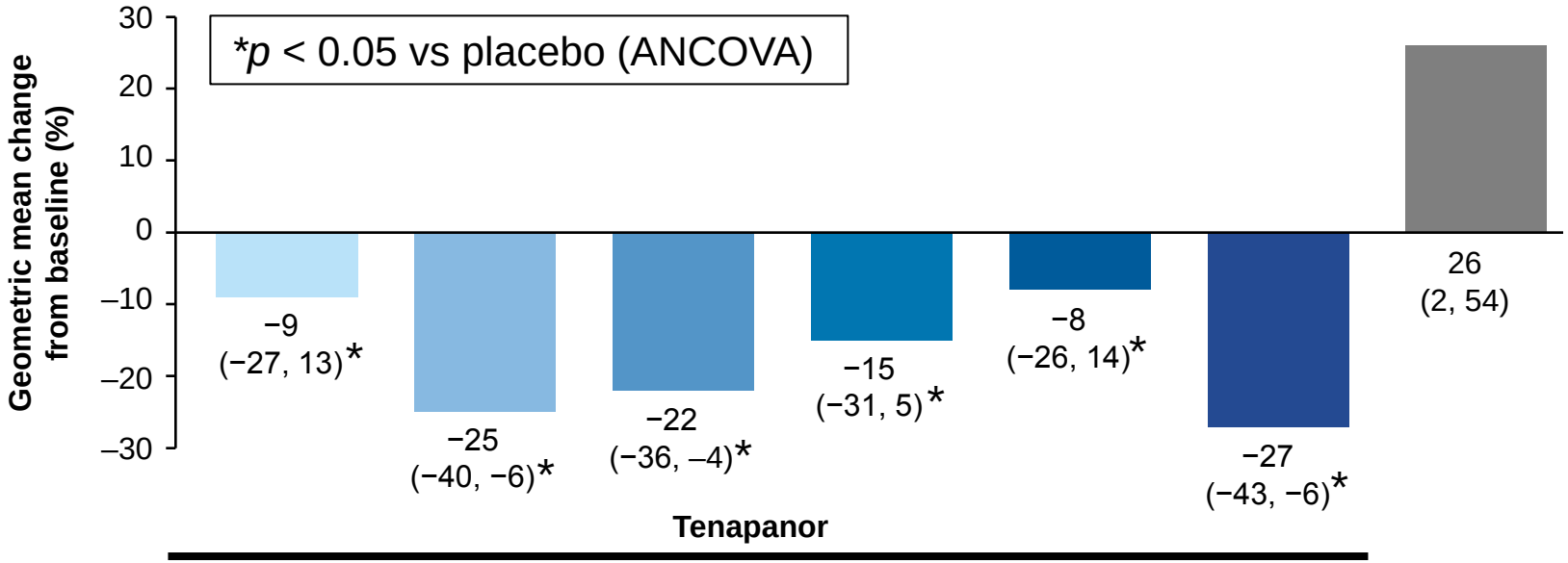
	Tenapanor						
	1 mg b.i.d.	3 mg b.i.d.	10 mg b.i.d.	30 mg b.i.d.	3 mg q.d.	30 mg q.d.	Placebo
Baseline serum phosphate (mg/dL)[a]	7.55 ± 1.00	7.32 ± 1.01	7.92 ± 1.06	7.76 ± 1.18	7.73 ± 1.28	7.61 ± 0.85	7.87 ± 1.49
Change from baseline at EOT/ET (mg/dL)[b]	−0.47 (−1.18, 0.24)	−1.18 (−1.93, −0.44)	−1.70 (−2.41, −0.99)	−1.98 (−2.67, −1.28)	−0.56 (−1.28, 0.17)	−1.11 (−1.85, −0.37)	−0.54 (−1.21, 0.13)
n (baseline, EOT/ET)	23, 23	21, 21	23, 23	25, 24	22, 22	21, 21	26, 26



- 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.
[a]mean ± standard deviation of last washout value; [b]LS 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



	1 mg b.i.d.	3 mg b.i.d.	10 mg b.i.d.	30 mg b.i.d.	3 mg q.d.	30 mg q.d.	Placebo
Median baseline serum FGF-23 level (pg/mL)[a]	4154 (487–47 687)	2341 (234–19 975)	6448 (152–43 283)	6423 (152–73 769)	3116 (160–32 428)	4862 (128–53 699)	4848 (202–99 000)
n (baseline, EOT/ET)	21, 19	21, 19	22, 22	23, 21	22, 20	19, 15	24, 22

- 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

	Tenapanor						Placebo
	1 mg b.i.d. (n = 23)	3 mg b.i.d. (n = 21)	10 mg b.i.d. (n = 23)	30 mg b.i.d. (n = 25)	3 mg q.d. (n = 22)	30 mg q.d. (n = 21)	(n = 26)
Any AE	10 (43)	12 (57)	16 (70)	19 (76)	13 (59)	13 (62)	11 (42)
Deaths	1 (4)[a]	0	0	0	0	0	0
Serious AEs	2 (9)[a]	2 (10)	3 (13)	2 (8)	1 (5)	0	4 (15)
Treatment-related AEs[b]	7 (30)	7 (33)	12 (52)	16 (64)	6 (27)	10 (48)	6 (23)
Diarrhea[c]	6 (26)	6 (29)	12 (52)	16 (64)	4 (18)	10 (48)	2 (8)
Hyperphosphatemia	1 (4)	0	0	0	1 (5)	0	2 (8)
AEs leading to discontinuation of study drug[d]	3 (13)	3 (14)	3 (13)	9 (36)	1 (5)	7 (33)	2 (8)
Diarrhea[c]	2 (9)	3 (14)	3 (13)	8 (32)	0	6 (29)	0
Hyperphosphatemia	1 (4)	0	0	0	1 (5)	0	2 (8)

- 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 ≥ 2 patients in any treatment group; [c]including fecal incontinence; [d]data shown for ≥ 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

	Tenapanor						Placebo
	1 mg b.i.d. (n = 23)	3 mg b.i.d. (n = 21)	10 mg b.i.d. (n = 23)	30 mg b.i.d. (n = 25)	3 mg q.d. (n = 22)	30 mg q.d. (n = 21)	(n = 26)
Blood and lymphatic system disorders	0	0	0	0	1 (5)	0	1 (4)
Ear and labyrinth disorders	0	3 (14)	0	0	0	0	0
Cardiac disorders	1 (4)	1 (5)	0	0	0	1 (5)	2 (8)
GI disorders	7 (30)	9 (43)	15 (65)	19 (76)	5 (23)	12 (57)	5 (19)
Diarrhea[a]	6 (26)	7 (33)	13 (57)	17 (68)	4 (18)	11 (52)	3 (12)
Nausea	0	1 (5)	1 (4)	1 (4)	2 (9)	1 (5)	1 (4)
Abdominal pain	0	0	0	2 (8)	1 (5)	0	1 (4)
Vomiting	0	1 (5)	0	0	1 (5)	2 (10)	0
General disorders and administration site conditions	2 (9)	0	0	2 (8)	2 (9)	0	0
Infections and infestations	0	1 (5)	1 (4)	0	2 (9)	1 (5)	3 (12)
Investigations	0	1 (5)	0	0	1 (5)	0	1 (4)
Injury, poisoning and procedural complications	2 (9)	2 (10)	1 (4)	2 (8)	1 (5)	0	0
Metabolism and nutrition disorders	1 (4)	1 (5)	2 (9)	1 (4)	1 (5)	1 (5)	2 (8)
Musculoskeletal and connective tissue disorders	0	1 (5)	0	2 (8)	0	2 (10)	2 (8)
Nervous system disorders	1 (4)	1 (5)	1 (4)	2 (8)	2 (9)	3 (14)	0
Psychiatric disorders	0	0	0	2 (8)	1 (5)	0	2 (8)
Respiratory, thoracic, and mediastinal disorders	0	1 (5)	0	0	1 (5)	0	1 (4)
Skin and subcutaneous tissue disorders	0	0	1 (4)	0	2 (9)	0	1 (4)
Vascular disorders	2 (9)	2 (10)	0	1 (4)	0	1 (5)	2 (8)

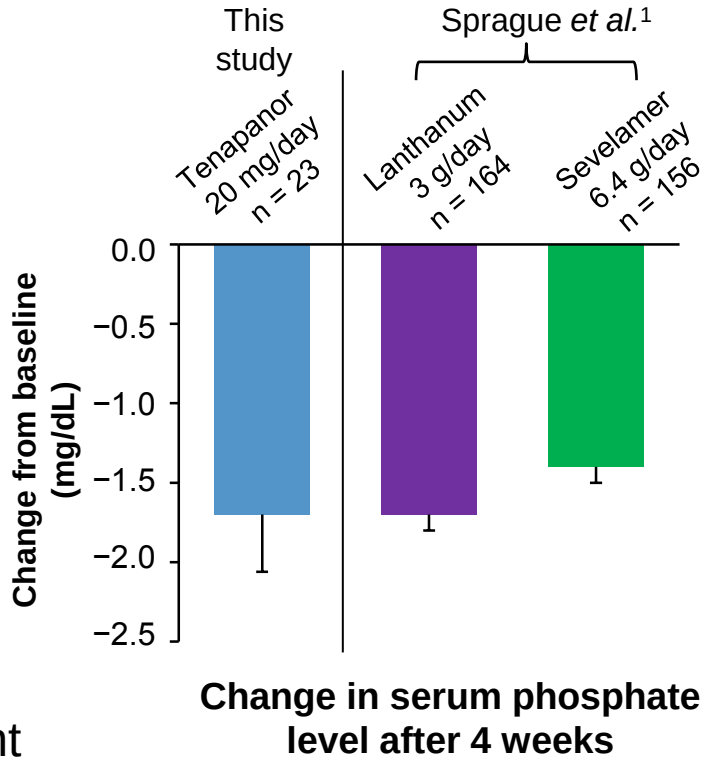
Data are number of patients (%); data shown for system organ class (and preferred terms for GI disorders) in which ≥ 2 patients experienced an AE across all treatment groups, irrespective of relationship of the AE to the study drug.

[a]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 × 2.4 g] + [1 × 1.6 g]) in a two-way crossover trial.[1]

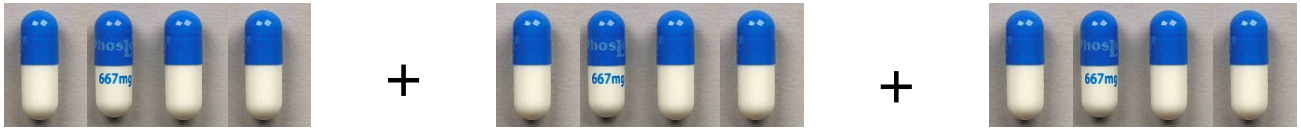
b.i.d., twice daily; LS, least-squares; t.i.d., three times daily.

1. Sprague SM *et al. Clin Nephrol* 2009;72:252–58.

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

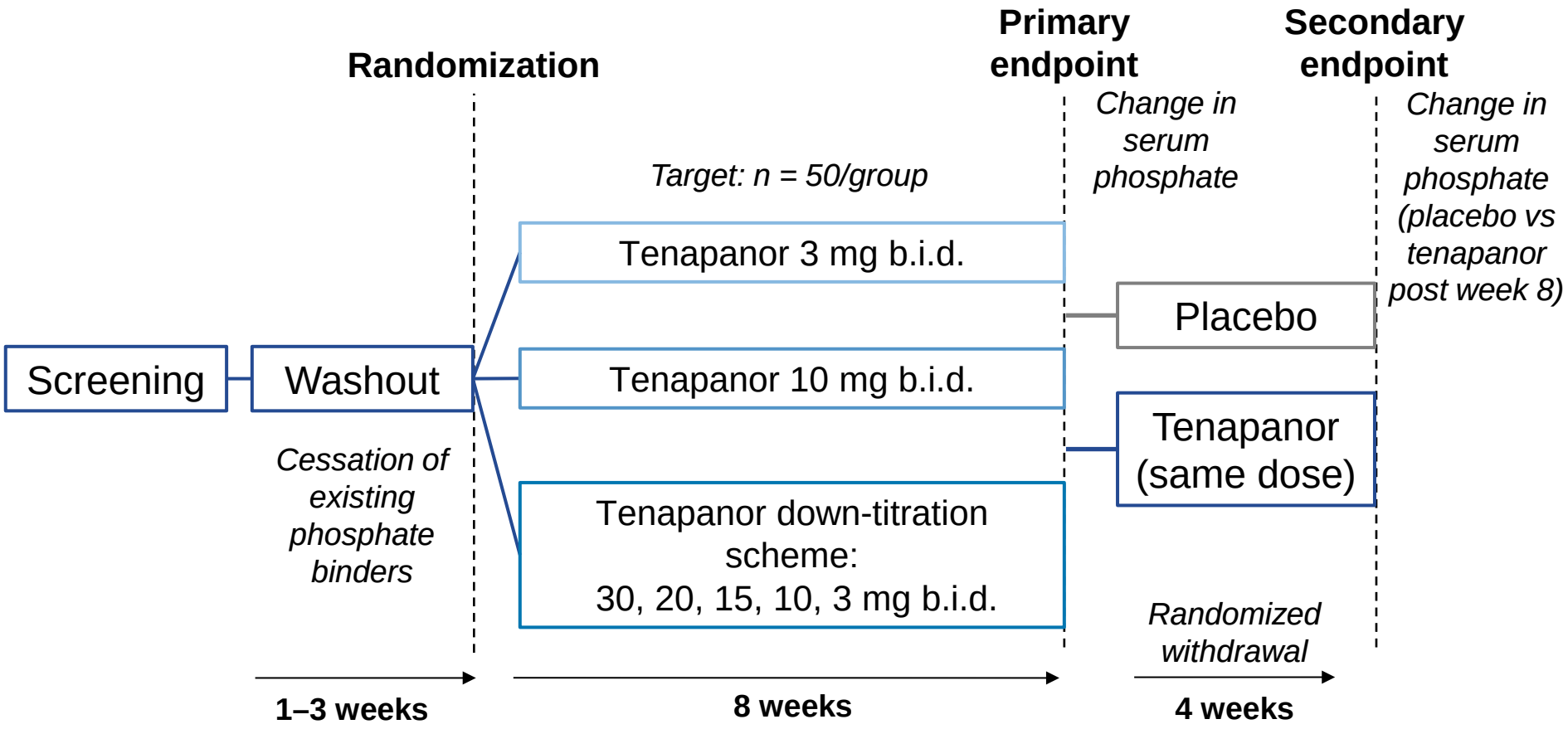
Tenapanor hydrochloride

- 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



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