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CLINICAL RESEARCH

A Pan-Inhibitor of Phosphate Transporters AP306 in Hemodialysis Patients

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Introduction: Hyperphosphatemia in patients undergoing dialysis is not well-controlled. AP306 is a pan-inhibitor of phosphate transporters, designed to block the active uptake of phosphate through the gastrointestinal tract.

Methods: In this phase 2 randomized, active-controlled, open-label study, hemodialysis patients with serum phosphate between 5.5 and 9.0 mg/dl were randomized to receive either AP306 or sevelamer carbonate for 12 weeks. The primary outcome was the change in serum phosphate levels from baseline until the therapy ceased. AP306 was initiated at 75 mg and adjusted stepwise to 125 mg and 150 mg orally thrice daily every 4 weeks, to maintain serum phosphate between 3.5 and 5.5 mg/dl. Sevelamer levels were adjusted using the same criteria and frequency.

Results: A total of 27 patients were randomized to receive AP306 and 28 to receive sevelamer. At the end-of-treatment, both AP306 and sevelamer resulted in a significant decrease from baseline in serum phosphate by 2.51 mg/dl (95% confidence interval [CI]:−3.07 to −1.92; $P < 0.001$) and 1.08 mg/dl (95% CI: −1.58 to −0.59), respectively. The proportions of patients achieving the recommended range as per the Kidney Disease: Improving Global Outcomes guidelines (2.5–4.5 mg/dl) were about 20% higher in AP306 than in sevelamer, starting from treatment week 5. The most reported adverse events (AEs) associated with AP306 were gastrointestinal disorders (51.9%), most of which were mild to moderate diarrhea (44.4%).

Conclusion: AP306 monotherapy significantly reduced serum phosphate levels and substantially improved the serum phosphate control rate in hemodialysis patients with hyperphosphatemia. AP306 was safe and well-tolerated.

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Hyperphosphatemia, a common complication of chronic kidney disease, becomes increasingly prevalent as kidney function declines and is found in nearly all patients with end-stage kidney disease.[1,2] A sizeable body of clinical research has shown that hyperphosphatemia is associated with mortality, cardiovascular events, and fractures in patients receiving maintenance dialysis.[3,4]

Current management of hyperphosphatemia includes optimization of dialysis regimen, restriction of dietary

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phosphate, and administration of intestinal phosphate binders, as well as controlling secondary hyperparathyroidism, which can contribute to hyperphosphatemia through release of phosphate from bone.[5] The Kidney Disease: Improving Global Outcomes clinical practice guidelines suggest that patients with chronic kidney disease G3a-G5D should lower serum phosphate concentrations within the population reference (''normal'') range of 2.5 to 4.5 mg/dl.[6,7] Despite the provision of 1 or more intestinal phosphate binders, often requiring 3 to 6 or more capsules or tablets 3 or more times per day, the majority of patients fail to achieve target serum phosphate concentrations, and the vast majority are unable to do so consistently.[8]

Given the current clinical landscape, drugs with novel mechanisms of action must be developed. Tenapanor hydrochloride (Xphozah), a recently licensed phosphate-lowering drug, inhibits the intestinal sodium-hydrogen exchanger 3. Sodium-hydrogen exchanger 3 inhibition induces an alteration of tight junctions and reduces phosphate-specific paracellular permeability.[9] A series of clinical trials demonstrated that tenapanor, either alone or combined with phosphate binders, significantly but modestly lowered mean serum phosphate concentrations.[10-12]

Two different mechanisms—passive paracellular transport via tight junctions and active sodium-dependent transcellular transport via ion cotransporters—contribute to the intestinal absorption of phosphate. Phosphate binders and tenapanor help reduce the absorption of intestinal phosphate by predominantly restricting passive paracellular phosphate transport. As the luminal phosphate gradient declines, phosphate binders may upregulate the expression of sodium-dependent transporters in the gastrointestinal tract and promote compensatory active transport, reducing or eliminating their efficacy, resulting in suboptimal control of hyperphosphatemia.[13] Consequently, the development of interventions aimed at active transport represents a rational approach to hyperphosphatemia.

The active transport of phosphate involves the sodium-dependent phosphate transporter type IIb (NaPi-IIb), phosphate transporter-1 (PiT-1), and phosphate transporter-2 (PiT-2). The inhibition of these transporters may help control hyperphosphatemia.[14,15] AP306 (formerly known as EOS789), developed by Chugai Pharmaceutical, acts as a pan-inhibitor of phosphate transporters that inhibits NaPi-IIb, PiT-1, and PiT-2. In rats, AP306 suppressed intestinal phosphate absorption and reduced serum phosphate in a dose-dependent manner.[16] In healthy volunteers, AP306 elicited a dose-dependent increase in fecal phosphate elimination. In patients receiving maintenance dialysis with hyperphosphatemia, AP306 100 mg thrice daily reduced intestinal phosphate absorption compared to placebo.[17] Therefore, we conducted a phase 2 clinical trial to evaluate the relative efficacy and safety of AP306 compared with sevelamer in patients receiving hemodialysis with hyperphosphatemia.

METHODS

Trial Design and Oversight

This randomized, open-label, active-controlled clinical trial was conducted at 11 centers across China (Supplementary Table S1). The regulatory authorities and ethics committees of each center reviewed and approved the trial. The trial was conducted following the principles of the Declaration of Helsinki, the International Council for Harmonization's Good Clinical Practice guidelines, all applicable rules, and the principles of the Declaration of Helsinki. Written informed consent was obtained from all the patients.

Patients

Adult patients (aged $\geq$ 18 years) on maintenance hemodialysis for at least 12 weeks with single-pooled $Kt/V_{urea} \geq 1.2$, estimated with pre- and postdialysis blood urea nitrogen concentrations, were eligible for participation.[18] If patients were receiving phosphate binders within 2 weeks before the informed consent sign-off, they were required to discontinue their current phosphate binders for a washout period of 2 to 3 weeks. If their serum phosphate levels were between 5.5 and 9.0 mg/dl at the end of washout, they were eligible for the study drug treatment. Patients not treated with phosphate binders were eligible if they met the aforementioned range of serum phosphate levels at the screening visit. Stable doses of calcitriol or active vitamin D analogs and/or calcimimetics were required for at least 2 weeks before starting the study drug and throughout the study.

Trial Procedures

In this study, we used SAS statistical software (Version 9.4; SAS Institute Inc., Cary, NC) to generate a randomized sequence and randomly assigned all eligible participants in a 1:1 ratio to the AP306 group or the active comparator, sevelamer carbonate group. The treatment duration was 12 weeks, with instructions to maintain a reduced phosphate diet and a stable hemodialysis regimen.

To ensure balance between the treatment groups, we adopted a block randomization method, with every 2 or 4 participants as a block; half of the patients were assigned to the AP306 group and half to the sevelamer group in each block. Patients were assigned a random number and allocated to the corresponding treatment group according to the order of

enrollment, using an interactive response technology system. The randomization process was designed and supervised by a third-party statistical agency.

After treatment, all patients were followed-up for 3 weeks without any study drugs or phosphate binders. Serum phosphate levels were measured weekly during treatment.

The initial dose of AP306 was 75 mg 3 times daily, orally and with meals. The AP306 dose was adjusted stepwise among 75 mg, 125 mg, and 150 mg capsules thrice daily every 4 weeks (Supplementary Figure S1), to achieve serum phosphate within the target range of 3.5 to 5.5 mg/dl, which followed Kidney Disease Outcomes Quality Initiative guidelines.[19] The initial dose of sevelamer was 800 mg or 1600 mg thrice daily, administered orally with meals. The dose of sevelamer was adjusted every 4 weeks as per its prescribing information, aiming to achieve the same serum phosphate range. We calculated adherence to study drug prescriptions based on the pill counts conducted by the study staff every 2 weeks.

If patients experienced serum phosphate concentrations $>$ 8.5 mg/dl after 2 dose escalations, as confirmed at the subsequent weekly visit, they were given "rescue" therapy. Rescue therapy was allowed for any phosphate binder, including sevelamer carbonate, as determined by the investigator.

Study visits were scheduled on the same day of hemodialysis after a short interdialytic interval. Vital signs, physical examination, electrocardiography, and laboratory tests were performed before hemodialysis, except for postdialysis blood urea nitrogen.

Outcomes

The primary efficacy outcome was the within-group change in serum phosphate levels from baseline to end-of-treatment or the beginning of rescue therapy. Time to first occurrence of serum phosphate $\leq$ 5.5 mg/dl, change in serum phosphate from baseline over time, and the proportion of patients with serum phosphate concentration between 3.5 and 5.5 mg/dl over time were among the secondary efficacy outcomes. The exploratory efficacy outcome was a between-group comparison of the change in serum phosphate levels from baseline to end-of-treatment or at the beginning of rescue therapy. Serum phosphate levels were determined at the local laboratories affiliated with the clinical sites. Safety outcomes were based mainly on AEs and laboratory assessments.

We conducted a *post hoc* analysis of the proportion of patients who achieved serum phosphate concentrations within the population reference (Kidney Disease: Improving Global Outcomes–recommended) range of 2.5 to 4.5 mg/dl.

Statistical Analysis

We estimated that 25 patients per group would provide at least 90% power at a 2-sided α level of 0.05 to detect a within-group change in serum phosphate of 1.5 mg/dl with an SD of 1.7 mg/dl accounting for a dropout rate of 35%.

All analyses included randomized patients who received at least 1 dose of the study drug. Primary efficacy analysis was performed using a simple sample *t* test. A between-group comparison of the change in serum phosphate levels from baseline was performed using a 2-sample *t* test. The end-of-study value was derived from the last nonmissing value on the last dosing date or 7 days before the last dose was administered. A multiple imputation approach was used if there were missing data. For continuous secondary efficacy endpoints, 95% CIs were calculated based on a simple sample *t* test. For binary efficacy endpoints, 95% CIs were calculated based on the exact method. For time-to-event endpoints, 95% CIs were calculated based on the Kaplan-Meier method. Descriptive statistics were reported for all endpoints. All analyses were performed using SAS statistical software.

RESULTS

Patients

From February to September 2023, 99 patients receiving hemodialysis 3 times weekly were screened, and 55 were enrolled; 27 were randomized to receive AP306 and 28 to receive sevelamer carbonate. These patients were used for all efficacy and safety analyses. Four patients in the AP306 group terminated treatment early: 1 patient due to AEs, 1 patient due to withdrawal of informed consent, and 2 patients due to hypophosphatemia (serum phosphate $<$2.5 mg/dl at 2 consecutive weekly visits). All the other patients completed 12 weeks of treatment (Figure 1). All the patients were maintained on a stable hemodialysis regimen throughout the study period. Their single-pooled Kt/V_{urea} was $\geq$ 1.2 and the dialysate calcium concentration remained unaltered at baseline and the study end.

At baseline, the mean age ($\pm$ SD) of the patients was 49.6 $\pm$ 11.1 years; 38% were women. The median dialysis vintage (time since initiation of dialysis) was 7.38 (interquartile range: 3.47–9.11) years. The most frequently reported concurrent conditions were nephrogenic anemia, secondary hyperparathyroidism, hyperuricemia, and hyperkalemia. The most frequently used phosphate binders at baseline were sevelamer (42%) and lanthanum carbonate (31%); 7% of patients received 2 phosphate binders in combination

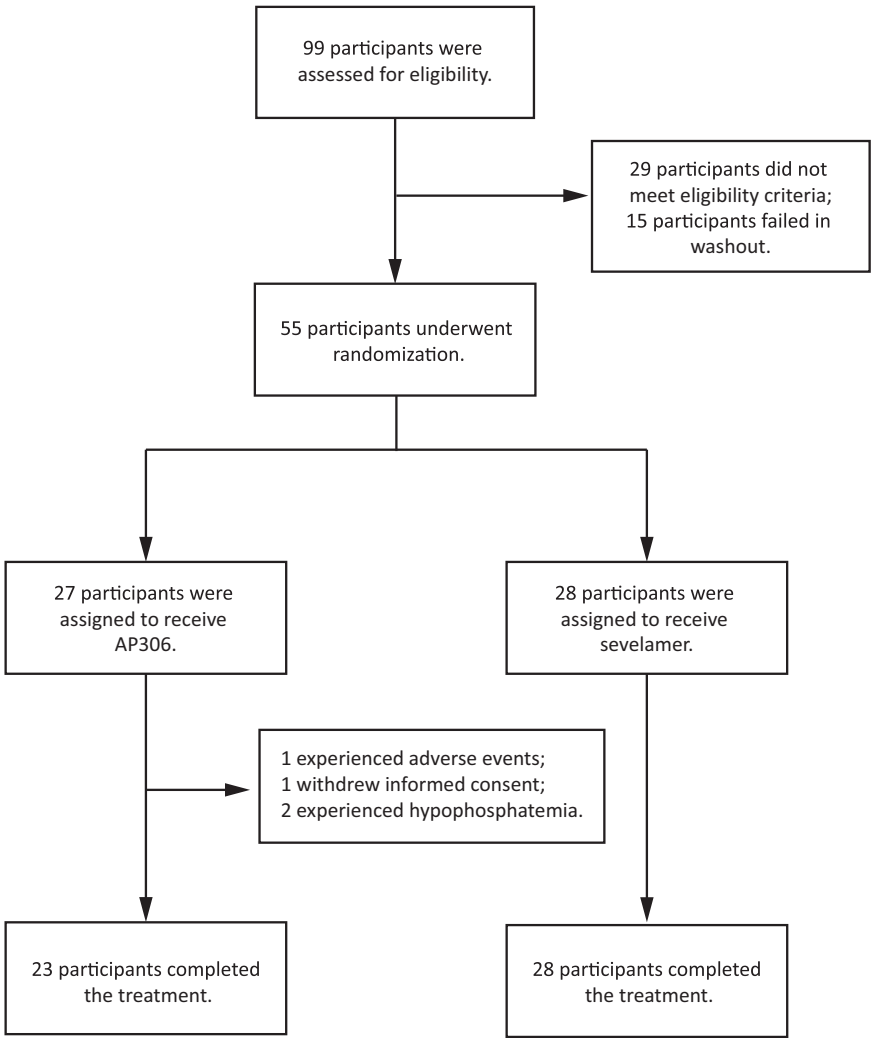

Figure 1. Patient disposition. The patient who withdrew informed consent experienced diarrhea before withdrawing.

(Table 1, Supplementary Table S2, and Supplementary Table S3). The most commonly administered concomitant medications were erythropoietin, paricalcitol, and cinacalcet. Concurrent conditions and concomitant medications reflected the hemodialysis patient population.

Table 1. Characteristics of patients at baseline

Characteristics	AP306 (n = 27)	Sevelamer (n = 28)
Female sex, n (%)	8 (29.6)	13 (46.4)
Age, yr (SD)	49.2 (11.66)	49.9 (10.73)
Asian race, n(%)	27 (100)	28 (100)
BMI, kg/m^2 (SD)[a]	23.27 (2.55)	23.09 (3.56)
Median duration of HD – yr (IQR)	5.75 (2.78–9.08)	7.47 (4.36–14.15)
Previous phosphate binder use – n (%)		
None[b]	8 (29.6)	5 (17.9)
1 phosphate binder	15 (55.6)	23 (82.1)
2 phosphate binders	4 (14.8)	0 (0)
Mean serum phosphate – mg/dl (SD)	7.06 (0.99)	6.57 (0.87)
Mean serum calcium – mg/dl (SD)	8.98 (1.00)	9.34 (0.68)
iPTH – pg/ml		
Mean (SD)	425.75 (200.09)	411.04 (190.00)
Median (IQR)	381.04 (243.96–585.57)	444.53 (246.98–551.98)

BMI, body mass index; CKD, chronic kidney disease; HD, hemodialysis; iPTH, intact parathyroid hormone; IQR, interquartile range.
[a]BMI is the weight in kilograms divided by the square of the height in meters.
[b]The patients did not receive any phosphate binders within 2 weeks before informed consent was signed.

The baseline characteristics were generally similar between the 2 groups, except for a lower proportion of women and a slightly higher baseline serum phosphate level in patients randomized to the AP306 group. This discrepancy is likely because of the relatively small sample size and randomness.

Exposure

The mean daily doses (± SD) of AP306 were 221 ± 77 mg, 312 ± 74 mg, and 288 ± 82 mg for three 4-week periods (Supplementary Figure S2 and Table S4). The mean daily doses (± SD) of sevelamer were 2676 ± 784 mg, 3926 ± 1232 mg, and 4651 ± 1899 mg, respectively.

Efficacy Outcomes

At end-of-treatment, the mean serum phosphate decreased from baseline in both groups as follows: AP306, −2.51 mg/dl (95% CI:−3.07 to −1.92, $P <$ 0.0001) and sevelamer,−1.08 mg/dl (95% CI:−1.58

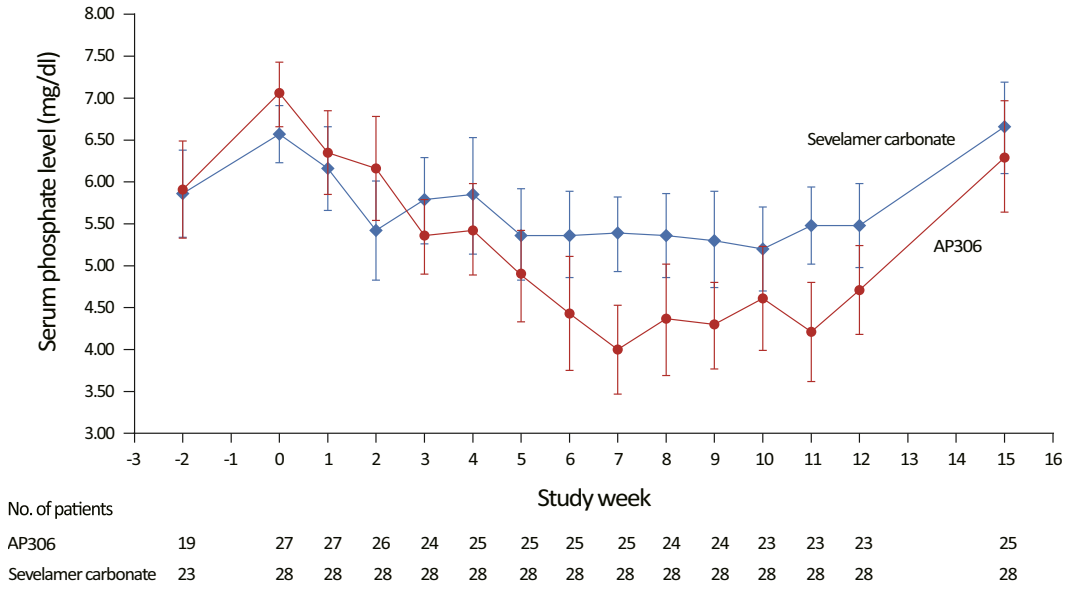

Figure 2. Serum phosphate concentration over time. Mean serum phosphate values for each week of the study are presented. Vertical lines indicate 95% confidence intervals. Week 2 marks the beginning of washout; week 0, baseline; weeks 4 and 8, dose adjustment; week 12, end of the treatment period; and week 15, the follow-up visit. If patients were not within the designated target range (3.5–5.5 mg/dl), the dose of the study drug was titrated.

to −0.59, $P < 0.0001$), corresponding to a mean difference between groups of −1.42 mg/dl (95% CI:−2.16 to −0.68; $P < 0.001$). No patient required rescue therapy. There were no missing data on the primary efficacy outcomes.

The median duration to the first occurrence of serum phosphate ≤ 5.5 mg/dl was 14 days in both groups (Supplementary Table S5). Serum phosphate concentrations in both groups decreased after the first week of treatment, and this reduction was maintained until the end of the 12-week treatment period. The magnitude of this reduction was more pronounced in the AP306 group (Figure 2 and Supplementary Table S6). Serum phosphate concentrations returned to near baseline values 3 weeks after discontinuation of the study drugs. The proportion of patients with serum phosphate concentrations between 2.5 and 4.5 mg/dl was consistently higher among those randomized to the AP306 group after 5 weeks of treatment (48% vs. 25%) and was maintained until the end of the 12-week treatment period (44% vs. 21%) (Figure 3b and Supplementary Table S7).

The changes in serum calcium and intact parathyroid hormone levels were small, and the within-group and between-group comparisons were not statistically significant (Supplementary Table S8).

Safety Outcomes

Over the 12-week treatment period, 93% and 68% of the patients in the AP306 and sevelamer groups, respectively, experienced at least one AE (Table 2 and Supplementary Table S9). The most common AEs in the AP306 group were gastrointestinal disorders (52%) and diarrhea (44%). All diarrhea events were assessed as grade 1 or 2, according to the Common Terminology Criteria for AEs, but rarely interrupted, reduced, or discontinued AP306 dosing. Most cases of diarrhea resolved within 2 weeks, with or without symptomatic treatment, and none led to volume depletion or hypernatremia or hyponatremia. One patient was unwilling to continue AP306 treatment because of diarrhea and informed consent was withdrawn. Although the sample size was small, there was a suggestion that gastrointestinal events in patients treated with AP306 may have been dose-related (Supplementary Table S10). One patient in the AP306 group experienced an AE leading to discontinuation of the study drug, which was reported as hypersensitivity. This event occurred 9 days after the start of treatment and manifested as a localized rash accompanied by itching. Antihistamines were administered and AP306 was withdrawn. This event resolved after AP306 discontinuation. Two patients in the sevelamer group experienced serious AEs, pneumonia and pulmonary embolism. None of the patients in the AP306 group experienced any serious AEs.

DISCUSSION

In this randomized, active-controlled, open-label clinical trial conducted in patients receiving hemodialysis with hyperphosphatemia, we aimed to achieve serum phosphate concentrations between 3.5 and 5.5 mg/dl using AP306 or sevelamer carbonate. The control of

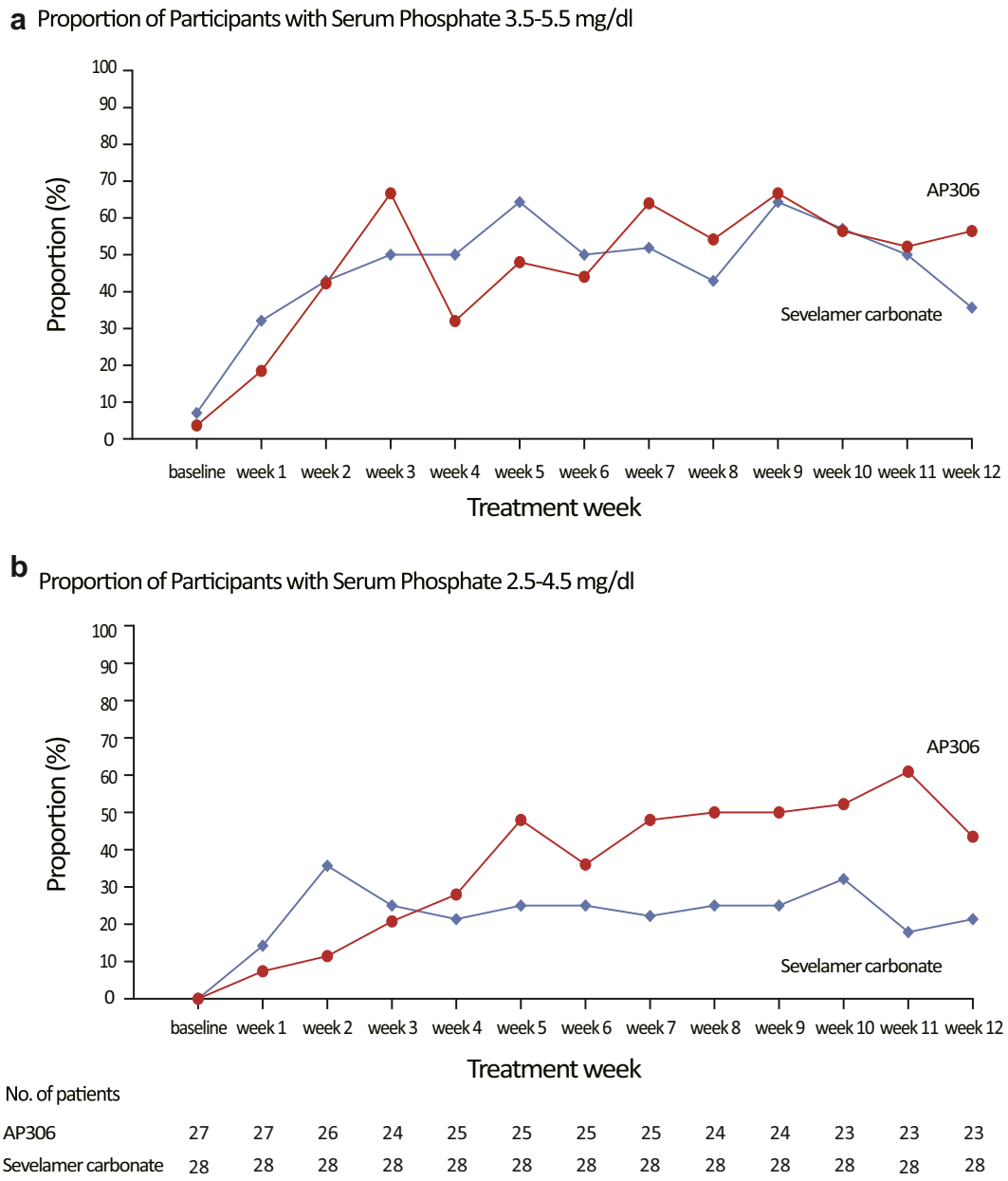

Figure 3. The proportion of patients within designated target ranges. The proportion of patients with serum phosphate concentrations within the different target ranges for each week of treatment is shown. (a) The proportions were calculated within the range of 3.5 and 5.5 mg/dl. (b) The proportions were calculated with a range of 2.5 and 4.5 mg/dl.

Table 2. Adverse events

Adverse events	AP306	Sevelamer
Adverse events, *n* (%)	**(*n* = 27)**	**(*n* = 28)**
Patients who reported adverse events	25 (92.6)	19 (67.9)
Patients who reported serious adverse events	0	2 (7.1)
Patients who reported adverse events with CTCAE Grade ≥ 3	1 (3.7)	3 (10.7)
Gastrointestinal events	14 (51.9)	6 (21.4)
Diarrhea	12 (44.4)	0
Nausea	3 (11.1)	0
Vomiting	3 (11.1)	1 (3.6)
Abdominal distension	2 (7.4)	2 (7.1)
Constipation	0	3 (10.7)

CTCAE, the National Cancer Institute Common Terminology Criteria for Adverse Events.

hyperphosphatemia was superior with AP306, whether assessed by a reduction in mean serum phosphate or the proportion of trial participants achieving more stringent (exploratory) target serum phosphate concentrations. There were no serious AEs in the AP306-treated patients. AP306 was generally well-tolerated, and the majority of AEs were mild to moderate diarrhea that resolved without sequelae. Differences in safety and tolerability should be considered in the context of this being an open-label trial and one in which a sizeable fraction of patients treated with the active control (sevelamer carbonate) were previously treated with and presumably tolerant of the same agent.

To the best of our knowledge, AP306 is the first pan-inhibitor of phosphate transporters developed clinically. The pronounced reduction in serum phosphate levels observed in this study may be attributed to its novel mechanism of suppressing the active transport of phosphate in the gastrointestinal tract by inhibiting NaPi-IIb, PiT-1, and PiT2. Three drugs targeting NaPi-IIb (ASP3325, DS2330B, and nicotinamide) have been evaluated in clinical trials but failed to produce a significant clinical effect in lowering serum phosphate.[20–22] Chugai's data showed that PiT-2 dominates phosphate transporter expression in the human intestine. This observation may explain the difference in serum phosphate reduction elicited by AP306 in contrast to agents that only targeted NaPi-IIb.

At present, there is an absence of data from prospective clinical outcome studies demonstrating that lowering serum phosphate levels in patients undergoing dialysis improves clinical outcomes such as cardiovascular events or mortality. However, hyperphosphatemia is strongly associated with worsened outcomes in dialysis patients, as observed in several datasets of major dialysis providers.[4,23] Considering epidemiological data and biological plausibility, all medications for hyperphosphatemia were approved based on their effects on a surrogate endpoint, reduction in serum phosphate. Nevertheless, the magnitude of the treatment should be clinically meaningful compared with other approved serum phosphate-lowering products. The decrease in serum phosphate induced by AP306 in this study was 2.51 mg/dl, which was higher than the 1.5 to 2.2 mg/dl decrease reported in other phosphate binder studies and considered clinically meaningful.[24–26]

In this study, the sevelamer group showed a serum phosphate reduction of 1.08 mg/dl, which was lower than the decrease reported in other phosphate binder studies, despite dose adjustments made in accordance with published prescription recommendations and the same phosphate range as the AP306 group. This discrepancy might be attributable to the lower mean serum phosphate concentration at baseline in our study (6.57 mg/dl) relative to the phase 3 trials of several intestinal phosphate binders and tenapanor (approximately 7.50 mg/dl).

It is noteworthy that the daily dose of AP306 was stabilized below 300 mg after 2 dose-level adjustments, suggesting that no more than 3 tablets daily would be required in clinical practice, assuming a formulation of tablets containing 100 or 150 mg.

The most common AEs in the AP306 group were gastrointestinal. This observation is consistent with the mechanism of action of AP306 and is consistent with the findings of previous clinical trials. Among the gastrointestinal events, diarrhea was reported most frequently. These events were assessed as Common Terminology Criteria for AEs grade 1 or 2 in severity and rarely necessitated any interruption or dose reduction of AP306. Furthermore, they were both reversible and manageable. Although the incidence of gastrointestinal events appeared to increase with escalating doses of AP306, the limited sample size, particularly the small number of patients ($n = 2$) receiving 150 mg 3 times daily, precludes the ability to draw robust conclusions at this stage.

The present study had several limitations. First, this was an open-label, active-controlled trial. The open-label design may have influenced patient behaviors, such as dietary choices, which could in turn affect the primary efficacy parameter, serum phosphate. This design was selected to avoid the increased pill burden associated with the double-dummy approach in a double-blinded setting. Sevelamer carbonate, a widely accepted and utilized phosphate binder in China, was selected as an active comparator to assess the potential clinical relevance of AP306 as an investigational drug with a novel mechanism of action. To minimize the potential bias, patients were instructed to maintain a reduced phosphate diet and stable hemodialysis throughout the treatment period. Following this proof-of-concept study, double-blind placebo-controlled studies are planned to assess the net effect of AP306 on serum phosphate levels.

Second, the sample size was relatively small. An imbalance in the baseline serum phosphate level may be due to the small sample size, even after randomization. However, the study drug dose was adjusted for all patients based on the same titration range and frequency. The similar proportions of patients within the titration range (Supplementary Table S11) of serum phosphate observed in patients assigned to AP306 and sevelamer carbonate suggest that this limitation is unlikely to have a major influence on the study findings.

In conclusion, AP306, a pan-inhibitor of active phosphate transporters, significantly reduced serum phosphate levels relative to baseline and appeared to be safe and reasonably well-tolerated. The efficacy of AP306 was superior to that of the active control (sevelamer carbonate), whose dose required uptitration during the trial. Placebo- and/or active-controlled clinical trials that are larger in size and longer in duration need to be conducted to better understand the relative safety and efficacy of AP306 and its potential role as a monotherapy or in combination with intestinal phosphate binders for the treatment of hyperphosphatemia.

DISCLOSURE

LZ serves as a scientific advisor for Alebund Pharmaceuticals. WZ, YCL, and QZ are full-time employees of Alebund Pharmaceutical. All the other authors declared no competing interests.

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DATA AVAILABILITY STATEMENT

This study was conducted in Mainland China and enrolled all Chinese citizens. Sharing individual participants' data was not possible because of the Personal Information Protection Law of the People's Republic of China (Presidential Decree No. August 91, 2021). The Study Protocol and Statistical Analysis Plan are available on request.

AUTHOR CONTRIBUTIONS

All the authors were involved in the design and implementation of the trial, and the sponsor (Alebund Pharmaceuticals) analyzed the data. Each author had access to the data, evaluated the submitted manuscript, and attested to the trial's adherence to the agreed-upon protocol, accuracy, and completeness.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Timing and criteria for AP306 dose adjustment.

Figure S2. Participant flow of dose modification in the AP306 group.

Table S1. List of sites and investigators.

Table S2. Baseline characteristics of participants.

Table S3. Concomitant use of vitamin D, vitamin D analogs, and calcimimetics at baseline.

Table S4. Exposure by dose and total compliance.

Table S5. Duration to the first occurrence of serum phosphate $\leq$ 5.5 mg/dl.

Table S6. Change in serum phosphate from baseline by week.

Table S7. Proportion of participants with serum phosphate 2.5 to 4.5 mg/dl by week.

Table S8. Change in serum calcium and iPTH from baseline.

Table S9. Treatment-emergent adverse events by treatment and preferred terms.

Table S10. Treatment-emergent adverse events under gastrointestinal disorders in the AP306 group by dose level.

Table S11. Proportions of participants with serum phosphate 3.5 to 5.5 mg/dl by week.

Table S12. Proportions of participants with serum phosphate $\leq$ 5.5 mg/dl by week.

CONSORT Checklist.

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