TH-PO655

# A phase 2 study on the effect of tenapanor on albuminuria in patients with type 2 diabetes mellitus and chronic kidney disease

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## Overview and conclusions

- Tenapanor is a first-in-class inhibitor of the sodium/hydrogen exchanger isoform 3 (NHE3, also known as SLC9A3) that reduces uptake of intestinal sodium and phosphate.
- Tenapanor is being developed for renal and constipation-related indications.
- This phase 2, placebo-controlled study was designed to evaluate whether treatment with tenapanor could reduce proteinuria in patients with type 2 diabetes mellitus (T2DM), moderate renal impairment (chronic kidney disease [CKD] stage 3) and albuminuria (urinary albumin-to-creatinine ratio [UACR] > 200 mg/g) receiving renin–angiotensin–aldosterone system (RAAS) inhibitors.
- The tolerability profile of tenapanor was consistent with previous studies, with diarrhea reported more frequently by patients receiving tenapanor than those receiving placebo.
- The pharmacodynamic effects of tenapanor were confirmed, as shown by softer stool consistency, increased frequency of bowel movements and numerically reduced urinary sodium and phosphorus excretion following tenapanor treatment.
- The observed pharmacodynamic effects did not translate into effects on albuminuria.
  - There was no significant change in UACR from baseline to week 12 in patients receiving tenapanor compared with those receiving placebo (primary endpoint).

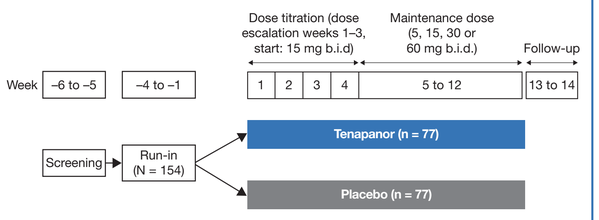
## Background

- Patients with T2DM and CKD are typically treated with RAAS inhibitors to slow the decline in renal function.
  - The effectiveness of RAAS inhibition is limited by high sodium intake.[1]
- Tenapanor (AZD1722, RDX5791), a small molecule with minimal systemic availability, is an NHE3 inhibitor that reduces absorption of sodium and phosphate from the gut.[2,3] (See Block *et al.*[4] oral presentation and other posters[5,6] at this meeting.)
- This trial evaluated the effects of tenapanor on albuminuria levels (an increase in which is associated with renal function decline) in patients with T2DM and CKD stage 3 who were receiving RAAS inhibitors.

## Methods

- This was a phase 2, multicenter, randomized, placebo-controlled, 12-week study (ClinicalTrials.gov identifier: NCT01847092) in patients with a UACR of 200–3500 mg/g (Figure 1).

**Figure 1. Study design.**




Tenapanor (as tenapanor hydrochloride) was administered orally just before breakfast and dinner. Doses could be escalated stepwise from 15 mg b.i.d. in week 1 to 30 mg b.i.d. in week 2 then to 60 mg b.i.d. in week 3, based on tolerability. Doses could also be maintained or down-titrated stepwise to as low as 5 mg b.i.d. according to gastrointestinal tolerability during the first 4 weeks. The dose achieved after titration was maintained for the remainder of the treatment period.
b.i.d., twice daily.

- Key inclusion criteria were:
  - estimated glomerular filtration rate (eGFR) of 25–70 mL/min/1.73 m$^2$
  - systolic blood pressure (BP) of 130–180 mmHg
  - diagnosis of T2DM and current use of at least one glucose-lowering medication
  - treatment with an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker for at least 3 months before randomization.
- The starting dose of tenapanor hydrochloride was 15 mg twice daily (b.i.d.). This was titrated over 4 weeks (5–60 mg b.i.d.) based on gastrointestinal tolerability; the optimal dose was then maintained for 8 weeks.
- The primary endpoint was the change in UACR from baseline to week 12 with tenapanor vs placebo.
- Other assessments included:
  - eGFR and BP monitoring
  - 24-hour urinary sodium and phosphorus excretion
  - stool frequency and consistency (as measured by the Bristol Stool Form Scale[7]).
- This study was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent.

## Results

### Patients

- A total of 154 patients were randomly assigned to treatment: 77 patients to tenapanor and 77 to placebo (Table 1).
  - The mean age of study participants was 65 years and the majority were men (68%).
  - Fewer patients receiving tenapanor (n = 51) completed the study compared with those receiving placebo (n = 66).

### Efficacy evaluations

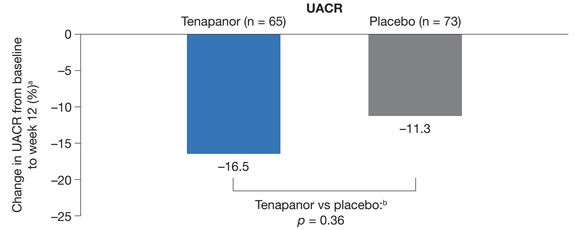
- Reductions in UACR from baseline to week 12 were numerically greater with tenapanor than placebo (16.5% vs 11.3%, respectively), though the difference was not significant ($p$ = 0.36; Figure 2).
  - *Post hoc* analyses of subgroups (completers, 5 mg b.i.d. vs 15–60 mg b.i.d., or patients without diarrhea) did not reveal any relevant effects on UACR.

**Table 1. Patient disposition, demographics and baseline characteristics.**

| | Tenapanor (n = 77) | Placebo (n = 77) |
|---|---|---|
| Disposition | | |
| Randomized, n (%) | 77 (100.0) | 77 (100.0) |
| Completed, n (%) | 51 (66.2) | 66 (85.7) |
| Demographics | | |
| Age, years | 65.6 ± 8.8 | 64.6 ± 8.8 |
| Men, n (%) | 52 (67.5) | 52 (67.5) |
| White, n (%) | 53 (68.8) | 53 (68.8) |
| BMI, kg/m$^2$ | 33.2 ± 5.3 | 34.3 ± 6.5 |
| Duration of T2DM, years | 16.1 ± 9.2 | 17.7 ± 9.6 |
| Baseline characteristics | | |
| UACR, mg/g | 1205.4 ± 886.6 | 1051.7 ± 926.5 |
| eGFR, mL/min/1.73 m$^2$ | 41.6 ± 9.6 | 45.1 ± 15.4 |
| Serum creatinine, mg/dL | 1.8 ± 0.4 | 1.7 ± 0.5 |
| Urinary sodium, mmol/day | 182.2 ± 80.9 | 189.2 ± 85.3 |
| Urinary phosphorus, mmol/day | 27.4 ± 14.7 | 24.6 ± 11.6 |
| Mean sitting systolic BP, mmHg | 146.2 ± 13.1 | 146.4 ± 12.0 |
| Mean sitting diastolic BP, mmHg | 78.3 ± 9.7 | 78.4 ± 11.2 |
| Mean 24-h ambulatory systolic BP, mmHg | 141.4 ± 13.4 | 138.8 ± 12.4 |
| Mean 24-h ambulatory diastolic BP, mmHg | 75.0 ± 11.0 | 71.1 ± 9.5 |
| Mean weekly stool consistency, BSFS score | 4.0 ± 1.0 | 4.0 ± 1.2 |
| Mean weekly stool frequency, stools per day | 1.3 ± 0.7 | 1.6 ± 1.1 |
| Prior diuretics | | |
| Thiazide diuretic, n (%) | 30 (39.0) | 28 (36.4) |
| Loop diuretic, n (%) | 28 (36.4) | 35 (45.5) |

Unless otherwise stated, data are shown as mean ± standard deviation.
BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; T2DM, type 2 diabetes mellitus; UACR, urinary albumin-to-creatinine ratio.

**Figure 2. The reduction in UACR in patients receiving tenapanor vs placebo from baseline to week 12 (primary endpoint).**




[a]LS geometric mean ratio of week 12/baseline as percentage reduction.
[b]LS geometric mean ratio percentage of week 12/baseline: tenapanor, 83.6; placebo, 88.7; LS geometric mean ratio of tenapanor vs placebo (95% confidence interval): 94.1 (68.1, 130.1), $p$ = 0.36.
LS, least-squares; UACR, urinary albumin-to-creatinine ratio.

- Tenapanor had no observed effect on systolic or diastolic BP, mean 24-hour ambulatory BP or eGFR.
- Tenapanor treatment resulted in numerical reductions in urinary sodium and phosphorus excretion, as well as a softer consistency and increased frequency of stool, compared with placebo (Figure 3).
  - Notably, daily sodium chloride intake was about 11 g, approximately double the recommended intake in this population.[8]

### Safety and tolerability

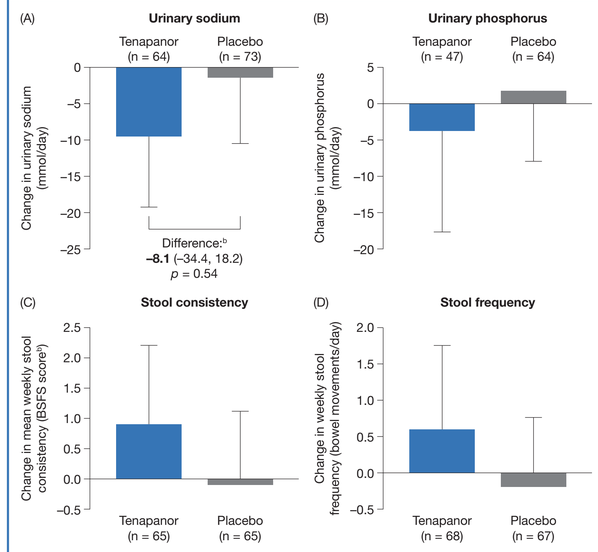
- Adverse events (AEs) were reported by more patients receiving tenapanor than on placebo (n = 62 [81%] vs n = 48 [62%]; Table 2).
  - Diarrhea was the most common AE (51 [66%] patients receiving tenapanor vs five [7%] receiving placebo).
  - The majority of the diarrhea reports were considered treatment-related (45 patients [58%] receiving tenapanor vs four [5%] receiving placebo).
- Serious AEs were reported by six patients receiving tenapanor and four receiving placebo, the most common of which was hyperkalemia (one patient in each treatment group; one patient receiving tenapanor also experienced a serious AE of increased blood potassium).

**Table 2. Summary of adverse events.**

| | Tenapanor (n = 77) | Placebo (n = 77) |
|---|---|---|
| Any AE | 62 (80.5) | 48 (62.3) |
| Treatment-related AE[a] | 46 (59.7) | 13 (16.9) |
| Serious AE[b] | 6 (7.8) | 4 (5.2) |
| AE leading to discontinuation | 20 (26.0) | 3 (3.9) |
| Specific AEs by preferred term[c] | | |
| Diarrhea | 51 (66.2) | 5 (6.5) |
| Nasopharyngitis | 2 (2.6) | 5 (6.5) |
| Blood glucose increased | 1 (1.3) | 5 (6.5) |
| Hypoglycemia | 2 (2.6) | 4 (5.2) |
| Influenza | 4 (5.2) | 2 (2.6) |
| Nausea | 5 (6.5) | 1 (1.3) |
| Blood creatinine increased | 3 (3.9) | 2 (2.6) |
| Blood creatinine phosphokinase increased | 0 | 5 (6.5) |
| Cough | 3 (3.9) | 2 (2.6) |
| Hyperglycemia | 3 (3.9) | 2 (2.6) |
| Upper respiratory tract infection | 3 (3.9) | 2 (2.6) |

Values are numbers of individuals experiencing at least one treatment-emergent event, n (% of treatment group).
[a]As judged by the investigator.
[b]Serious AEs experienced by patients receiving tenapanor included one report each of hyperkalemia, ataxia, increased blood potassium levels, coronary artery disease, deep vein thrombosis, acute renal failure and rhabdomyolysis; serious AEs experienced by patients receiving placebo included one report each of hyperkalemia, congestive heart failure, colon adenoma, generalized edema and thrombophlebitis. Note that a patient could have more than one serious AE.
[c]AEs reported by five or more participants.
AE, adverse event.

**Figure 3. The pharmacodynamic effects on urinary sodium (A) and urinary phosphorus (B) excretion, stool consistency (C) and daily stool frequency (D) in patients receiving tenapanor vs placebo from baseline to week 12.**




Data for urinary sodium are shown as LS mean (LS standard error).
Data for urinary phosphorus, stool consistency and bowel movements per day are shown as mean (standard deviation).
[a]Difference = tenapanor – placebo, given as LS mean (95% confidence interval).
[b]Stool consistency rated at each bowel movement from 1 (hard) to 7 (liquid) according to the BSFS.[7]
BSFS, Bristol Stool Form Scale; LS, least-squares.

- Discontinuation of study drug due to AEs occurred in 20 patients receiving tenapanor vs three receiving placebo and was commonly due to diarrhea (15 patients receiving tenapanor vs none receiving placebo).
- AEs other than diarrhea were balanced between the groups.
- With the exception of a reduction in urinary phosphorus, there were no clinically meaningful changes in serum or urinary electrolytes.

## References

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## Disclosures

BS, MLZ and AML are employees of AstraZeneca; DPR is an employee of and has ownership interest in Ardelyx Inc.; PJG is an employee of and has ownership interest in AstraZeneca.

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