Clinical Kidney Journal, 2024, vol. 17, no. 1, 1–9

https://doi.org/10.1093/ckj/sfad216
Advance Access Publication Date: 11 October 2023
Original Article

ORIGINAL ARTICLE

Tenapanor in Chinese ESRD patients with hyperphosphatemia on haemodialysis: a randomised, phase 3 trial

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ABSTRACT

Background. The efficacy and safety of tenapanor has not been confirmed in Chinese end-stage renal disease (ESRD) patients with hyperphosphatemia on haemodialysis (HD).

Methods. This was a randomised, double blind, phase 3 trial conducted at 26 dialysis facilities in China (https://www.chictr.org.cn/index.aspx; CTR20202588). After a 3-week washout, adults with ESRD on HD with hyperphosphatemia were randomised (1:1) using an interactive web response system to oral tenapanor 30 mg twice a day or placebo for 4 weeks. The primary endpoint was the change in mean serum phosphorous level from baseline to the endpoint visit (day 29 or last serum phosphorus measurement). Efficacy was analysed in the intention-to-treat population. Safety was assessed in all patients who received at least one dose of the study drug.

Received: 19.6.2023; Editorial decision: 23.8.2023

Results. Between 5 March 2021 and 8 June 2022, 77 patients received tenapanor and 73 received placebo. Tenapanor treatment ($n = 75$) resulted in a significantly greater least squares (LS) mean reduction in serum phosphate at the endpoint visit versus placebo ($n = 72$): LS mean difference −1.17 mg/dl (95% CI −1.694 to −0.654, $P < .001$). More patients receiving tenapanor achieved a serum phosphorous level <5.5 mg/dl at the endpoint visit (44.6% versus 10.1%). The most common treatment-related adverse event was diarrhoea [tenapanor 28.6% (22/77), placebo 2.7% (2/73)], which was mostly mild and led to treatment discontinuation in two patients receiving tenapanor.
Conclusions. Tenapanor significantly reduced the serum phosphorous level versus placebo in Chinese ESRD patients on HD and was generally well tolerated.

Keywords: dialysis, end-stage renal disease, hyperphosphatemia, sodium/hydrogen exchanger isoform 3, tenapanor

INTRODUCTION

Chronic kidney disease (CKD) is a leading global public health problem, the burden of which is expected to increase in the future [1]. CKD is progressive and many individuals with this condition will progress to end-stage renal disease (ESRD), which requires renal replacement therapy [haemodialysis (HD), peritoneal dialysis (PD) or kidney transplant] and is a leading cause of mortality globally [2]. The incidence and prevalence of ESRD is increasing and by 2030 an estimated 5.439 million people worldwide will require renal replacement therapy, with 2.162 million living in Asia [2]. In China, the prevalence of CKD is ≈10.8% [1] and is increasing, largely driven by the rising prevalence of type 2 diabetes in recent decades [3]. In 2014, almost 400 000 patients with ESRD in China underwent HD [4].

Patients with ESRD experience dysregulation of calcium and phosphorus metabolism, resulting in elevated parathyroid hormone (PTH) and serum phosphorous and low serum calcium [5]. The prevalence of hyperphosphatemia in Chinese patients undergoing dialysis, based on the Kidney Disease: Improving Global Outcomes criteria, is as high as 76% [6]. Hyperphosphatemia is an independent risk factor for mortality in patients with CKD, with the risk of death increasing by 18% for every 1 mg/dl increase in serum phosphorous level [7]. Therapeutic interventions to manage hyperphosphatemia include restricting dietary phosphate intake, adapting dialysis and drug therapy [8]. Phosphate binders are the mainstay of pharmacologic therapy for hyperphosphatemia in patients with CKD [8]. Oral phosphate binders commonly used in China include sevelamer and lanthanum carbonate [6]. However, despite the wide availability of these oral phosphate binders, only ≈40% of Chinese patients with CKD undergoing dialysis have serum phosphorous levels within the suggested targets of the Kidney Disease Outcomes Quality Initiative guideline [6]. In addition, the use of sevelamer and lanthanum may be limited by adverse gastrointestinal reactions [8]. Furthermore, the natural ores used in metal-based phosphate binders can be contaminated, and their accumulation, while not acutely toxic, has unknown long-term effects in patients with no or limited renal function [8].

Tenapanor is an oral, minimally absorbed inhibitor of intestinal sodium–hydrogen exchanger isoform 3 (NHE3) that reduces the absorption of phosphate in the gastrointestinal tract [9]. Tenapanor was approved for the treatment of irritable bowel syndrome with constipation by the US Food and Drug Administration in 2019 [10]. In phase 3 trials conducted in the USA, twice daily (BID) tenapanor significantly reduced elevated serum phosphorous levels in patients with CKD receiving maintenance dialysis compared with placebo [11]. In addition, tenapanor is well tolerated, with adverse events largely limited to diarrhoea, which is related to its mechanism of action (increasing stool sodium and hence water content) [12]. Although tenapanor has been investigated in clinical trials in the USA and Japan, its phosphate-lowering efficacy and safety has not been confirmed in a Chinese patient population.

The present study was undertaken to investigate the efficacy and safety of tenapanor for the treatment of hyperphosphatemia in Chinese ESRD patients undergoing HD.

MATERIALS AND METHODS

Study design and patients

This randomised, double blind, placebo-controlled phase 3 trial was conducted at 26 dialysis facilities in China between 5 March 2021 and 8 June 2022. The study had a 9-week duration, consisting of a washout period of 1–3 weeks before randomisation, a 4-week treatment period and a 2-week follow-up period (Supplementary Fig. 1). The study protocol was approved by the Ethics Review Board of Peking University People's Hospital (approval 2020PHA046-001) and the study was conducted following the principles outlined in the Declaration of Helsinki and subsequent amendments and the International Conference on Harmonization Good Clinical Practice guidelines. All participants provided written, informed consent before inclusion.

The study included adults (≥18–≤80 years of age) with ESRD who had received maintenance HD three times a week for ≥3 months, had received ≥3 weeks of phosphate binder therapy with a stable dose for 3 weeks and had serum phosphorous levels of 4.0–7.0 mg/dl and who were able to maintain a consistent dialysis regimen for the duration of the trial. Following the 1- to 3-week washout period, eligible patients were required to have a ≥1.5 mg/dl increase in serum phosphate and an absolute serum phosphorous level of 9.0–10.0 mg/dl (after 1 week of washout) or 6.0–10.0 mg/dl (after 2 or 3 weeks of washout). Additional inclusion criteria included stable vascular access, a fractional urea clearance (Kt/V) ≥1.2 measured <3 months before screening and serum calcium levels at screening >8.40 mg/dl. Patients receiving either vitamin D or calcimimetic were required to have maintained the dose level for 4 weeks prior to the screening period and throughout the study.

Key exclusion criteria included serum calcium level <8.0 mg/dl or >11.0 mg/dl after the washout period, serum intact parathyroid (iPTH) >1200 pg/ml, persistent metabolic acidosis with serum carbon dioxide binding capacity or serum bicarbonate <18 mmol/l on two consecutive measurements, clinical signs of hypovolaemia at the time of randomisation, a history of inflammatory bowel disease or diarrhoea-type irritable bowel syndrome, diarrhoea or loose stools within 1 week prior to randomisation (defined as three or more bowel movements for ≥2 days with a Bristol Stool Form Scale ≥6) [13], planned kidney transplantation during the study period, switching to PD or home HD, hepatic dysfunction, any active

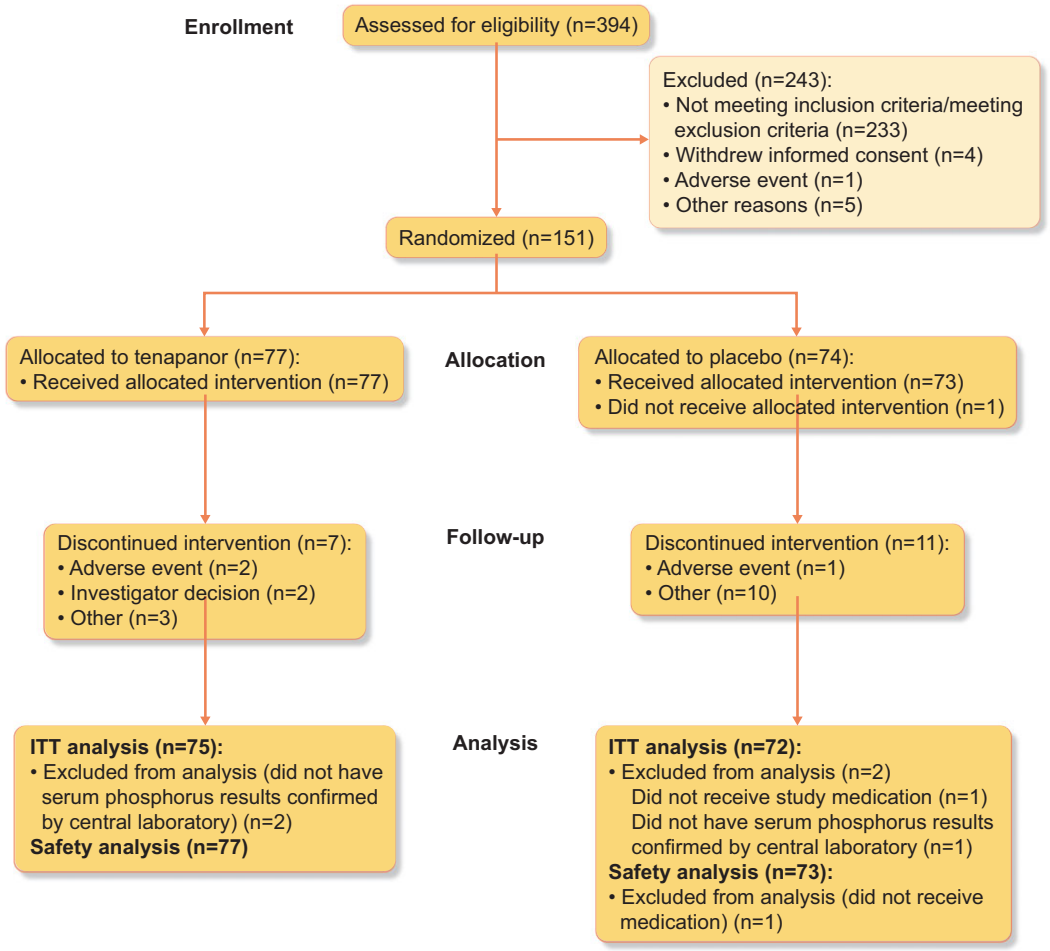


Figure 1. Patient flow diagram.

infection requiring systemic therapy within 3 weeks prior to the first dose of tenapanor and life expectancy <6 months.

Randomisation and masking

After the washout period, eligible patients were randomised (1:1) to tenapanor or placebo for 4 weeks. Randomization was implemented centrally using a randomization table with a block size of 4 and was managed via an interactive web response system. Randomization was not stratified. Investigators assigned patients consecutively in the order of screening and a unique treatment code was used to designate the subject's treatment allocation. The investigators and patients were blinded to treatment allocation. Tenapanor and placebo tablets had an identical appearance and packaging to facilitate treatment masking. An unblinded list of treatment groups was provided to the Drug Safety Department. All patients were asked about gastrointestinal tolerability at each study visit to maintain blinding.

Procedures

All patients assigned to the tenapanor group initiated oral tenapanor at 30 mg BID and the dose could be reduced to 20 or 10 mg BID in a stepwise manner based on gastrointestinal tolerability and serum phosphorous level and adjusted up again at the discretion of the investigator. Study medication and placebo were administered as three tablets (10 mg) before breakfast and dinner (six tablets in total) except for treatment day 1, on which three tablets were received once before dinner. On the day of dialysis, patients did not take the study medication with the meal before dialysis, but before another meal on that day. Treatment was continued for 4 weeks or until patients met any of the following pre-specified conditions, at the investigator's discretion: serum phosphorous level ≤2.5 mg/dl at any time point or ≥10.0 mg/dl at week 2 or later after randomisation, serum bicarbonate level (or carbon dioxide concentration) <14 mmol/l despite medication or dialysate adjustment or serum calcium level ≤7.6 mg/dl at any time point or withdrawal of consent.

Study assessments during the treatment period were conducted after a short dialysis interval and pre-dialysis. Blood samples for measurement of serum phosphorous levels for the primary endpoint were taken on day 1 of treatment and at the final visit of the treatment period and sent to a central laboratory for testing. All other measurements of serum phosphate, as well as serum bicarbonate and iPTH, were conducted at local laboratories on blood samples taken before dialysis.

Outcomes

The primary study endpoint was the difference in the change of the mean serum phosphorous level from baseline to the

Table 1: Patient demographics and disease characteristics (intention-to-treat and safety population)

Characteristics	Tenapanor ($n = 75$)	Placebo ($n = 72$)
Asian, *n* (%)	75 (100)	72 (100)
Age (years)	53 (10.9)	54 (11.3)
Male, *n* (%)	44 (58.7)	45 (62.5)
Height (cm)	166.7 (7.99)	166.8 (8.25)
Pre-dialysis body weight (kg)	66.42 (10.738)	65.67 (11.954)
Body mass index (kg/m^2)	23.80 (3.486)	23.28 (2.975)
Serum phosphate (mg/dl)	7.39 (1.620)	7.42 (1.404)
Concomitant medication use[a], *n* (%)	77 (100)	73 (100)
Phosphorus binders (during follow-up period)		
Lanthanum carbonate	7 (9.1)	8 (11.0)
Sevelamer carbonate	6 (7.8)	14 (19.2)
Calcium acetate	0	3 (4.1)
Calcium carbonate	1 (1.3)	1 (1.3)
Vitamin D and its analogues		
Calcitriol	42 (54.5)	36 (49.3)
Alfacalcidol	8 (10.4)	9 (12.3)
Paricalcitol	18 (23.4)	13 (17.8)
Cholecalciferol	2 (2.6)	1 (1.4)
Calcium-sensing receptor agonists		
Cinacalcet hydrochloride	21 (27.3)	21 (28.8)

Data are presented as mean (SD) unless stated otherwise.
[a]Concomitant medication use was analysed in the safety population.

endpoint visit (week 4 of treatment or at the time of early between treatment groups discontinuation). Secondary endpoints were the change in the mean serum phosphorous level from baseline to the endpoint visit in each treatment group, the proportion of patients who achieved a serum phosphorous level <5.5 mg/dl during the 4-week treatment period, the change in iPTH from baseline to the endpoint visit and safety.

Demographic data collected at baseline included patient ethnicity (self-reported), age and sex. Safety assessments included recording of treatment-emergent adverse events (TEAEs; defined as AEs that occurred or worsened between the first dose of study medication and the final follow-up), stool profile and frequency using the Bristol Stool Form Scale [13], clinical laboratory tests, pre-dialysis body weight, vital signs, 12-lead electrocardiogram and physical examination. Treatment compliance and the use of concomitant medications were also recorded. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Statistics

Based on a pooled analysis of patients receiving tenapanor 30, 10 or 3 mg BID in a prior phase 2 trial [11], it was estimated that the mean change in serum phosphorous level from baseline to 4 weeks would be 1.64 mg/dl [standard deviation (SD) 1.856] with tenapanor and 0.58 mg/dl (SD 1.802) with placebo. Assuming a two-sample *t*-test allowing unequal variance with a one-sided alpha of 0.025, enrolment of 128 subjects (64 in each group) would provide 90% power to show that tenapanor is superior to placebo for the primary endpoint. Therefore, accounting for a predicted dropout of 20% based on previous trials, the final enrolment target was set at 160 patients (80 patients in each treatment group).

Efficacy was evaluated in all patients who met the inclusion criteria, received at least one dose of study drug and had at least one serum phosphate assessment during the 4-week treatment period [intention-to-treat (ITT) population]. The primary efficacy endpoint was also evaluated per protocol (PP) in all randomised patients who completed the 4-week treatment period or discontinued treatment early without major protocol violations. Safety was evaluated in all patients who received at least one dose of the study drug. Missing data for the primary efficacy endpoint were imputed using the last observation carried forward. If a patient was lost to follow-up, no further imputation was performed after the last contact date. No imputation was performed for missing safety or secondary efficacy data.

The primary efficacy endpoint was evaluated by estimating least squares (LS) mean changes in the serum phosphorous level from baseline and the corresponding 95% confidence intervals (CIs). Treatment differences in the primary and secondary efficacy variables were compared using an analysis of covariance (ANCOVA) model with study centre and serum phosphorous level at baseline as covariates and treatment group as the independent variable. Sensitivity analyses were performed for the primary efficacy endpoint using a mixed model for repeated measures with study centre, treatment group, visit and treatment–visit interaction as fixed factors, baseline as a covariate and patient as a random effect. Treatment adherence was calculated as each patient's actual cumulative dose/the planned cumulative dose × 100. Categorical data were summarized using frequencies and percentages and continuous data were summarized using mean (SD) or median (minimum–maximum). All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). The study was registered at https://www.chictr.org.cn/index.aspx (ChiCTR2300068249) and http://www.chinadrugtrials.org.cn/index.html (CTR20202588).

RESULTS

Between 5 March 2021 and 8 June 2022, a total of 394 patients were screened, of whom 151 met the inclusion criteria and were randomised to treatment. Of these patients, 150 received at least one dose of study treatment and 147 were included in the ITT analysis (tenapanor, $n = 75$; placebo, $n = 72$) (Fig. 1). Baseline characteristics were well balanced between the treatment groups (Table 1). The mean adherence to the study drug was 99.3% (SD 5.09) in the tenapanor group and 98.7% (SD 2.91) in the placebo group. The patients' medical history is summarized in Supplementary Table 2.

Among patients receiving tenapanor, a reduction in serum phosphorous level from baseline was observed at day 8 and maintained until day 29 (Fig. 2A). Patients receiving tenapanor achieved a significantly greater LS mean reduction in serum phosphorous level from baseline to the endpoint visit compared with placebo [−1.50 mg/dl (95% CI −1.902 to −1.098) versus −0.33 mg/dl (95% CI −0.725–0.073)] (Table 2). The primary study endpoint was met, with a statistically significant LS mean difference in the reduction of the serum phosphorous level from baseline to the endpoint visit between the tenapanor and placebo groups [−1.17 mg/dl (95% CI −1.694 to −0.654), $P < .001$]. A similar result was observed in the PP analysis group (Supplementary Table 1). A higher proportion of patients receiving tenapanor achieved a serum phosphorous level <5.5 mg/dl on days 8, 15, 22 and 29 versus those receiving placebo (Fig. 2B).

Patients in the tenapanor group achieved a reduction in iPTH from baseline to day 29 (LS mean −16.2 pg/ml), whereas those in the placebo group had an increase in iPTH levels (LS mean 51.6 pg/ml). However, the between-group difference was not statistically significant (Table 2).

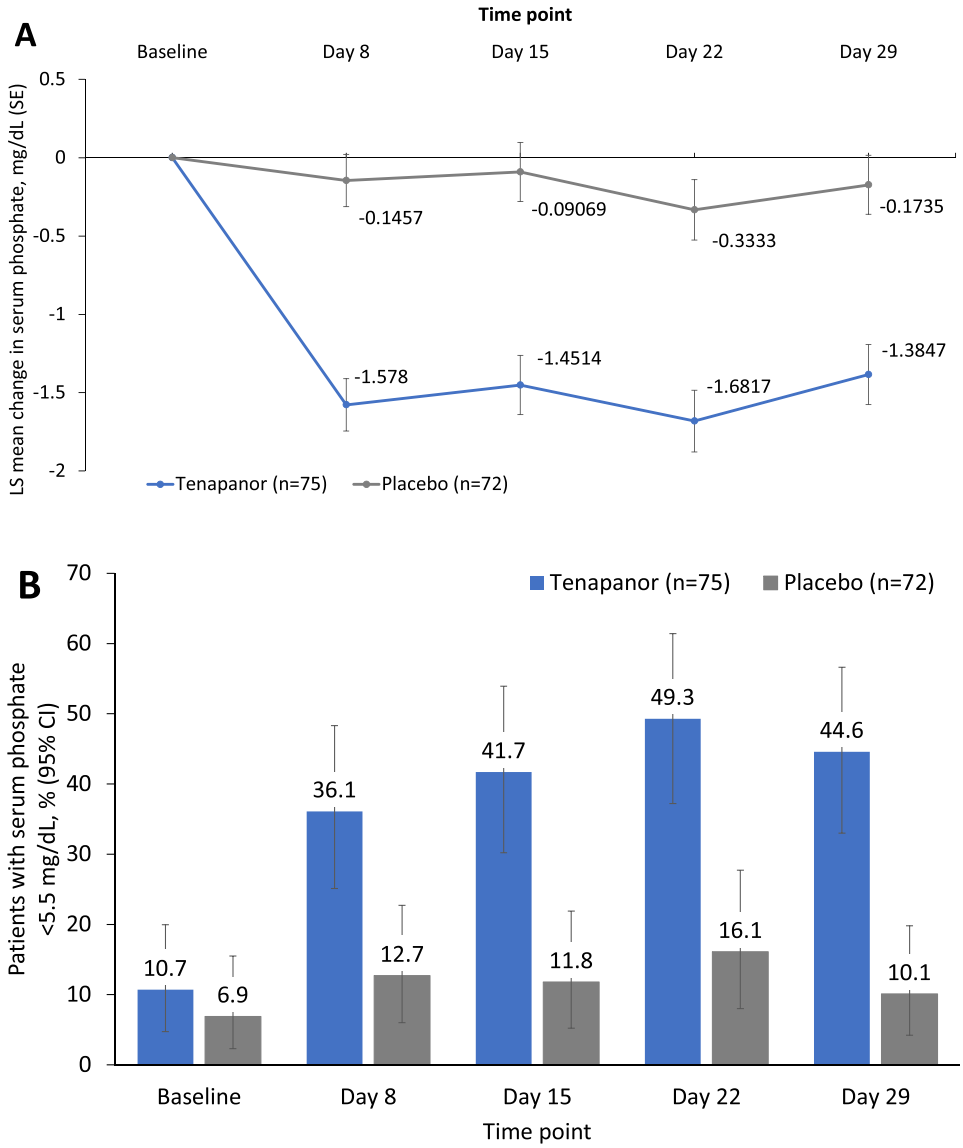


Figure 2. (A) LS mean change in serum phosphate levels over time (mixed effects model for repeated measures). **(B)** Proportion of patients achieving serum phosphate <5.5 mg/dl during the study (ITT population). SE: standard error.

Table 2: Efficacy endpoints (intention-to-treat population)

	Tenapanor (n = 75)	Placebo (n = 72)
Serum phosphate (mg/dl)		
Baseline	7.39 (1.620)	7.42 (1.404)
Day 29	5.99 (1.780)	7.22 (1.631)
LS mean change from baseline (95% CI)	−1.50 (−1.902 to −1.098)	−0.33 (−0.725 to 0.073)
LS mean change difference (95% CI)	−1.17 (−1.694 to −0.654)	
P-value[a]	<.001	
iPTH (pg/ml)		
Baseline	470.23 (291.270)	504.66 (310.216)
Day 29	440.60 (332.549)	555.76 (371.053)
LS mean change from baseline (95% CI)	−16.23 (−83.480 to 51.024)	51.60 (−14.934 to 118.144)
LS mean change difference (95% CI)	−67.83 (−155.435 to 19.770)	
P-value[a]	.128	

Data are presented as mean (SD) unless stated otherwise.
[a]P-value calculated using ANCOVA.

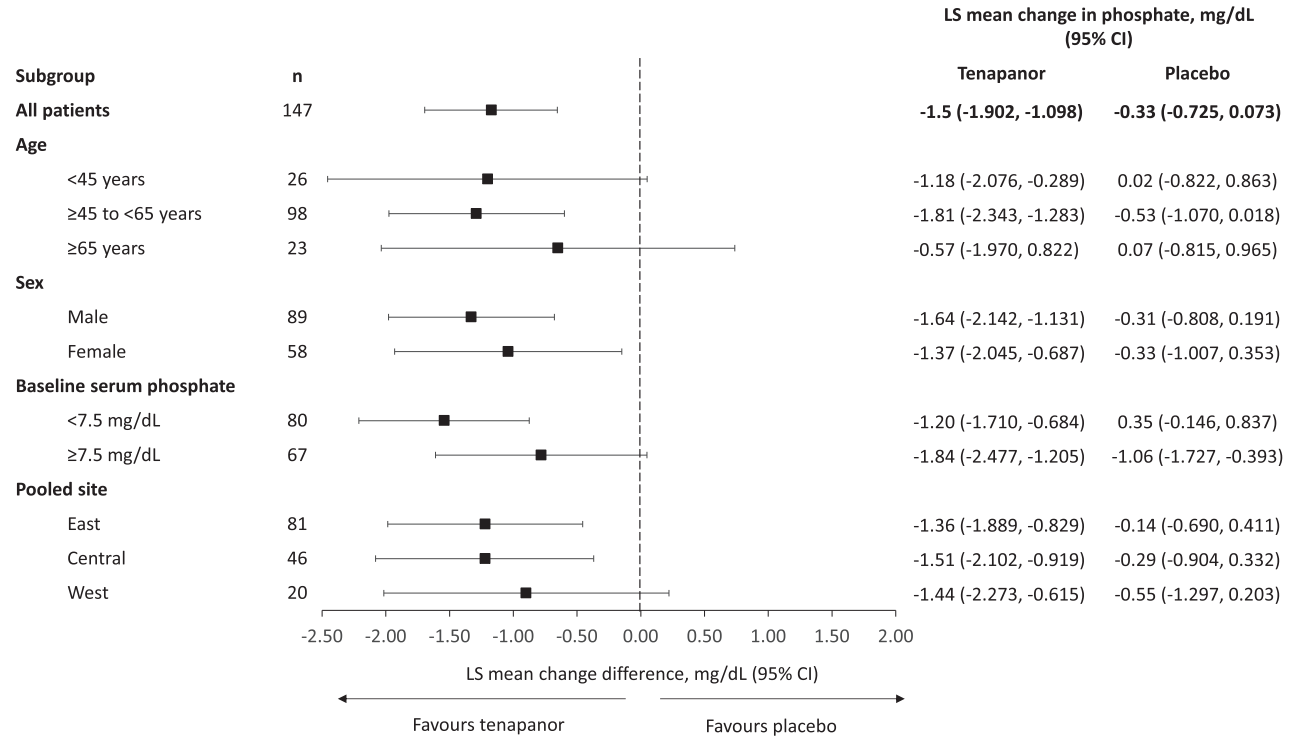


Figure 3. Subgroup analysis of LS mean change in serum phosphate from baseline (ITT population).

Subgroup analysis revealed a trend towards higher reductions in serum phosphorous levels across all subgroups for tenapanor versus placebo, consistent with the outcomes in the overall population (Fig. 3). However, the improvement in the reduction in serum phosphate only reached statistical significance in patients ≥45–<65 years of age, in both males and females, in patients with baseline serum phosphate <7.5 mg/dl and among patients enrolled at sites in eastern and central China.

The majority of TEAEs were gastrointestinal disorders, predominantly diarrhoea (Table 3). Among the patients with treatment-related diarrhoea, the majority of cases were mild [tenapanor: 13/22 (59.0%); placebo: 2/2 (100%)] or moderate (tenapanor: 7/22 [31.8%]; placebo: 0/2). Treatment discontinuation due to TEAEs occurred in two patients in the tenapanor group; both experienced diarrhoea considered related to treatment. One patient in the placebo group discontinued the study due to a TEAE considered unrelated to treatment (death from myocardial infarction). All serious AEs were considered unrelated to study treatment. The mean change in pre-dialysis body weight from baseline to the endpoint visit was comparable in the tenapanor and placebo treatment groups: −0.19 kg (0.899) and −0.18 kg (1.421).

Mean stool frequency was consistent from week 1 to 3 and decreased from week 4 to 5 in both the tenapanor and placebo groups (Fig. 4). The mean stool frequency was higher in the tenapanor group compared with the placebo group and more patients in the tenapanor group reported a Bristol Stool Form Scale of type 6 and 7 stools (Supplementary Fig. 2).

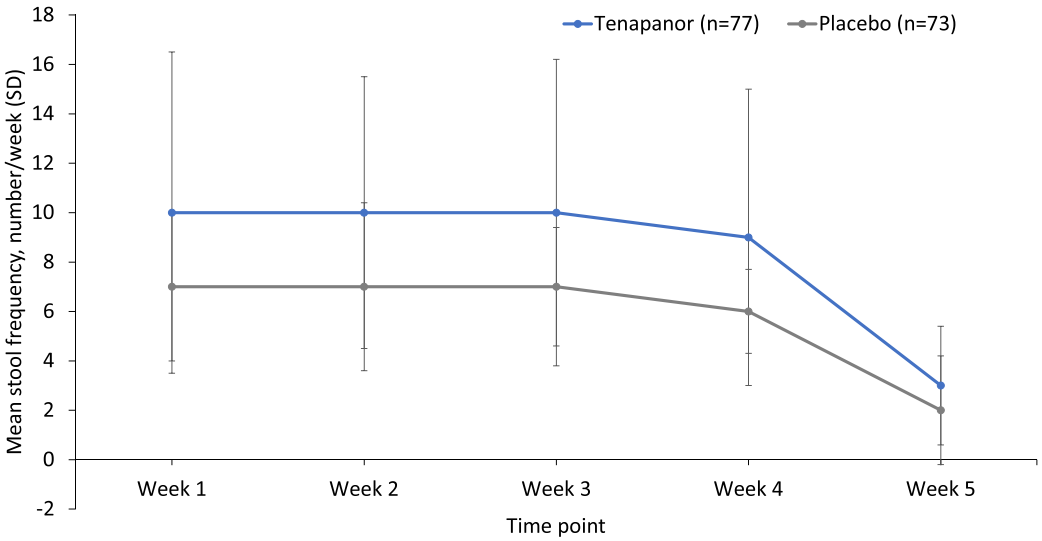
DISCUSSION

In this randomised, phase 3 trial, tenapanor 30 mg BID resulted in significantly greater reductions in serum

Table 3: Safety summary (safety population)

Characteristics	Tenapanor ($n = 77$)	Placebo ($n = 73$)
≥1 TEAE	40 (51.9)	30 (41.1)
Leading to discontinuation	2 (2.6)	1 (1.4)
Leading to treatment interruption	4 (5.2)	1 (1.4)
≥1 serious TEAE	2 (2.6)[a]	2 (2.7)[a]
≥1 treatment-related AE	27 (35.1)	6 (8.2)
Gastrointestinal disorders	24 (31.2)	2 (2.7)
Diarrhoea	22 (28.6)	2 (2.7)
Nausea	1 (1.3)	0
Abdominal pain	1 (1.3)	0
Metabolic and nutritional disorders	4 (5.2)	1 (1.4)
Metabolic acidosis	2 (2.6)	0
Hypophosphataemia	1 (1.3)	0
Hypercalcaemia	1 (1.3)	0
Hyperkalaemia	0	1 (1.4)
Skin and subcutaneous tissue disorders	0	2 (2.7)
Pruritus	0	2 (2.7)
Endocrine disorders	0	1 (1.4)
Secondary hyperparathyroidism	0	1 (1.4)
Investigations	0	1 (1.4)
Elevated α-hydroxybutyrate dehydrogenase	0	1 (1.4)
Psychiatric disorders	0	1 (1.4)
Insomnia	0	1 (1.4)

Data are presented as *n* (%).
Adverse events were coded using MedDRA version 25.0.
[a]Serious TEAEs in the tenapanor group were gastroenteritis and abdominal infection in one patient each and in the placebo group were spinal osteoarthritis (one patient) and acute myocardial infarction and gastrointestinal bleeding (both in one patient). None were considered related to treatment.



Patient number					
Tenapanor	77	74	74	73	22
Placebo	73	73	70	64	17

Figure 4. Bowel movement frequency (safety population).

phosphate compared with placebo in Chinese ESRD patients with hyperphosphatemia on HD. Tenapanor was generally well tolerated, with only 2.6% ($n = 2$) of patients who received tenapanor discontinuing treatment, both due to diarrhoea. No new safety signals were observed compared with previous trials of tenapanor in ESRD patients on HD conducted in the USA and Japan and, as expected, mild diarrhoea was the most common TEAE [11, 12, 14, 15].

Our efficacy findings are consistent with previous clinical trials conducted in the USA and Japan, which also showed tenapanor has a robust phosphate-lowering effect in CKD patients receiving HD [11, 12, 14, 15]. The reductions in iPTH observed with tenapanor 30 mg BID over 4 weeks in the present study were comparable to those reported in prior studies in the USA and Japan [11, 14]. The similarity of the findings in Chinese patients compared with those in the USA and Japan were expected based on the results of a phase 1 study conducted in China that found no effect of race/ethnicity on the pharmacokinetics of tenapanor (unpublished). Subgroup analysis results from the present study add to the findings of the US and Japanese trials and show similar reductions in serum phosphorous levels from baseline across multiple patient subgroups, including age, sex and baseline serum phosphorous level. This finding is comparable to a subgroup analysis of the ITT population included in the phase 3 PHREEDOM trial (NCT03427125), which showed more reductions in serum phosphate during a 12-week, double-blind, randomized withdrawal period with tenapanor versus placebo in all subgroups [15]. Although the improvement in the reduction in serum phosphate with tenapanor versus placebo only reached statistical significance in patients ≥45–<65 years, in both males and females, in patients with baseline serum phosphate <7.5 mg/dl and among patients enrolled at sites in eastern and central China in the present study, it should be noted that the patient numbers were relatively small in several of the subgroups.

Importantly, our safety findings show that tenapanor is generally well tolerated in the Chinese patient population, with a similar safety profile to that reported in studies conducted in the USA and Japan [11, 12, 14, 15]. Consistent with these prior trials, diarrhoea was the most common TEAE observed during tenapanor treatment, and the majority of cases were mild or moderate in severity and led to treatment discontinuation in only two patients. This safety profile is expected based on the mode of action of tenapanor, which increases stool sodium and water content and has been shown to lead to loose stool consistency and increased defecation frequency in healthy volunteers [10].

Although the clinical importance of reaching serum phosphate targets in CKD patients receiving dialysis is well understood, the current rate of achievement of these targets remains low [16]. This may be due to inherent limitations in the effectiveness of phosphate binders, which prevent absorption of phosphate from food and are associated with a high pill burden (often 9–12 or more tablets or capsules per day), often leading to poor compliance. Regulation of serum phosphorous levels depends on a complex pathway involving more than simply the net ingestion and excretion of phosphate [17–19]. As shown in the present study, tenapanor, which has a novel mechanism of action and reduces the absorption of phosphate in the gastrointestinal tract, can produce a remarkable reduction in serum phosphorous level and reduce the pill burden for patients requiring phosphate-lowering therapy [20]. Tenapanor can also be combined with phosphate binders to reduce phosphorus absorption synergistically and better manage serum phosphorous levels in CKD patients on dialysis [21, 22]. In addition, no significant drug interactions between phosphate binders and tenapanor have been observed in humans [23].

A key limitation of the present study is the relatively short 4-week duration of treatment and observation of safety, which precludes making conclusions about the long-term efficacy and safety of tenapanor. However, in the US phase 3 trial

and a 52-week randomised phase 3 trial (PHREEDOM) of tenapanor, patients receiving 30 mg BID achieved steady serum phosphate levels, suggesting a consistent effect with longer treatment [11, 15].

In conclusion, tenapanor resulted in significantly greater reductions in serum phosphorous levels from baseline to week 4 compared with placebo in Chinese ESRD patients with hyperphosphatemia receiving HD and was well tolerated with no new safety events observed. The phosphate-lowering effect of tenapanor was generally consistent across patient subgroups, including age, sex and baseline phosphate level. These results are consistent with findings from clinical trials conducted in the USA and Japan.

SUPPLEMENTARY DATA

Supplementary data are available at *CKJ* online.

ACKNOWLEDGEMENTS

The study protocol was approved by the Ethics Review Board of Peking University People's Hospital (approval 2020PHA046-001). We thank all the participants and investigators for supporting this study and appreciate the following for their enrolment contributions to the study: Feng Shi (Hebei Petrochina Central Hospital), Zhaohui Ni (Renji Hospital, Shanghai Jiao Tong University School of Medicine), Li Yao (First Hospital of China Medical University), Fanna Liu (First Affiliated Hospital of Jinan University), Yu Wang (First Affiliated Hospital of Nanchang University), Qiang Zhu (North China Petroleum Administration General Hospital), Deguang Wang (Second Affiliated Hospital of Anhui Medical University), Jialiang Pang (Xinxiang First People's Hospital), Ping Zhang (First affiliated Hospital, Zhejiang University School of Medicine), Deqiong Xie (Second People's Hospital of Yibin) and Jianqiang He (Affiliated Hospital of Jiangsu University). Editorial support for this manuscript was provided by Jake Burrell (Rude Health Consulting Ltd) and was paid for by Shanghai Fosun Pharmaceutical Development Co., Ltd.

AUTHORS' CONTRIBUTIONS

G.W., Y.Z. and L.Z. were responsible for the study conception and design. L.G., L.X., Y.X., L.Z., H.J., X.S., T.G., P.L., J.W., F.S., Z.G., M.G. and J.G. were responsible for data acquisition. W.Z. was responsible for data analysis. L.G., L.X., Y.X., L.Z., H.J., X.S., T.G., P.L., J.W., F.S., Z.G., M.G., J.G., G.W., Y.Z. and L.Z. were responsible for data interpretation. All authors reviewed the manuscript draft and approved the final version.

FUNDING

This study was funded by Wanbang Biopharmaceuticals, a member enterprise of Fosun Pharma.

DATA AVAILABILITY STATEMENT

The data are available from zuoli@bjmu.edu.cn. Requests for access will be reviewed by the corresponding authors to ensure that use of data protects the interests of the participants and researchers according to the terms of ethics approval and principles of equitable data sharing. Access to individual de-identified patient data will be made available following publication upon reasonable request.

CONFLICT OF INTEREST STATEMENT

G.W. and W.Z. are employees of Fosun Pharma. Y.Z. is employee of Wanbang Biopharmaceuticals. All other authors have declared no conflicts of interest.

REFERENCES

1. Zhang L, Wang F, Wang Li *et al*. Prevalence of chronic kidney disease in China: a cross-sectional survey. *Lancet* 2012;**379**:815–22. https://doi.org/10.1016/S0140-6736(12)60033-6.
2. Liyanage T, Ninomiya T, Jha V *et al*. Worldwide access to treatment for end-stage kidney disease: a systematic review. *Lancet* 2015;**385**:1975–82. https://doi.org/10.1016/S0140-6736(14)61601-9.
3. Zhang L, Long J, Jiang W *et al*. Trends in chronic kidney disease in China. *N Engl J Med* 2016;**375**:905–6. https://doi.org/10.1056/NEJMc1602469.
4. Li PK, Lui SL, Ng JK-C *et al*. Addressing the burden of dialysis around the world: a summary of the roundtable discussion on dialysis economics at the First International Congress of Chinese Nephrologists 2015. *Nephrology* 2017;**22**(Suppl 4):3–8. https://doi.org/10.1111/nep.13143.
5. Rastogi A, Bhatt N, Rossetti S *et al*. Management of hyperphosphatemia in end-stage renal disease: a new paradigm. *J Ren Nutr* 2021;**31**: 21–34. https://doi.org/10.1053/j.jrn.2020.02.003.
6. Liu Z-H, Yu X-Q, Yang J-W *et al*. Prevalence and risk factors for vascular calcification in Chinese patients receiving dialysis: baseline results from a prospective cohort study. *Curr Med Res Opin* 2018;**34**:1491–500. https://doi.org/10.1080/03007995.2018.1467886.
7. Palmer SC, Hayen A, Macaskill P *et al*. Serum levels of phosphorus, parathyroid hormone, and calcium and risks of death and cardiovascular disease in individuals with chronic kidney disease: a systematic review and meta-analysis. *JAMA* 2011;**305**:1119–27. https://doi.org/10.1001/jama.2011.308.
8. Floege J. Phosphate binders in chronic kidney disease: an updated narrative review of recent data. *J Nephrol* 2020;**33**:497–508. https://doi.org/10.1007/s40620-019-00689-w.
9. King AJ, Siegel M, He Y *et al*. Inhibition of sodium/hydrogen exchanger 3 in the gastrointestinal tract by tenapanor reduces paracellular phosphate permeability. *Sci Transl Med* 2018;**10**:eaam6474. https://doi.org/10.1126/scitranslmed.aam6474.
10. US Food and Drug Administration. Ibsrela prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/211801s004lbl.pdf (accessed October 2022).
11. Block GA, Rosenbaum DP, Yan A *et al*. Efficacy and safety of tenapanor in patients with hyperphosphatemia receiving maintenance hemodialysis: a randomized phase 3 trial. *J Am Soc Nephrol* 2019;**30**:641–52. https://doi.org/10.1681/ASN.2018080832.
12. Block GA, Rosenbaum DP, Leonsson-Zachrisson M *et al*. Effect of tenapanor on serum phosphate in patients receiving hemodialysis. *J Am Soc Nephrol* 2017;**28**:1933–42. https://doi.org/10.1681/ASN.2016080855.
13. Lewis SJ, Heaton, KW. Stool form scale as a useful guide to intestinal transit time. *Scand J Gastroenterol* 1997;**32**:920–4. https://doi.org/10.3109/00365529709011203.
14. Inaba M, Une Y, Ikejiri K *et al*. Dose–response of tenapanor in patients with hyperphosphatemia undergoing

hemodialysis in Japan–a phase 2 randomized trial. *Kidney Int Rep* 2022;**7**:177–88. https://doi.org/10.1016/j.ekir.2021.11.008.
15. Block GA, Bleyer AJ, Silva AL *et al*. Safety and efficacy of tenapanor for long-term serum phosphate control in maintenance dialysis: a 52-week randomized phase 3 trial (PHREEDOM). *Kidney360* 2021;**2**:1600–10. https://doi.org/10.34067/KID.0002002021.
16. Arbor Research Collaborative for Health. Number of MBD markers out of range. https://www.dopps.org/DPM-HD/DPMSlideBrowser.aspx?type¼Topic&id¼11 (accessed November 2022).
17. Miyagawa A, Tatsumi S, Takahama W *et al*. The sodium phosphate cotransporter family and nicotinamide phosphoribosyltransferase contribute to the daily oscillation of plasma inorganic phosphate concentration. *Kidney Int* 2018;**93**:1073–85. https://doi.org/10.1016/j.kint.2017.11.022.
18. Nomura K, Tatsumi S, Miyagawa A *et al*. Hepatectomy-related hypophosphatemia: a novel phosphaturic factor in the liver-kidney axis. *J Am Soc Nephrol* 2014;**25**:761–72. https://doi.org/10.1681/ASN.2013060569.
19. Zheng J, Glezerman IG, Sadot E *et al*. Hypophosphatemia after hepatectomy or pancreatectomy: role of the nicotinamide phosphoribosyltransferase. *J Am Coll Surg* 2017;**225**:488–497.e2. https://doi.org/10.1016/j.jamcollsurg.2017.06.012.
20. Wang S, Anum EA, Ramakrishnan K *et al*. Reasons for phosphate binder discontinuation vary by binder type. *J Ren Nutr* 2014;**24**:105–9. https://doi.org/10.1053/j.jrn.2013.11.004.
21. Pergola PE, Rosenbaum DP, Yang Y *et al*. A randomized trial of tenapanor and phosphate binders as a dual-mechanism treatment for hyperphosphatemia in patients on maintenance dialysis (AMPLIFY). *J Am Soc Nephrol* 2021;**32**:1465–73. https://doi.org/10.1681/ASN.2020101398.
22. Shigematsu T, Une Y, Ikejiri K *et al*. Therapeutic effects of add-on tenapanor for hemodialysis patients with refractory hyperphosphatemia. *Am J Nephrol* 2021;**52**:496–506. https://doi.org/10.1159/000516156.
23. 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**:448–56. https://doi.org/10.1002/cpdd.307.

Received: 19.6.2023; Editorial decision: 23.8.2023