

Effect of Food Intake on the Pharmacodynamics of Tenapanor: A Phase I Study

Clinical Pharmacology in Drug Development
2017, 6(5) 457–465
© 2017 The Authors.
Clinical Pharmacology in Drug Development Published by Wiley Periodicals, Inc. on behalf of The American College of Clinical Pharmacology
DOI: 10.1002/cpdd.341

Susanne A. Johansson¹, Mikael Knutsson¹, Maria Leonsson-Zachrisson¹, and David P. Rosenbaum²

Abstract

Tenapanor (RDX5791/AZD1722) is a minimally systemic small-molecule inhibitor of the sodium/hydrogen exchanger NHE3. Tenapanor acts in the gut to reduce absorption of sodium and phosphate. This phase I open-label, 3-way crossover study (NCT02226783) evaluated the effect of food on the pharmacodynamics of tenapanor. Eighteen volunteers completed a randomized sequence of three 4-day treatments with tenapanor hydrochloride 15 mg twice daily: before food, after food, and while fasting. Participants received a diet standardized for sodium content. Stool sodium was significantly higher with tenapanor administration before versus after food (difference, +8.8 mmol/day, $P = .006$) or while fasting (+11.8 mmol/day, $P = .0004$). Differences in urinary sodium were not significant. Stool phosphorus was not significantly different with tenapanor before versus after food and significantly higher before food versus while fasting (+4.9 mmol/day, $P = .006$). Urinary phosphorus was significantly lower when tenapanor was administered before (−3.9 mmol/day, $P = .0005$) or after food (−3.7 mmol/day, $P = .0009$) versus while fasting. No serious adverse events were reported. These data suggest the effect of tenapanor on sodium absorption is most pronounced when administered before meals, whereas the effect on phosphate is similar whether administered before or after meals. This may support different timings of tenapanor administration with respect to food for sodium- and phosphate-related indications.

Keywords

dietary sodium, food–drug interactions, pharmacology, sodium-hydrogen exchanger 3, tenapanor

Tenapanor (RDX5791, AZD1722) is a first-in-class minimally systemic small-molecule inhibitor of the sodium/hydrogen exchanger isoform 3 (NHE3).¹ In the gastrointestinal tract, NHE3 plays an important role in sodium/fluid homeostasis,^{2,3} which if disturbed can contribute to various conditions including constipation-related disorders and chronic kidney disease (CKD).⁴ Studies in animals and humans demonstrate that tenapanor reduces the absorption of sodium from the intestine, as evidenced by increases in stool sodium content of 20–50 mmol/day with concomitant reductions in urinary sodium in healthy volunteers administered tenapanor 15–90 mg twice daily over 7 days.^{1,5,6} By diverting a portion of dietary sodium to the stool, tenapanor treatment results in an increase in stool fluid content¹ and promotes gastrointestinal motility and is therefore being evaluated for the treatment of constipation-predominant irritable bowel syndrome (IBS-C).^{7,8} In patients with CKD, impaired sodium excretion can contribute to fluid overload and accelerated CKD progression^{9,10}; the effect of

tenapanor on these processes has been investigated in an additional 2 clinical trials.^{11,12}

In addition to its effects on dietary sodium absorption, preclinical and clinical studies indicate that tenapanor reduces the absorption of phosphate from the intestine.^{5,6,13} In healthy volunteers treated with tenapanor for 7 days, mean stool phosphorus content was increased by up to 20 mmol/day versus placebo.^{5,6} As a result of these findings, tenapanor is currently being

¹AstraZeneca Gothenburg, Mölndal, Sweden

²Ardelyx, Inc., Fremont, CA, USA

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

Submitted for publication 22 September 2016; accepted 18 January 2017.

Corresponding Author:

David P. Rosenbaum, PhD, Ardelyx, Inc., 34175 Ardenwood Boulevard, Suite 200, Fremont, CA 94555
(e-mail: drosenbaum@ardelyx.com)

evaluated in clinical trials for the treatment of hyperphosphatemia in patients with CKD on dialysis.¹⁴ The mechanism by which tenapanor reduces gastrointestinal phosphate uptake is currently being investigated; ongoing work suggests that it does not involve direct inhibition of intestinal phosphate transporters type 1 (PiT1) or NaPi2b (also known as NpT2b).¹³

Studies assessing the effect of food on orally administered investigational drugs are an important step in establishing the optimal timing for dosing in later clinical trials and for drug labeling.¹⁵ This is typically assessed by evaluating the systemic exposure of the investigational drug with different timings of administration with regard to meals. In the case of drugs that act locally in the gut with minimal systemic exposure, it is necessary to use different measures, such as the pharmacodynamic activity of the drug, to assess the effects of food.

The purpose of this phase 1 study was to investigate whether the timing of food intake affects the pharmacodynamic activity of tenapanor, as measured by the absorption of both dietary sodium and phosphate in healthy volunteers.

Materials and Methods

Study Design

This phase 1 open-label, randomized, single-center, 3-way crossover study (ClinicalTrials.gov identifier: NCT02226783) was conducted at Quintiles Phase One Services (Overland Park, Kansas). The study protocol, amendments, and informed consent forms were ap-

proved by the MidLands Independent Review Board (Overland Park, Kansas). All participants provided written informed consent, and the study was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonisation, and Good Clinical Practice guidelines.

Participants

Healthy men and women aged 18–65 years with a body mass index of 18–30 kg/m² and a body weight of 50–100 kg were eligible to participate in the study. Women of childbearing potential were required to have a negative pregnancy test at screening, use effective contraception, and not be lactating. Volunteers were required to have regular bowel habits of at least 1 bowel movement (or stool portion) per day.

Key exclusion criteria were loose stools for 2 or more days during the week before randomization (based on a Bristol Stool Form Scale [BSFS]¹⁶ score of 6 or higher); use of treatments or supplements known to affect stool consistency or gastrointestinal motility, including fiber supplements, probiotic medications or supplements, antidiarrheals, prokinetic drugs and enemas, in the week before randomization; and use of salt or electrolyte supplements containing sodium, potassium, chloride, or bicarbonate formulations in the week before randomization.

Study Treatment

The study consisted of three 4-day treatment periods with a run-in period of 2 days before the

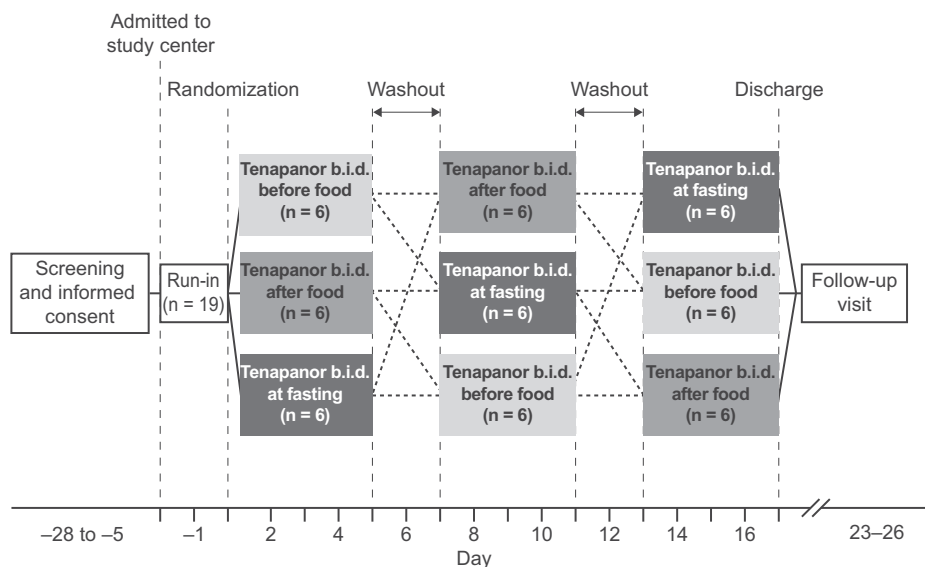


Figure 1. Study design. Volunteers were randomly assigned to 1 of 6 possible treatment sequences based on 3 tenapanor hydrochloride administration regimens (all 15 mg administered orally twice daily): before food (5–10 minutes before the start of breakfast and dinner), after food (30 minutes after the start of breakfast and dinner) or while fasting (1 hour before breakfast and 3 hours after dinner/1 hour before an evening snack). b.i.d., twice daily.

first treatment and a 2-day washout between treatments (Figure 1). The duration of the washout period was based on observations from a previous healthy volunteer study,¹ in which there was a rapid return to baseline stool and urinary sodium levels on the day after tenapanor treatment ended. Participants were randomly assigned to a sequence of treatments that comprised oral administration of tenapanor hydrochloride 15 mg immediate-release tablets twice daily: before food (5–10 minutes before the start of breakfast and dinner); after food (30 minutes after the start of breakfast and dinner); or while fasting (1 hour before breakfast and 3 hours after dinner/1 hour before an evening snack).

Volunteers were admitted to the study center in the morning 2 days before randomization (day –2) and remained in the study center until discharge on day 17. A follow-up visit occurred 7–10 days after the last dose of tenapanor on day 16. All participants received the same meals on the same study days in each treatment period, thereby enabling consistent sodium and phosphate intake between participants and treatment periods: their diet was standardized for sodium content (approximately 1.5 g [65 mmol] in each of 3 main meals) throughout their stay at the study center.

Study Assessments

Pharmacodynamic assessments included sodium and phosphorus content in stools and urine collected over 24-hour intervals on days –2 to 17. Stool frequency, stool consistency (as measured by the Bristol Stool Form Scale),¹⁶ and total stool weight were also assessed in each 24-hour interval. Electrolyte analyses of stool were performed by RTI International (Research Triangle Park, North Carolina) and of urine by Quintiles QLAB (Marietta, Georgia). Safety assessments included vital signs (during the run-in period preceding randomization and before dosing on each day of the treatment periods), physical examinations, clinical laboratory evaluations (clinical chemistry, hematology, and urinalysis; days –1, 5, 11, and 17), electrocardiograms (days 1, 7, 13, and 17), and adverse event (AE) monitoring. Blood samples for measurement of plasma tenapanor concentrations were collected before and 1, 2, and 4 hours after the morning dose on days 1, 4, 7, 10, 13, and 16. Plasma tenapanor concentrations were determined by Covance Laboratories (Madison, Wisconsin).

Analytical methods for determining stool and urinary electrolyte levels and plasma tenapanor content have been described elsewhere.⁵

Statistical Analysis

The pharmacodynamic analysis set included all volunteers who received at least 1 dose of tenapanor, had at least 1 postdose pharmacodynamic measurement

recorded, and had not met any criteria for protocol deviations. The safety analysis set included all volunteers who received at least 1 dose of tenapanor and for whom any postdose data were available.

Least-squares (LS) means (95% confidence intervals [CI]) of average daily stool and urinary sodium and average daily stool and urinary phosphorus were estimated for each treatment based on data from the 4-day treatment periods, using the pharmacodynamic analysis set. For each volunteer and treatment period, average daily stool and urinary sodium and phosphorus content were calculated as the sum of all available measurements following assignment to treatment divided by the number of days of treatment for which measurements were available. Treatment regimen comparisons were then performed using an analysis of variance model with fixed effects for treatment, sequence, and period and a random effect for volunteer within sequence to account for within-volunteer differences. LS mean differences, 90% CIs, and *P* values were determined for all pairwise comparisons between treatment regimens. Stool and urinary sodium and phosphorus levels on day –1 (the first day of the run-in period) were presented as the arithmetic mean and standard deviation (SD), based on all volunteers in the pharmacodynamic analysis set.

Descriptive statistics were determined for stool frequency, consistency, and weight. For each individual, mean BSFS score was calculated as the mean for each 24-hour period, and the 24-hour means over the full treatment period were used to provide the average daily BSFS score. Average daily stool frequency and weight were determined as for urinary and stool electrolytes. The day –1 values for each of these pharmacodynamic variables were also based on all volunteers in the pharmacodynamic analysis set.

Statistical analyses were performed by Quintiles Phase One Services using SAS version 9.2 (SAS Institute, Inc., Cary, North Carolina).

Results

Study Participants

In total, 19 volunteers were randomly assigned to a treatment sequence, received at least 1 dose of tenapanor, and were included in the safety analysis. One individual was removed from the study owing to not fulfilling the eligibility criteria for participation (exclusion criterion: loose stools on 2 or more days during the 7 days before randomization). This individual received 3 doses of tenapanor before discovery of the protocol deviation and discontinuation from the study. The remaining 18 volunteers completed the study and were included in the pharmacodynamic analyses. Mean age \pm SD was 35 ± 11 years (range, 21–60 years), and 14 of the 19 volunteers were men.

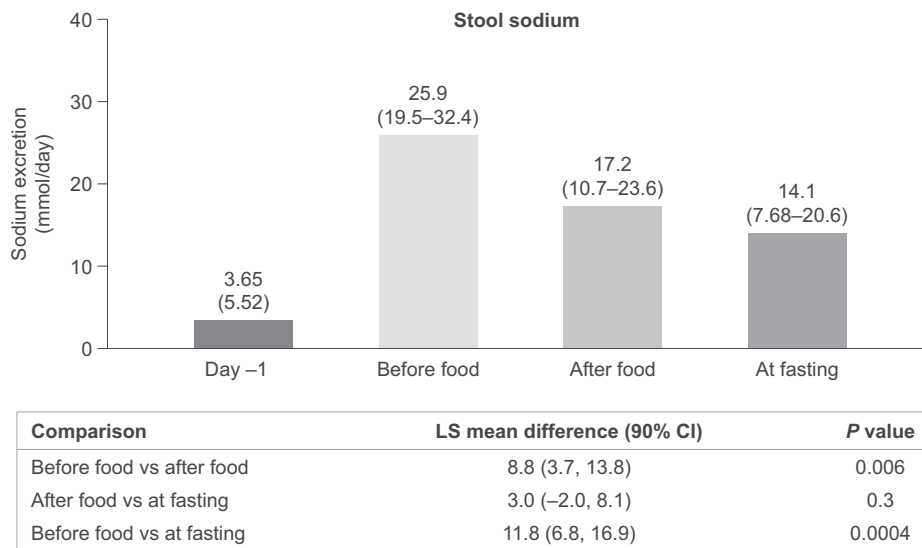


Figure 2. Average daily stool sodium excretion. Day -1 data are arithmetic mean (standard deviation), $n = 18$; treatment period data are least-squares mean (95% confidence interval) over 4 days of treatment ($n = 18$). Comparisons between treatment regimens were performed using an analysis of variance model with fixed effects for treatment, sequence, and period and a random effect for volunteer within sequence. CI, confidence interval; LS, least-squares.

Pharmacodynamic Evaluations

Stool and urinary electrolytes. Over 4 days' treatment, the LS mean for stool sodium content was significantly higher when volunteers received tenapanor before food (25.9 mmol/day) than when receiving the drug after food (17.2 mmol/day) or while fasting (14.1 mmol/day); see Figure 2. LS mean difference (90%CI) in stool sodium content was 8.8 mmol/day (3.7–13.8 mmol/day), $P = .006$, for tenapanor administration before food versus after food and 11.8 mmol/day (6.8–16.9 mmol/day), $P = .0004$, before food versus while fasting. The LS mean for urinary sodium content ranged from 127 to 134 mmol/day, and there were no statistically significant differences between treatment regimens (Figure 3).

Over 4 days' treatment, the LS mean for stool phosphorus content in volunteers receiving tenapanor before food (27.3 mmol/day) and after food (25.6 mmol/day) did not significantly differ, although the LS mean when receiving tenapanor while fasting (22.3 mmol/day) was significantly lower than when receiving the drug before food (Figure 4). The LS mean difference (90%CI) was 1.6 mmol/day (-1.2 to 4.5 mmol/day), $P = .3$, for tenapanor treatment before food versus after food, and 4.9 mmol/day (2.1–7.7 mmol/day), $P = .006$, before food versus while fasting. The LS mean for urinary phosphorus content ranged from 21.4 mmol/day when volunteers received tenapanor before food to 25.3 mmol/day when receiving tenapanor while fasting (Figure 5). There was no significant difference in urinary phosphorus when

tenapanor was administered before food versus after food (LS mean difference [90%CI], -0.2 mmol/day [-1.9 to 1.5 mmol/day]; $P = .8$), but this value was significantly lower when tenapanor was administered before food or after food versus while fasting (LS mean differences [90%CI], -3.9 mmol/day [-5.6 to -2.2 mmol/day]; $P = .0005$; and -3.7 mmol/day [-5.4 to -2.0 mmol/day]; $P = .0009$, respectively; Figure 5).

Stool frequency, consistency, and weight. Average daily stool frequency was similar for all treatment regimens (Table 1). The mean \pm SD stool consistency scores (using the Bristol Stool Form Scale)¹⁶ were similar across the treatment regimens (4.7 ± 1.1 , 4.2 ± 1.3 , and 4.1 ± 1.0 for administration of tenapanor before food, after food, and while fasting, respectively) and higher than during the run-in period ($day -1$, 2.7 ± 1.1 ; Table 1). Compared with administration of tenapanor while fasting, administration before or after food appeared to be associated with a slightly higher average daily stool weight (Table 1).

Pharmacokinetic Evaluations

Serum tenapanor levels were below the limit of quantification (0.5 ng/mL) in all 392 plasma samples taken during the study.

Safety and Tolerability

No safety concerns were identified in volunteers who received tenapanor treatment. There were no serious AEs or discontinuations because of AEs during the study; all reported AEs were of mild intensity. No

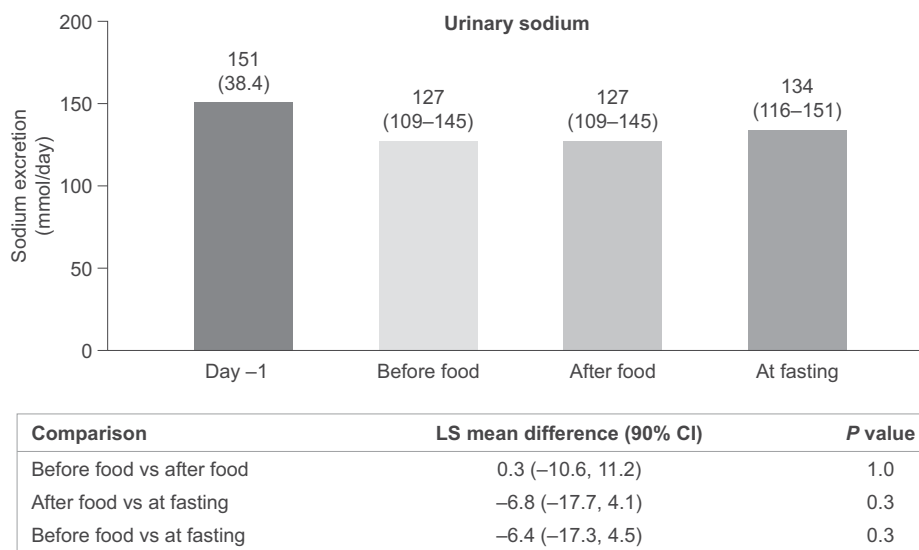


Figure 3. Average daily urinary sodium excretion. Day -1 data are arithmetic mean (standard deviation), n = 18; treatment period data are least-squares mean (95% confidence interval) over 4 days of treatment (n = 18). Comparisons between treatment regimens were performed using an analysis of variance model with fixed effects for treatment, sequence, and period and a random effect for volunteer within sequence. CI, confidence interval; LS, least-squares.

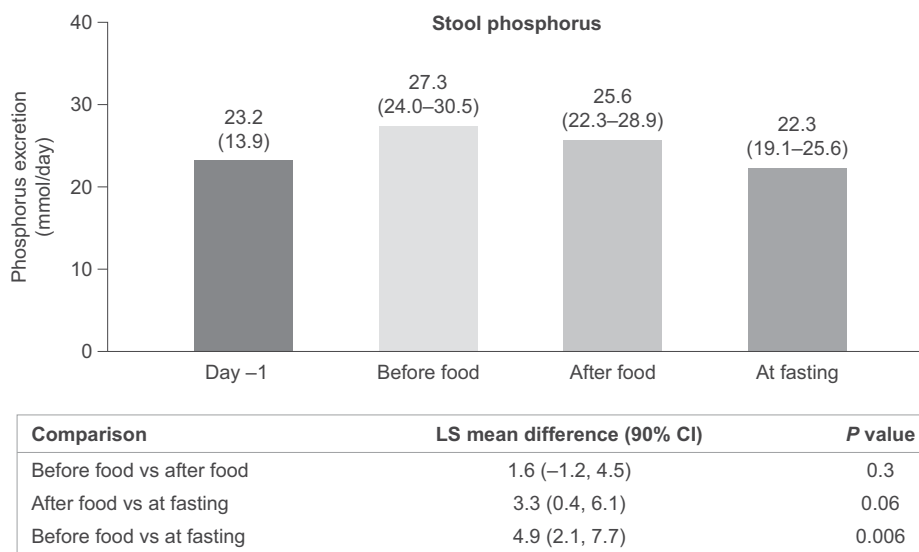
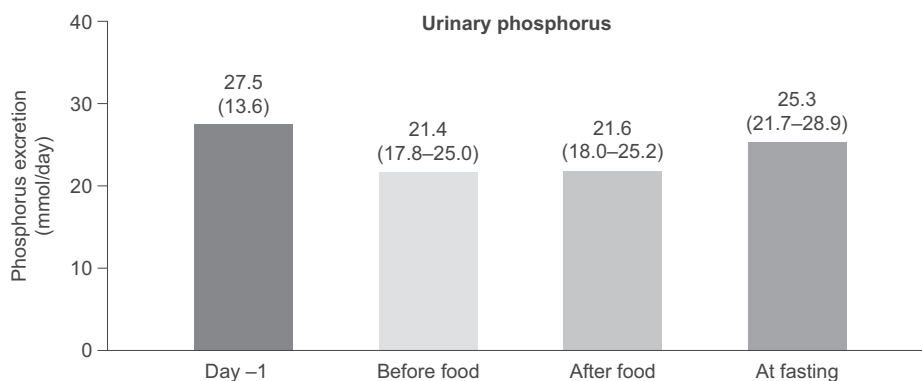


Figure 4. Average daily stool phosphorus excretion. Day -1 data are arithmetic mean (standard deviation), n = 18; treatment period data are least-squares mean (95% confidence interval) over 4 days of treatment (n = 18). Comparisons between treatment regimens were performed using an analysis of variance model with fixed effects for treatment, sequence, and period and a random effect for volunteer within sequence. CI, confidence interval; LS, least-squares.

clinically relevant trends were observed in the frequency of AEs between treatments or in the individual AEs reported.

Nine volunteers reported a total of 12 AEs; 2 volunteers experienced AEs during their before-food treatment period, 4 volunteers experienced AEs during their after-food treatment period, and 4 volunteers reported AEs during their at-fasting treatment period.

The most frequently reported AEs (reported by 2 or more volunteers) were diarrhea (before food, n = 1; while fasting, n = 1), dyspepsia (before food, n = 1; while fasting, n = 1), and oropharyngeal pain (after food, n = 1; while fasting, n = 1). No trends or clinically relevant changes were observed in clinical laboratory results, vital signs, electrocardiograms, or physical examinations during the study.



Comparison	LS mean difference (90% CI)	P value
Before food vs after food	-0.2 (-1.9, 1.5)	0.8
After food vs at fasting	-3.7 (-5.4, -2.0)	0.0009
Before food vs at fasting	-3.9 (-5.6, -2.2)	0.0005

Figure 5. Average daily urinary phosphorus excretion. Day -1 data are arithmetic mean (standard deviation), $n = 18$; treatment period data are least-squares mean (95% confidence interval) over 4 days of treatment ($n = 18$). Comparisons between treatment regimens were performed using an analysis of variance model with fixed effects for treatment, sequence, and period and a random effect for volunteer within sequence. CI, confidence interval; LS, least-squares.

Table 1. Other Pharmacodynamic Variables

	Day -1 (Run-in Period), $n = 18$	Tenapanor Administration		
		Before Food ($n = 18$)	After Food ($n = 18$)	While Fasting ($n = 18$)
Average daily stool frequency, bowel movements/day	1.4 (0.5)	1.6 (0.6)	1.4 (0.5)	1.4 (0.5)
Average daily stool consistency, Bristol Stool Form Scale score	2.7 (1.1)	4.7 (1.1)	4.2 (1.3)	4.1 (1.0)
Average daily total stool weight, g/day	157 (106)	235 (116)	185 (82.6)	169 (57.3)

For day -1 data, means (SDs) were calculated from daily measurements across all study participants. Treatment period data are means (SDs) over 4 days of treatment. The Bristol Stool Form Scale assesses stool consistency on a scale from 1 (harder) to 7 (liquid).¹⁶ SD, standard deviation.

Discussion

Tenapanor, a small molecule that has minimal systemic availability, is an inhibitor of the sodium transporter NHE3. Studies in animals and humans have shown that tenapanor acts locally in the gut to selectively reduce absorption of sodium and phosphate.^{1,5,6,13} These effects may be beneficial in the management of constipation-related disorders and CKD; tenapanor is currently being evaluated for the treatment of patients with IBS-C^{7,8} and hyperphosphatemia in patients with CKD on dialysis.¹⁴ This phase I study evaluated the influence of the timing of food intake in relation to tenapanor administration on the pharmacodynamic effects of the drug in healthy volunteers.

Based on stool sodium content, a direct measure of changes in absorption of dietary sodium in the gut, the results of our study indicate that the effect of tenapanor on sodium absorption is greatest when the drug is administered shortly before meals.

Compared with administration of tenapanor after meals or while fasting, administration before meals was associated with a significantly higher amount of stool sodium. The effect of tenapanor on the absorption of dietary phosphate in this study, as measured by stool phosphorus levels, differed from the effect on stool sodium: there was no statistically significant difference in stool phosphorus when tenapanor was administered before compared with after food. Stool phosphorus content was significantly higher only for tenapanor administration before meals relative to a fasted state.

Stool weight varied depending on the timing of administration: tenapanor given either before or after food appeared to be associated with a slightly higher stool weight than when administered while fasting. Consistent with previous results in healthy volunteers,^{1,5} this study showed that tenapanor had minimal systemic availability, and treatment with tenapanor raised no safety concerns in healthy volunteers.

No serious AEs or discontinuations because of AEs were reported, and no clinically relevant changes in clinical or laboratory parameters were observed.

Food-effect studies are usually based on the measurement of pharmacokinetic parameters. However, given that tenapanor acts locally in the gut and has minimal systemic availability,¹ it was not appropriate or possible to evaluate the effect of food on tenapanor activity based on pharmacokinetic parameters. Therefore, the effect of food intake had to be evaluated using pharmacodynamic parameters; a similar approach has been taken in clinical pharmacology studies of other agents that act in the gut.^{17–21} The need to use pharmacodynamic parameters rather than pharmacokinetic parameters has also been noted when testing the bioequivalence of drugs that are locally acting and have no or minimal systemic exposure.²⁰ Using pharmacodynamic parameters rather than pharmacokinetic parameters to evaluate the influence of food on a drug such as tenapanor could be considered an advantage because it means the analysis focuses on the effect at the site of drug action. The influence of food intake on pharmacodynamics is of additional interest given that expression of NHE3 in the gut, the target of tenapanor, is regulated by digestive processes,²² as discussed further below.

There are several possible mechanisms that may contribute to the effect of food intake on the reduction of sodium absorption by tenapanor. If tenapanor is administered after a meal, it is possible that some sodium from the food already in the gut is absorbed before tenapanor is able to inhibit this process. However, if tenapanor is administered before a meal and binds to NHE3, it may inhibit uptake of sodium as soon as food arrives in the gut. The amount of tenapanor that can bind to NHE3 is dependent on the number of NHE3 transporters present on the surface of gut epithelial cells, which may change during digestion. In vitro studies indicate that NHE3 recycles between the plasma membrane and intracellular compartments and that normal digestive processes may regulate this recycling, thus affecting the levels of NHE3 on the cell surface.^{22,23} For example, if the cell-surface level of NHE3 were lower in a fasting state and increased during the initial stages of digestion, tenapanor might be expected to have a greater effect if administered just before food rather than 30 minutes after food or while fasting. The amount of tenapanor available to bind NHE3 may be expected to fluctuate with changes in gastric pH because the solubility of the drug in vitro is pH dependent, which could influence its pharmacodynamic effects, depending on when it is administered in relation to food intake.

Reduction of phosphate absorption by tenapanor is via a mechanism distinct from direct inhibition of gas-

trointestinal phosphate transporters (PiT1, NaPi2b)¹³ or direct binding of intestinal phosphate to tenapanor. Furthermore, NHE3 does not physically interact with phosphate. This may explain why there is no significant difference in phosphate absorption between administration of tenapanor before or after meals, as the potential mechanisms discussed above for the effect of food on reduction of sodium absorption by tenapanor would not be applicable. The precise details of the mechanism by which tenapanor reduces intestinal phosphate absorption are currently being elucidated.

In addition to the focus on pharmacodynamic parameters rather than pharmacokinetics, there were some other differences between the design of the present study and the methods recommended by the US Food and Drug Administration (FDA) for the conduct of food-effect studies.¹⁵ The FDA advises that fasting conditions consist of no food intake for at least 10 hours and no water intake for 1 hour before and after drug administration. Because pharmacodynamic assessments of tenapanor require repeated dosing over several days, a 10-hour period without food was not achievable before the evening dose in the present study. To ensure that volunteers were in as near to a fasting state as possible, the evening dose was not administered until 3 hours after dinner during the fasting treatment period. Volunteers were restricted to eating and drinking only the standardized meals and drinks and had to adhere to the fasting periods and meal times specified in the protocol. The FDA also recommends that participants receive high-fat, high-calorie meals in association with dosing of the study drug because such meals are likely to have the greatest effect on gastrointestinal physiology and therefore the greatest effect on systemic availability of an oral drug. The present study involved “normal” meals rather than high-fat, high-calorie meals because repeated dosing of tenapanor over several days was required for the pharmacodynamic analyses, rather than the single dose and single meal usually required for pharmacokinetic analyses in food-effect studies of systemically available drugs. It was not considered realistic or ethical to ask volunteers to adhere to a high-fat, high-calorie diet for the entire residential period of the study (19 days). Consistent with the methodology of other studies of tenapanor in healthy volunteers, all participants received a diet standardized for sodium content, with the same meals provided on the same days in each study period.

The effects of tenapanor on stool and urinary sodium observed in the present study are broadly consistent with previous studies in healthy volunteers, in which tenapanor doses of 15–90 mg twice daily resulted in increases in stool sodium of 20–50 mmol/day (equivalent to 1.2–2.9 g table salt/day) versus placebo,

with concomitant reductions in urinary sodium of a similar magnitude.^{1,5,6} Also in line with previous studies in healthy volunteers,⁵ increased sodium retention in the gut following tenapanor treatment in this study resulted in softer stools and an increase in stool weight. Tenapanor has also been shown to have an antinociceptive effect in an IBS animal model of visceral pain.²⁴ Results from a phase 2b study of tenapanor indicate that these effects translate into clinically meaningful improvements in constipation and abdominal pain in patients with IBS-C.⁷ In patients with CKD, limited sodium excretion owing to impaired kidney function can lead to fluid overload and hypertension and accelerated renal and cardiovascular dysfunction.^{9,10} A study in patients with CKD on dialysis showed no significant differences in interdialytic weight gain (an assessment of fluid overload) between tenapanor- and placebo-treated patients, although the pharmacodynamic effect of tenapanor was confirmed in this patient group, as evidenced by a significant increase in stool sodium and weight in patients treated with tenapanor versus placebo.¹¹

The effect of tenapanor on dietary phosphate absorption in the present study was consistent with previous studies in healthy volunteers, in which tenapanor treatment for 7 days resulted in increases in mean stool phosphorus content of up to 20 mmol/day versus placebo, with concomitant reductions in urinary phosphorus.^{5,6} In a rat model of CKD and vascular calcification, tenapanor significantly decreased ectopic calcification, serum creatinine, phosphorus and fibroblast growth factor-23 levels, and heart mass.¹³ Collectively, these findings have led to clinical trials of tenapanor for the treatment of hyperphosphatemia in patients with CKD on dialysis, in which the pharmacodynamic effects of the drug have been found to translate into clinically meaningful reductions in serum phosphate versus placebo.¹⁴

The dose of tenapanor selected for this study, 15 mg twice daily, was anticipated to be a clinically relevant dose for the treatment of patients with CKD-related disorders. On the basis of results from a previous study,¹⁴ doses of 3–30 mg twice daily are being tested in an ongoing trial of tenapanor for the treatment of hyperphosphatemia in patients with CKD on hemodialysis.²⁵ A higher dose of tenapanor, 50 mg twice daily, is being used in clinical trials in patients with IBS-C.^{7,26,27} However, owing to the drug's stool-softening effect potentially increasing the risk of diarrhea, administration of this higher dose to healthy volunteers over three 4-day periods was considered inappropriate for the purposes of this food-effect study.

In conclusion, this study found that inhibition of dietary sodium absorption by tenapanor, as judged by stool sodium content, was most pronounced when

the drug was administered 5–10 minutes before meals. This effect was not observed when evaluating inhibition of dietary phosphate absorption by tenapanor, with no significant difference in stool phosphorus content when tenapanor was administered before or after meals. These observations support administration of tenapanor shortly before meals to maximize its effect on sodium absorption; however, administration of tenapanor before or after meals may be adequate for its effect on phosphate absorption. These results may have implications for the design of future clinical trials and drug labeling.

Acknowledgments

We thank the study participants, the study centers, and the clinical teams involved in this work.

Declaration of Conflicting Interests

S.A.J. is an employee of and has ownership interests in AstraZeneca. D.P.R. is an employee of and has ownership interests in Ardelyx. M.K. and M.L.Z. are employees of AstraZeneca.

Funding

This study was funded by AstraZeneca. Medical writing support was provided by Steven Inglis, PhD, and Richard Claes, PhD, of PharmaGenesis London, London, UK, and was funded by AstraZeneca Gothenburg, Mölndal, Sweden, and Ardelyx, Inc., Fremont, California.

References

1. Spencer AG, Labonte ED, Rosenbaum DP, et al. Intestinal inhibition of the Na⁺/H⁺ exchanger 3 prevents cardiorenal damage in rats and inhibits Na⁺ uptake in humans. *Sci Transl Med*. 2014;6:227ra236.
2. Schultheis PJ, Clarke LL, Meneton P, et al. Renal and intestinal absorptive defects in mice lacking the NHE3 Na⁺/H⁺ exchanger. *Nat Genet*. 1998;19:282–285.
3. Tse CM, Brant SR, Walker MS, Pouyssegur J, Donowitz M. Cloning and sequencing of a rabbit cDNA encoding an intestinal and kidney-specific Na⁺/H⁺ exchanger isoform (NHE-3). *J Biol Chem*. 1992;267:9340–9346.
4. Girardi AC, Di Sole F. Deciphering the mechanisms of the Na⁺/H⁺ exchanger-3 regulation in organ dysfunction. *Am J Physiol Cell Physiol*. 2012;302:C1569–C1587.
5. Johansson S, Rosenbaum DP, Knutsson M, Leonsson-Zachrisson M. A phase 1 study of the safety, tolerability, pharmacodynamics, and pharmacokinetics of tenapanor in healthy Japanese volunteers [published online ahead of print 2016]. *Clin Exp Nephrol*. doi:10.1007/s10157-016-1302-8.

6. Johansson S, Leonsson-Zachrisson M, Knutsson M, et al. Preclinical and healthy volunteer studies of potential drug-drug interactions between tenapanor and phosphate binders. *Clin Pharmacol Drug Dev.* 2017;6:448–456.
7. Chey WD, Lembo AJ, Phillips JA, Rosenbaum DP. Efficacy and safety of tenapanor in patients with constipation predominant irritable bowel syndrome: a 12-week, double-blind, placebo-controlled, randomized phase 2b trial. *Gastroenterol.* 2015;148(suppl 1):S191–S192.
8. Zielinska M, Wasilewski A, Fichna J. Tenapanor hydrochloride for the treatment of constipation-predominant irritable bowel syndrome. *Expert Opin Investig Drugs.* 2015;24:1093–1099.
9. Shemin D, Dworkin LD. Sodium balance in renal failure. *Curr Opin Nephrol Hypertens.* 1997;6:128–132.
10. Spencer AG, Greasley PJ. Pharmacologic inhibition of intestinal sodium uptake: a gut centric approach to sodium management. *Curr Opin Nephrol Hypertens.* 2015;24:410–416.
11. Block GA, Rosenbaum DP, Leonsson-Zachrisson M, et al. Effect of tenapanor on interdialytic weight gain in patients on hemodialysis. *Clin J Am Soc Nephrol.* 2016;11:1597–1605.
12. Stefansson BV, Rosenbaum DP, Greasley PJ, Leonsson-Zachrisson M, Langkilde A-M. A phase 2 study on the effect of tenapanor on albuminuria in patients with T2DM and CKD. *J Am Soc Nephrol.* 2015;26:239A.
13. Labonté ED, Carreras CW, Leadbetter MR, et al. Gastrointestinal inhibition of sodium-hydrogen exchanger 3 reduces phosphorus absorption and protects against vascular calcification in CKD. *J Am Soc Nephrol.* 2015;26:1138–1149.
14. Block GA, Rosenbaum DP, Leonsson-Zachrisson M, et al. Effect of tenapanor on serum phosphate in patients receiving hemodialysis. *J Am Soc Nephrol.* 2017. doi:10.1681/ASN.2016080855.
15. Food and Drug Administration. Guidance for industry: food-effect bioavailability and fed bioequivalence studies. 2002. <http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126833.pdf>. Accessed March 17, 2015.
16. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. *Scand J Gastroenterol.* 1997;32:920–924.
17. Pierce D, Hossack S, Robinson A, Zhang P, Martin P. Assessment of pharmacodynamic equivalence and tolerability of lanthanum carbonate oral powder and tablet formulations: a single-center, randomized, open-label, 2-period crossover study in healthy subjects. *Clin Ther.* 2012;34:1290–1300.
18. Di Marco M, Marier JF, Ducharme MP, et al. Pharmacodynamic equivalence of two orlistat capsule formulations in healthy volunteers under fed conditions. *Int J Clin Pharmacol Ther.* 2008;46:319–326.
19. Kumar S, Monif T, Arora R, et al. The pharmacodynamic equivalence of Orlistat 60 mg capsule. An open label, balanced, randomized, multiple-dose, cross-over pharmacodynamic end-point bioequivalence study in healthy, adult, human Asian Indian subjects under fed conditions. *Clin Res Reg Aff.* 2013;30:55–62.
20. Li S. Pharmacodynamic bioequivalence testing. *J Clin Pharm Ther.* 2012;37:497–498.
21. Lee S, Chung JY, Hong KS, et al. Pharmacodynamic comparison of two formulations of Acarbose 100-mg tablets. *J Clin Pharm Ther.* 2012;37:553–557.
22. Zachos NC, Tse M, Donowitz M. Molecular physiology of intestinal Na⁺/H⁺ exchange. *Annu Rev Physiol.* 2005;67:411–443.
23. Donowitz M, Li X. Regulatory binding partners and complexes of NHE3. *Physiol Rev.* 2007;87:825–872.
24. Eutamene H, Charmot D, Navre M, Bueno L. Visceral antinociceptive effects of RDX5791, a first-in-class minimally systemic NHE3 inhibitor on stress-induced colorectal hypersensitivity to distension in rats. *Gastroenterology.* 2011;140:S-57–S-58.
25. Ardelyx. An 8-week study to evaluate tenapanor in the treatment of hyperphosphatemia in end-stage renal disease patients on hemodialysis (ESRD-HD). ClinicalTrials.gov. <https://clinicaltrials.gov/ct2/show/NCT02675998>. Accessed December 8, 2016.
26. Ardelyx. A 12-week study with a 4-week randomized withdrawal period to evaluate the efficacy and safety of tenapanor for the treatment of IBS-C (T3MPO-1). ClinicalTrials.gov. <https://clinicaltrials.gov/ct2/show/NCT02621892>. Accessed December 14, 2016.
27. Ardelyx. A 26-week study to evaluate the efficacy and safety of tenapanor in IBS-C (T3MPO-2). ClinicalTrials.gov. <https://clinicaltrials.gov/ct2/show/NCT02686138>. Accessed December 14, 2016.