

# NaPi-IIb Inhibition for Hyperphosphatemia in CKD Hemodialysis Patients



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**Introduction:** Chronic kidney disease (CKD) has a prevalence of 9.1% globally, and frequently results in elevated serum phosphate, increasing cardiovascular morbidity and mortality risk in hemodialysis (HD) patients. DS-2330b, an oral NaPi-IIb inhibitor, reduced intestinal phosphate absorption in preclinical studies, but its effect in patients with CKD is unknown. This 2-part, randomized, placebo- and active-controlled, single- and repeated-dose, phase 1b study evaluated safety and efficacy of DS-2330b in patients with CKD on HD.

**Methods:** Part A, a 2-period, 2-way study, evaluated safety and pharmacokinetics of DS-2330b 250 mg in solution and tablet formulations. Part B assessed the safety of DS-2330b in solution (chosen based on results of part A) and its effect on serum phosphate. Patients were randomized to placebo 3 times daily (TID), DS-2330b 400 mg TID, DS-2330b 400 mg with sevelamer 1.6 g TID, and sevelamer 1.6 g with placebo TID for 14 days. Safety endpoints included adverse event (AE) monitoring.

**Results:** Six patients completed part A. Two patients experienced serious AEs considered unrelated to DS-2330b treatment. Thirty-two patients enrolled and completed part B. Serum phosphate mean change from baseline  $\pm$  SD was  $-2.2 \pm 1.5$  mg/dl versus  $-1.9 \pm 1.1$  mg/dl for DS-2330b monotherapy versus placebo. Patients receiving DS-2330b with sevelamer or sevelamer with placebo experienced the greatest serum phosphate decrease from baseline. Nine patients (28.1%) experienced  $\geq 1$  treatment-emergent AE (TEAE); 7 patients experienced drug-related TEAEs. The TEAE incidence was comparable between DS-2330b and control groups.

**Conclusions:** DS-2330b, alone or in combination with sevelamer, was safe and well tolerated but did not demonstrate clinically meaningful efficacy in HD patients.

*Kidney Int Rep* (2021) 6, 675–684; <https://doi.org/10.1016/j.ekir.2020.12.017>

KEYWORDS: chronic kidney disease; clinical study; hemodialysis; hyperphosphatemia; NaPi-IIb inhibitor

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## See Commentary on Page 557

CKD occurs in approximately 9.1% of the global population, and is characterized by evidence of kidney damage and impaired renal function.<sup>1</sup> Hyperphosphatemia is a common metabolic manifestation of stage 4 and stage 5 CKD, occurring in up to 70% of patients during end-stage renal failure.<sup>2</sup> Increased serum phosphate is associated with greater risk of cardiovascular morbidity and mortality, cardiovascular calcification, and secondary hyperparathyroidism in patients undergoing HD.<sup>3,4</sup> Current clinical guidelines recommend regular monitoring and management of

hyperphosphatemia through the use of dietary modifications and phosphate binders.<sup>5,6</sup>

Two families of sodium-dependent phosphate cotransporters (NaPi) are involved in transporting phosphate across membranes: inorganic phosphate transporters and NaPi-II.<sup>7</sup> Three subtypes of NaPi-II have been identified: NaPi-IIa and NaPi-IIc, expressed primarily in the kidneys, and NaPi-IIb, expressed primarily in the small intestine. NaPi-IIb is believed to play a significant role in intestinal phosphate uptake.<sup>8</sup> In a normally functioning system, phosphate absorption takes place through phosphate transporters or NaPi transporters, with NaPi-IIb accounting for approximately 50% of total serum phosphate uptake in mice, whereas excessive phosphate intake is balanced by urine or fecal excretion.<sup>8,9</sup> In patients with CKD, however, this balance is disrupted due to decreased phosphate excretion, resulting in increased systemic

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Received 30 September 2020; revised 10 December 2020; accepted 15 December 2020; published online 23 December 2020

phosphate. This hyperphosphatemia, along with altered metabolism of phosphate and calcium, leads to increased phosphate bone resorption and mineral deposits in soft tissues, such as the vasculature, ultimately contributing to vascular calcification.<sup>10</sup> Several therapies are approved to control serum phosphate in patients with CKD on HD, including the widely used phosphate binder sevelamer carbonate.<sup>11</sup> Additional investigational therapies include inhibition of the sodium-hydrogen exchanger 3 and inhibition of the NaPi-IIb cotransporter in the small intestine.<sup>12,13</sup>

DS-2330b is an oral NaPi-IIb inhibitor that inhibits the uptake of phosphate via NaPi-IIb in the small intestine in animal and *ex vivo* studies, resulting in reduced intestinal phosphate absorption. These findings formed the basis for the single ascending dose (SAD) and multiple ascending dose (MAD) studies.

The SAD and MAD studies enrolled young, healthy volunteers (56 subjects and 32 subjects, respectively), to assess the safety and tolerability of DS-2330b. Dosing schedules are described in [Supplementary Figure S1](#). All doses of DS-2330b tested in the SAD and MAD studies were well tolerated with no concerning safety signals. Pharmacokinetic (PK) measurements of the maximum concentration ( $C_{max}$ ) and area under the curve (AUC) generally increased with increasing DS-2330b doses in both studies. No dose-related changes in pharmacodynamic markers (serum phosphate and urinary phosphate excretion) were observed after treatment with DS-2330b compared with placebo in the SAD study. In the MAD study, all treatment groups, including placebo, demonstrated a decrease in urinary phosphate excretion and an increase in fecal phosphate excretion independent of dose or treatment. The positive preclinical data, safety, and tolerability in the healthy volunteer studies and the anticipated upregulation of the NaPi-IIb cotransporters in patients with CKD compared with healthy patients justified progression of DS-2330b into clinical studies in HD patients.

The results presented here are from a 2-part phase 1b study (NCT03305471) investigating the safety and efficacy of DS-2330b as monotherapy and in combination with sevelamer in patients with CKD on HD. Part A was a crossover study that investigated the PKs of DS-2330a (the free form of DS-2330b) in patients on HD after a single dose of tablet or solution prepared with powder in bottle (PIB) formulations, both at 250 mg. Following the evaluation of results from part A, part B tested the efficacy of DS-2330b 400 mg PIB (3 times daily [TID]), as monotherapy or in combination with sevelamer carbonate 1.6 g (TID) in patients with CKD on HD. This is the first study to assess the safety, tolerability, PK, and pharmacodynamics of repeated doses of DS-2330b in patients with CKD on HD.

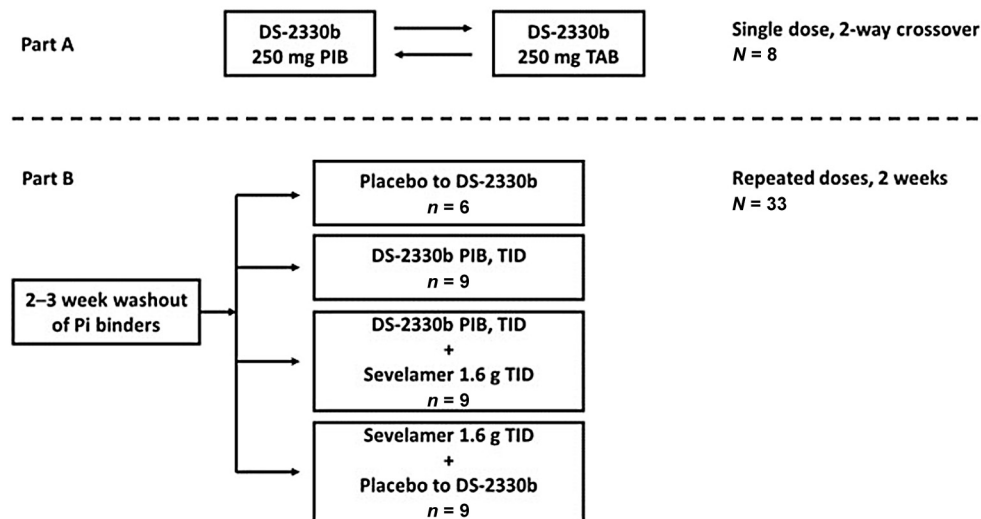
## METHODS

### Study Design

This was a 2-part, randomized, placebo- and active-controlled phase 1b study. The study was conducted in accordance with the principles of the Declaration of Helsinki. The study was initiated at a total of 4 clinical pharmacology units (CPUs) with in-house HD facilities, after obtaining approval by each local institutional review board. All patients provided written informed consent before the participation in any study procedures. The study was registered at [ClinicalTrials.gov](#) (NCT03305471).

Part A was a 2-period, open-label, randomized, 2-way crossover study in which 8 patients undergoing HD received a single dose of DS-2330b 250 mg PIB or a single 250-mg tablet ([Figure 1](#)). Within 48 hours of receiving an HD treatment, patients began day 1 of the first period in which they received a single dose of the study drug. Before HD, blood samples for PK analysis were collected predose and postdose at hours 1, 2, 3, 5, 6, 7, 8, 10, 11, 12, 13, 24, 36, and 48. After completing treatment with the first formulation of DS-2330b, a washout period of at least 72 hours was required; all patients had a washout period of 7 days before starting treatment with the alternate formulation. Patients returned for a follow-up visit 7 to 10 days after the last dose of study drug in the second period.

Part B of the study began after evaluating the safety and PK data of part A ([Figure 1](#)). Based on model and simulation projections from the data to date, DS-2330b at 400 mg PIB TID was selected for part B dosage. In part B, patients with CKD on HD were screened within a 4-week window before enrollment. Patients meeting screening criteria started a 2- to 3-week washout period from all phosphate binders before study initiation. Patients who met inclusion criteria for serum phosphate (6.0–10.0 mg/dl and >1.0 mg/dl increase from screening) and calcium (8.0–10.0 mg/dl at screening) at the end of or during washout enrolled into the study ([Figure 2](#)). Patients were randomized in a ratio of 2:3:3:3 to 1 of 4 treatment arms (planned 33 patients): placebo matched to DS-2330b TID, DS-2330b 400 mg PIB TID, DS-2330b 400 mg PIB TID co-administered with open-label sevelamer carbonate 1.6 g TID, and open-label sevelamer carbonate 1.6 g TID with placebo matched to DS-2330b TID. The placebo was the same solution used to dissolve PIB. Patients and investigators were blinded to the treatments associated with DS-2330b. Patients were admitted to the CPUs on day -1 and remained in-house with a controlled diet (potassium content ranging 1800–2700 mg and phosphate content ranging 700–1300 mg) for the 14-



**Figure 1.** Study design schematic. Part A was an open-label, randomized, 2-way crossover study with a single dose of DS-2330b 250 mg in PIB or tablet formulation in 2 periods. All patients stayed in a CPU during each treatment period. There were at least 7 days of washout between treatments. Part B was a double-blinded, randomized, placebo- and active-controlled study with 4 arms. Placebo is the same solution used to dispense DS-2330b PIB; Placebo is matching to DS-2330b PIB. CPU, clinical pharmacology unit; Pi, phosphate; PIB, powder in bottle; TAB, tablet; TID, 3 times daily.

day dosing period. Patients started treatment on study day 1 and continued for 14 days. Study drugs were administered within 10 minutes after each meal with 240 ml water. Blood samples for PK analyses were collected predose, and after the morning dose at hours 1, 2, 3, 5, 6, 7, 8, 10, 11, 12, and 13 on day 1 and day 13 (non-HD days). Patients fasted for at least 4 hours after the morning dose. Hemodialysis clearance of DS-2330a (the free form of DS-2330b) was assessed on day 11.

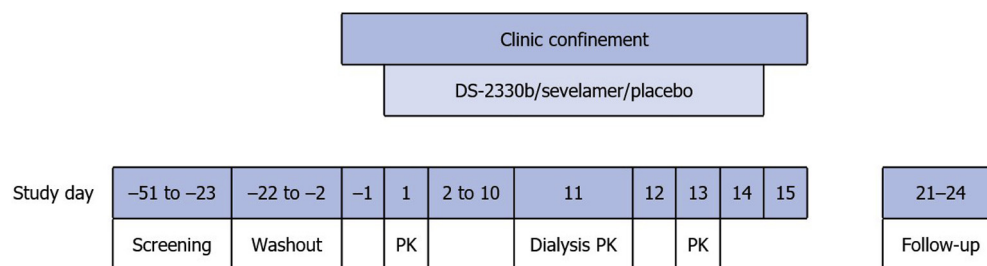
## Patients

The study enrolled male and female patients between 18 and 80 years of age on chronic HD (defined as prescribed maintenance HD, 3 times per week for  $\geq 3$  months) with adequacy demonstrated by an efficacy of HD of  $\geq 1.2$  Kt/V and who met all of the inclusion and none of the exclusion criteria (Supplementary Table S1).

## Outcomes

The primary objective for part A was assessment of plasma PK parameters for 2 formulations of DS-2330b. Secondary objectives for part A were assessment of the safety and tolerability of single dose DS-2330b 250 mg PIB and tablet formulations. The PIB formulation was chosen for part B as the most suitable formulation to test NaPi-IIb inhibition in HD patients.

The primary objectives for part B were assessment of the safety, tolerability, and effects on serum phosphate of 14-day, repeated doses of DS-2330b PIB when given alone or co-administered with sevelamer carbonate (Figure 2). The secondary objectives were assessment of the safety and tolerability of sevelamer when administered with placebo matching to DS-2330b, and assessment of the plasma PKs of DS-2330a following administration of DS-2330b PIB alone and when co-administered with sevelamer on day 1 and day 13. The exploratory objectives of part B were assessment of



**Figure 2.** Study schedule for part B. Patients with CKD were screened within a 4-week period before enrollment. Screened patients began a 2- to 3-week washout of all phosphate binders. Patients who met serum phosphate of 6.0 mg/dl to 10.0 mg/dl, and demonstrated a  $>1.0$  mg/dl serum phosphate increase from screening were enrolled. The follow-up period was 21–24 days after the first treatment. CKD, chronic kidney disease; PK, pharmacokinetics.

the effects of DS-2330b on intact parathyroid hormone (iPTH) and fibroblast growth factor 23 (FGF-23) as markers of phosphate metabolism on day 1 and day 13 (Figure 2).

### Safety

The safety analysis included all patients receiving treatment in part A and part B. The safety endpoints included incidence of treatment-emergent adverse events (TEAEs), physical examination findings, vital sign measurements, triplicate 12-lead electrocardiogram recordings, and clinical laboratory test results including hematology and serum chemistry.

### Statistical Analyses

The number of patients in part A and part B were selected based on feasibility and contemporary phase I studies of serum phosphate lowering. Thirty-three patients in part B with the inclusion of an active control arm were estimated to be sufficient for assessment of study objectives. All statistical analyses and summary information were generated and finalized before database lock to preserve the integrity of the statistical analysis and study conclusions.

In part A, PK parameters were summarized by treatment arm (PIB vs. tablet) and time point. In part B, PK parameters were summarized for DS-2330b monotherapy and DS-2330b plus sevelamer combination treatment arms and were compared between those arms. The pharmacodynamic parameters for serum phosphate, albumin-corrected calcium, iPTH, FGF-23, and change from baseline were summarized by treatment at each planned assessment. The baseline value of each laboratory parameter was defined as the last value assessed before day 1 dose. All statistical analyses were performed using SAS version 9.3 or higher (SAS Institute, Cary, NC).

## RESULTS

### Patient Disposition, Baseline Demographics, and Clinical Characteristics

In part A, 14 patients were screened and a total of 8 patients enrolled; 6 patients (75.0%) completed the study. All patients in part A took  $\geq 1$  concomitant medication, including beta-blocking agents (8 patients, 100%) and antithrombotics (7 patients, 87.5%). All patients were male, and each treatment group had comparable baseline characteristics. Two patients (25.0%) discontinued due to serious AEs determined unrelated to study drug by the investigator.

In part B, 101 HD patients were screened; 33 patients were planned, but only 32 enrolled due to prolonged enrollment duration. All 32 patients completed the study. All patients took  $\geq 1$  concomitant medication,

**Table 1.** Patient demographics and baseline characteristics by treatment arm in part B

	PBO (n = 6)	DS-2330 (n = 9)	DS-2330 + sevelamer (n = 8)	Sevelamer + PBO (n = 9)
Sex, male, n (%)	5 (83.3)	9 (100)	7 (87.5)	7 (77.8)
Age, y, mean (SD)	52.5 (9.8)	54.8 (13.5)	49.4 (7.6)	54.2 (5.0)
Race, n (%)				
African American	6 (100)	8 (88.9)	6 (75.0)	5 (55.6)
Asian	0	0	1 (12.5)	0
White	0	1 (11.1)	1 (12.5)	4 (44.4)
Ethnicity				
Hispanic, n (%)	1 (16.7)	0	1 (12.5)	1 (11.1)
Weight, kg, mean (SD)	91.1 (14.8)	85.1 (17.1)	80.4 (12.5)	85.4 (20.9)
BMI, mean (SD)	30.0 (5.3)	27.4 (3.1)	26.4 (3.0)	26.2 (5.2)
Length of HD, y, mean (SD)	7.5 (7.3)	9.0 (6.4)	5.3 (4.5)	6.2 (4.2)
Reasons for HD				
Diabetic nephropathy	1 (16.7)	2 (22.2)	2 (25.0)	1 (11.1)
Nephrosclerosis	4 (66.7)	4 (44.4)	3 (37.5)	2 (22.2)
Other <sup>a</sup>	1 (16.7)	3 (33.3)	3 (37.5)	6 (66.6)

BMI, body mass index; HD, hemodialysis; PBO, placebo.

<sup>a</sup>Includes concomitant diabetic nephropathy and nephrosclerosis.

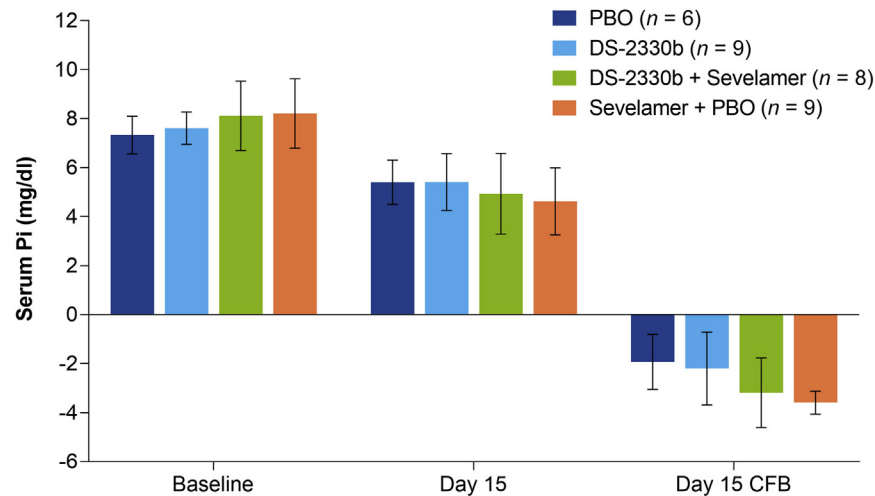
including antithrombotics (24 patients, 75.0%) and beta-blocking agents (22 patients, 68.8%). The mean age  $\pm$  SD was  $52.8 \pm 9.3$  years; there were no notable differences in baseline demographics between each study arm (Table 1). The most common causes of CKD were diabetic nephropathy and/or nephrosclerosis.

### Part A

Overall, systemic exposure of DS-2330a after a single dose of DS-2330b PIB 250 mg was comparable between the target population of HD patients and healthy volunteers in previous studies. The AUC of the tablet formulation was approximately 10% of that in the PIB formulation, which suggests the DS-2330b in the tablet is not absorbed as well as the PIB formulation.

In terms of safety, there were no notable differences in the incidence and severity of TEAEs with PIB or tablet formulation. There were total 3 serious AEs in 2 patients, all considered unrelated to DS-2330b treatment by the principal investigator. One patient, a 51-year-old man with hypertension, hyperlipidemia, and type 2 diabetes, died due to cardiac arrest during hospitalization for worsening of cellulitis, approximately 4 weeks after a single dose of DS-2330b tablet. A second patient, a 68-year-old man with a history of diabetes, diverticular abscess, and partial colectomy was hospitalized due to small bowel obstruction less than 2 days after receiving a single dose of DS-2330b PIB. This patient made a full recovery but withdrew from the study.





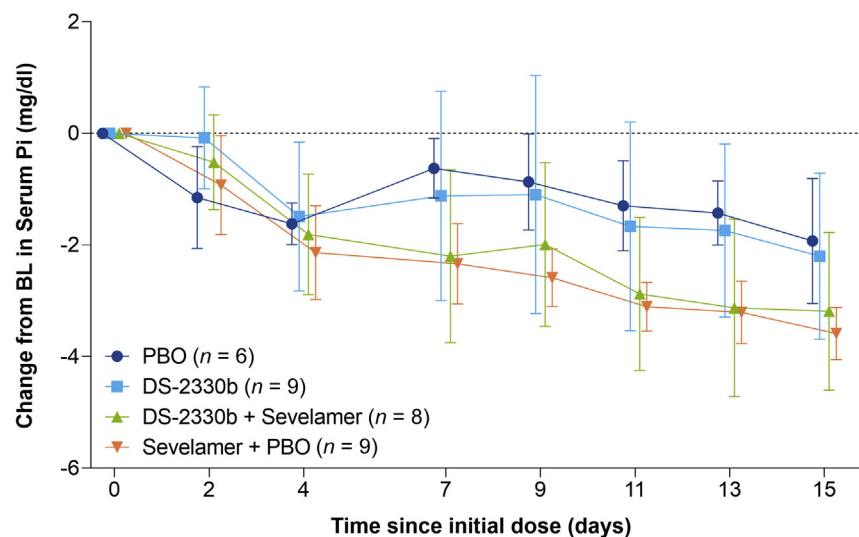
**Figure 3.** Changes in serum phosphate at baseline and day 15 of treatment in part B. PBO treatment arm (dark blue bar) received placebo to DS-2330b TID. DS-2330b treatment arm (light blue bar) received 400 mg DS-2330b in PIB formulation TID; DS-2330b + sevelamer group (green bar) received 400 mg DS-2330b PIB formulation co-administered with 1.6 g open-label sevelamer TID; Sevelamer + placebo treatment arm (orange bar) received open-label 1.6 g sevelamer co-administered with placebo TID. All treatment was given TID after each meal from day 1 to day 14. The data are shown as mean  $\pm$  SD. CFB, change from baseline; PBO, placebo; Pi, phosphate; PIB, powder in bottle; TID, 3 times daily.

### Part B Effects of Study Drugs on Serum Phosphate

Patients receiving HD enrolled in part B were randomized into 1 of 4 treatment arms: placebo (6 patients), DS-2330b monotherapy (9 patients), DS-2330b with sevelamer co-administration (8 patients), and sevelamer with placebo (9 patients). Serum phosphate decreased at day 15 compared with baseline in all treatment arms. The serum phosphate mean change from baseline  $\pm$  SD was  $-2.2 \pm 1.5$  mg/dl and  $-3.6 \pm 0.5$  mg/dl for DS-2330b monotherapy and sevelamer

with placebo, respectively (Figure 3). The mean serum phosphate in patients receiving DS-2330b monotherapy decreased from baseline to day 4 of treatment; however, the results did not differ from the placebo group (Figure 4).

The mean serum phosphate in patients receiving either DS-2330b with sevelamer, or sevelamer with placebo also decreased from baseline by day 4 of treatment and continually decreased from baseline to day 15 (Figure 4). No additive serum phosphate-lowering effects of drug co-administration were



**Figure 4.** Change in serum phosphate from baseline over time throughout study. PBO treatment arm (dark blue circles) received placebo to DS-2330b 400 mg TID. DS-2330b treatment arm (light blue squares) received 400 mg DS-2330b PIB formulation TID; DS-2330b + sevelamer group (green triangles) received 400 mg DS-2330b PIB formulation co-administered with 1.6 g open-label sevelamer TID; sevelamer + PBO treatment arm (orange triangles) received open-label 1.6 g sevelamer co-administered with placebo TID. The blood samples were collected after 10 hours of overnight before breakfast. On days 2, 4, 7, 9, and 11 (HD days), the samples were collected at pre-HD. The data are shown as mean  $\pm$  SD. BL, baseline; HD, hemodialysis; PBO, placebo; Pi, phosphate; PIB, powder in bottle; TID, 3 times daily.

**Table 2.** Serum concentration change from baseline in part B

	PBO <i>n</i> = 6	DS2330b <i>n</i> = 9	DS2330b + sevelamer <i>n</i> = 8	Sevelamer + PBO <i>n</i> = 9
Ca <sup>2+</sup> (mg/dl)	-0.267 ± 1.014	0.091 ± 0.3646	0.473 ± 0.5705	0.011 ± 0.4217
FGF-23 (pg/ml)	-442.6 ± 1119.6	-13120.9 ± 24313.5	-10079.9 ± 10201.0	-15754.9 ± 10283.3
iPTH (pg/ml)	88.8 ± 105.0	-55.3 ± 202.0	-83.1 ± 179.7	-81.0 ± 111.6

Ca<sup>2+</sup>, serum calcium; FGF-23, fibroblast growth factor 23; iPTH, intact parathyroid hormone; PBO, placebo.

All data are presented as mean ± SD. Values for Ca<sup>2+</sup> show the change between day 15 and baseline, and FGF-23 and iPTH show the change between day 13 and baseline.

observed in patients receiving DS-2330b with sevelamer compared with sevelamer with placebo.

### Calcium Pharmacodynamics

The albumin-corrected serum calcium fluctuated during the study in all treatment arms, but there were no clinically meaningful changes compared with baseline (Table 2).

### Pharmacokinetic Outcomes and Hemodialysis Clearance

PK properties of DS-2330a were assessed using data of DS-2330b monotherapy and DS-2330b co-administered with sevelamer groups on day 1 and day 13. In DS-2330b monotherapy, there was high variability in plasma DS-2330a concentration and systemic exposure levels among the patients (Table 3). The range of T<sub>max</sub> varied due to the variability of C<sub>max</sub> observed in the patient after each dose. There was an accumulation of plasma DS-2330a on day 13 compared with day 1 (accumulation ratio 1.21 in C<sub>max</sub>, 1.33 in AUC<sub>24h</sub>). The mean (90% confidence interval) C<sub>max</sub> for DS-2330b co-administered with sevelamer was lower than DS-2330b monotherapy treatment, comprising 32.6% (19.0%–56.0%) and 29.6% (15.2%–57.5%) of monotherapy C<sub>max</sub> on day 1 and day 13, respectively (Table 3). The mean (90% confidence interval) AUC<sub>24h</sub> for DS-2330b co-administered with sevelamer was lower than DS-2330b monotherapy treatment, 39.8% (23.8%–66.6%) and 26.9% (14.4%–50.4%) of monotherapy for AUC<sub>24h</sub> on day 1 and day 13, respectively (Table 3). The variability of plasma DS-2330a concentration was lower compared with DS-2330b monotherapy (Figure 5). DS-2330a concentration in dialysate was below detection range in most of the patients who received DS-2330b either by monotherapy or with sevelamer in HD clearance assessment on day 11.

### Safety

Overall, 9 patients (28.1%) experienced ≥1 TEAE, and of these patients, 7 (21.9%) experienced ≥1 TEAE that was considered drug-related. In the placebo arm, 2 patients (33.3%) experienced ≥1 TEAE, compared with 1 patient (11.1%) in the DS-2330b monotherapy treatment arm. In the DS-2330b with sevelamer arm, 3 patients (37.5%) experienced ≥1 TEAE, and 3 patients (33.3%) in the placebo with sevelamer treatment arm experienced ≥1 TEAE. There were no serious AEs; all

TEAEs were either mild or moderate, and all resolved (Table 4). The most common TEAEs were vomiting (6 patients, 18.8%), nausea (3 patients, 9.4%), and constipation (2 patients, 6.3%) (Table 5). The DS-2330b groups did not have an increased incidence of TEAEs, including gastrointestinal (GI)-related TEAEs, compared with placebo group. No clinically meaningful changes were reported in safety laboratory tests (hematology, serum chemistry, thyroid function), vital signs, electrocardiograms, and physical examinations from patients in DS-2330b monotherapy or in combination with sevelamer. No patient interrupted treatment or discontinued the study treatment due to abnormal serum calcium. Overall, no notable safety concerns were observed throughout treatment with DS-2330b monotherapy or in combination therapy with sevelamer.

## DISCUSSION

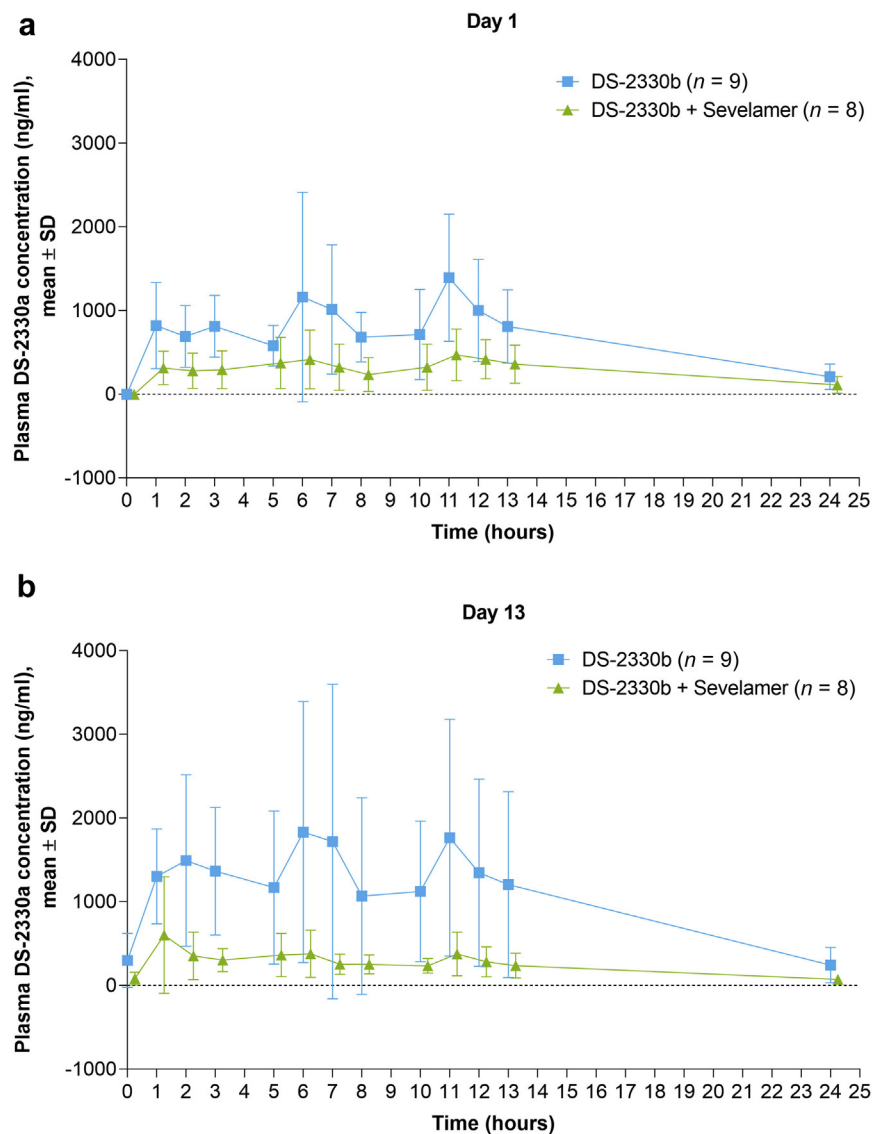
This was the first study to assess the safety, tolerability, PK, and pharmacodynamics of repeated doses of DS-2330b in patients with CKD on HD. Overall, DS-2330b was well tolerated when administered alone or in combination with sevelamer. Serum phosphate reduction was observed in all part B treatment groups, including the placebo arm, but DS-2330b produced only a minimal decrease in serum phosphate either as a single agent or in combination with sevelamer. Sevelamer with placebo treatment showed the highest reduction in serum phosphate among all treatment groups, with a mean decrease of 3.59 mg/dl from

**Table 3.** Pharmacokinetics of DS-2330a on day 1 and day 13 for DS-2330b and DS-2330b with sevelamer treatment groups

	C <sub>max</sub> (ng/ml), mean (SD)	T <sub>max</sub> (h), median (range)	AUC <sub>24h</sub> (ng·h/ml), mean (SD)
DS-2330b ( <i>n</i> = 9)			
Day 1	1895 (1211)	7.0 (2.0, 11.0)	15,355 (6943)
Day 13	2372 (1645)	6.0 (1.0, 12.0)	23,864 (16161)
Accumulation ratio	1.21		1.33
DS-2330b + sevelamer ( <i>n</i> = 8)			
Day 1	568 (276)	8.5 (1.0, 12.0)	6460 (4032)
Day 13	741 (622)	5.0 (1.0, 11.0)	5572 (3018)
Accumulation ratio	1.10		0.90

AUC<sub>24h</sub>, area under the curve 0–24 hours; C<sub>max</sub>, maximum serum concentration; T<sub>max</sub>, time to reach maximum serum concentration.

Accumulation ratio calculated as (mean of day 13)/(mean of day 1).



**Figure 5.** Analysis of DS-2330a plasma concentration during DS-2330b monotherapy and co-administration of DS-2330b with sevelamer on (a) day 1 and (b) day 13 of treatment. Blood samples for pharmacokinetic analysis were collected at predose (before breakfast), and each timepoints presented in the figure on day 1 and day 13 (both non-HD day). The 24-hour postdose sample was collected at pre-HD on day 2 and day 14. The patients fasted at least 4 hours after the morning dose. The data are shown as mean  $\pm$  SD. HD, hemodialysis.

baseline; this reflects a greater decrease in serum phosphate than in previous studies evaluating sevelamer in HD patients.<sup>11,14</sup> The lower plasma concentration of DS-2330a in patients receiving DS-2330b co-administered with sevelamer compared with DS-2330b alone could be explained by sevelamer competing with DS-2330b for phosphate binding sites, causing a reduction in bioavailability of DS-2330b. However, the high DS-2330a serum concentrations achieved in some patients when DS-2330b is administered as monotherapy suggest sufficient solubility and absorption of the drug from the GI tract. This seemingly associated with larger decreases in serum phosphate level than in patients with lower DS-2330a concentrations (Supplementary Figure S2). The absence of clinically meaningful efficacy is likely functional and may be

related to solubility in the GI tract. Interpretation of this relationship is limited due to the small sample size.

**Table 4.** Number of patients who experienced TEAE during treatment in part B

	PBO (n = 6)	DS-2330 (n = 9)	DS-2330 + sevelamer (n = 8)	Sevelamer + PBO (n = 9)
Any TEAE	2 (33.3)	1 (11.1)	3 (37.5)	3 (33.3)
Drug-related TEAE	1 (16.7)	1 (11.1)	2 (25.0)	3 (33.3)
Mild	2 (33.3)	1 (11.1)	1 (12.5)	1 (11.1)
Moderate	0	0	2 (25.0)	2 (22.2)
Severe TEAE	0	0	0	0
Serious TEAE	0	0	0	0
TEAE leading to withdrawal	0	0	0	0

PBO, placebo; TEAE, treatment-emergent adverse event. Data represented as n of patients (%). A patient was counted only once in correspondent treatment for most severe adverse event.

**Table 5.** Summary of TEAE in part B

	PBO (n = 6)	DS-2330 (n = 9)	DS-2330 + sevelamer (n = 8)	Sevelamer + PBO (n = 9)	Total (N = 32)
Any	2 (33.3)	1 (11.1)	3 (37.5)	3 (33.3)	9 (28.1)
GI disorders	2 (33.3)	1 (11.1)	2 (25.0)	3 (33.3)	8 (25.0)
Vomiting	0	1 (11.1)	2 (25.0)	3 (33.3)	6 (18.8)
Nausea	1 (16.7)	1 (11.1)	1 (12.5)	0	3 (9.4)
Constipation	0	0	0	2 (22.2)	2 (6.3)
Abdominal discomfort	0	0	0	1 (11.1)	1 (3.1)
Abdominal distension	1 (16.7)	0	0	0	1 (3.1)
Diarrhea	0	0	1 (12.5)	0	1 (3.1)
Dyspepsia	0	0	0	1 (11.1)	1 (3.1)
Flatulence	0	0	1 (12.5)	0	1 (3.1)
Lip blister	1 (16.7)	0	0	0	1 (3.1)
General disorders and administration site conditions	0	0	1 (12.5)	1 (11.1)	2 (6.3)
Peripheral swelling	0	0	0	1 (11.1)	1 (3.1)
Vessel puncture pain site	0	0	1 (12.5)	0	1 (3.1)
Nervous system disorders	1 (16.7)	1 (11.1)	2 (25.0)	0	4 (12.5)
Dizziness	1 (16.7)	0	0	0	1 (3.1)
Headache	0	0	1 (12.5)	0	1 (3.1)
Hypoesthesia	0	0	1 (12.5)	0	1 (3.1)
Migraine	0	1 (11.1)	0	0	1 (3.1)
Skin and subcutaneous tissue disorders	0	1 (11.1)	0	0	1 (3.1)
Angioedema	0	1 (11.1)	0	0	1 (3.1)

GI, gastrointestinal; PBO, placebo; TEAE, treatment-emergent adverse event. Data represented as n of patients (%).

Correlative comparisons between serum phosphate and FGF-23 showed a decrease in phosphate correlates with a decrease in FGF-23 from baseline concentrations in data from all groups at day 13 of the study ( $r = 0.740$ ) (Figure 6). Correlation was also observed between serum phosphate reduction and iPTH at day 13 ( $r = 0.262$ ) (Figure 7). This was consistent with FGF-23 reduction; however, the magnitude of iPTH change was smaller than FGF-23 reduction, and correlation was less compared with FGF-23.

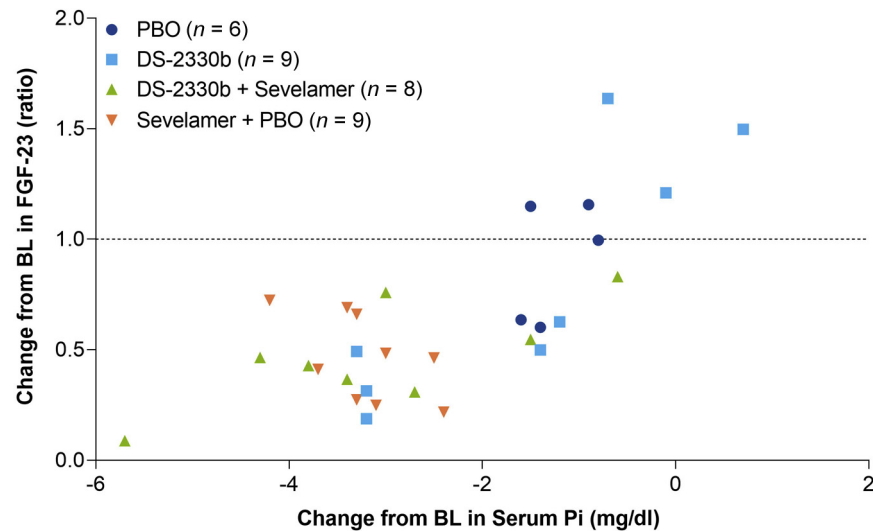
Outcomes from the present study are similar to a phase 1a, 2-arm study of the NaPi-IIb cotransporter inhibitor ASP3325, evaluated for use in patients with end-stage renal disease (NCT02500953 and NCT02510274).<sup>13</sup> The SAD and MAD studies of ASP3325 demonstrated that it was well tolerated with no concerning safety signals in healthy subjects, and the study then evaluated ASP3325 in patients with CKD with hyperphosphatemia on HD. Although no safety concerns were raised, ASP3325 failed to reduce serum phosphate or provide a reduction in phosphate metabolism biomarkers.<sup>13</sup> Interpretation of these results, however, were limited by the relatively small sample size, short treatment duration, and absence of a positive control arm.

Our present study shares the limitations of an overall small sample size and short treatment duration with previous NaPi-IIb studies; however, the inclusion of placebo as control and sevelamer as a positive control (monotherapy and in combination with DS-2330b) allows for definitive conclusions to be drawn with regard

to the efficacy of DS-2330b. Serum phosphate reductions, as well as correlative reductions in FGF-23 and iPTH seen with sevelamer, lend scientific validity to the study, although the magnitude of iPTH reduction was smaller than that of FGF-23. Performing direct sampling of GI fluid and local biopsies may provide a more direct measure of local GI drug concentration and NaPi-IIb cotransporter expression, respectively; however, these invasive procedures are not feasible or ethical in the HD patients in the clinical study setting.

Alternative clinical approaches with other oral inhibitors of active phosphate transport modulating NaPi-IIb have also yielded disappointing results. Niacin and nicotinamide (niacinamide) are known to downregulate NaPi-IIb transporter expression in small intestine in rats.<sup>15,16</sup> However, in a subpopulation of the Atherosclerosis Intervention in Metabolic syndrome with low HDL/High triglycerides: Impact on Global Health trial, in patients with CKD with an estimated glomerular filtration rate of  $<60$  ml/min per  $1.73$  m<sup>2</sup>, niacin minimally reduced the serum phosphate level compared with placebo after 3 years of treatment, and had no effect on FGF-23 or other markers of mineral metabolism.<sup>17</sup> Similarly, comparing nicotinamide to sevelamer treatment in chronic HD patients demonstrated a mean serum phosphorus reduction from baseline of  $0.25$  mmol/l ( $0.77$  mg/dl) versus  $0.40$  mmol/l ( $1.24$  mg/dl) for nicotinamide versus sevelamer, respectively.<sup>18</sup> Furthermore, nicotinamide treatment failed to induce changes in FGF-23 levels in HD patients, and also resulted in a higher



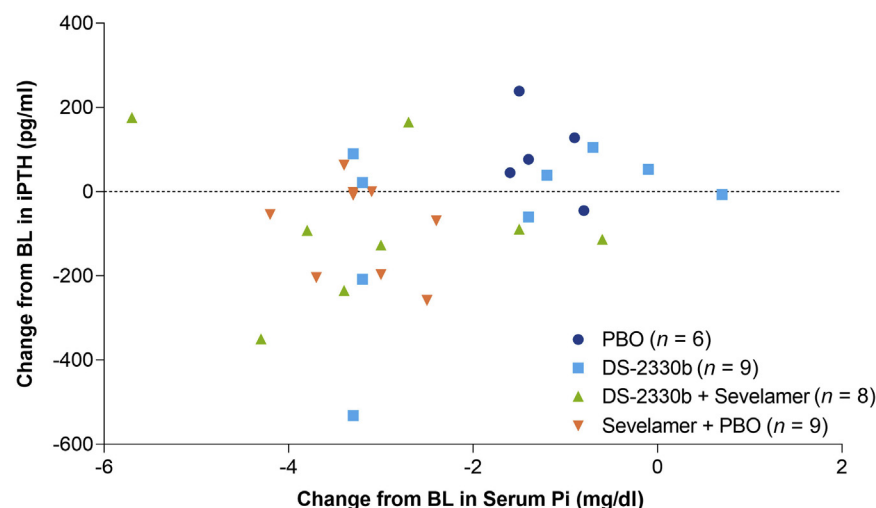


**Figure 6.** Relationship of serum phosphate change from baseline versus FGF-23 change from baseline (ratio) at day 13 of treatment. Serum phosphate change from baseline (mg/dl) shown in x-axis. The ratio of FGF-23 level at day 13 over day 1 is shown in y-axis. Placebo is represented by dark blue circles, DS-2330b by light blue squares, DS-2330b + sevelamer by green triangles, and sevelamer + placebo by orange triangles in the figure.  $r = 0.740$ . BL, baseline; FGF-23, fibroblast growth factor-23; PBO, placebo; Pi, phosphate.

discontinuation rate due to AEs. Downregulation of NaPi-IIb transporter in patients with CKD induces modest but not pronounced effects on serum phosphate lowering and is inferior to sevelamer as monotherapy. Taken together with the results of our DS-2330b study, it suggests the contribution of NaPi-IIb transport in overall phosphate homeostasis in humans may be limited.

In part B of our study, patients were confined for 16 days in a CPU for the duration of the study and on a standard phosphate diet. During the washout period before entering the CPU, some HD patients had intermittent increases in serum phosphate, which was likely caused by a non-experimentally controlled diet. Conversely, despite the controlled diet without

phosphate restriction in the CPU, we noted that serum phosphate decreased in all groups, including placebo. The greater serum phosphate reduction in the placebo and sevelamer arms compared with previously reported data could be due to the standardized diet and/or higher treatment adherence in this study as opposed to a more variable diet/treatment adherence that may occur in an outpatient setting. These observations reflect the challenges of conducting controlled phosphate-lowering clinical studies in HD patients and emphasize the importance of adherence to a controlled diet and treatment with a phosphate binder drug to control hyperphosphatemia in HD patients.



**Figure 7.** Relationship of serum phosphate change from baseline and iPTH change from baseline at day 13. Serum phosphate change from baseline (mg/dl) shown in x-axis. Change of iPTH levels (pg/ml) from day 1 to day 13 is shown in y-axis. Placebo is represented by dark blue circles, DS-2330b by light blue squares, DS-2330b + sevelamer by green triangles, and sevelamer + placebo by orange triangles in the figure.  $r = 0.262$ . BL, baseline; iPTH, intact parathyroid hormone; Pi, phosphate.

## CONCLUSION

Oral DS-2330b does not have clinically meaningful efficacy in HD patients when given as a monotherapy or in combination with the current standard of care phosphate binder. This takes into account the limitations of the study and the use of sevelamer as an active control in the study. Given these findings, DS-2330b does not warrant further clinical development.

## DISCLOSURES

SM is an employee of Daiichi Sankyo, Inc. TCM is an employee and equity owner of Orlando Clinical Research Center. JC is an employee of DaVita Clinical Research. DR is an employee of Kidney Specialists of Minnesota. WM is an employee of Daiichi Sankyo, Inc. CR is an employee of Daiichi Sankyo, Inc.

## ACKNOWLEDGMENTS

This study was funded by Daiichi Sankyo, Inc. (Basking Ridge, NJ). Medical writing and editorial support were provided by Lauren Hanlon, PhD, and Ian Perry, PhD, of AlphaBioCom, LLC (King of Prussia, PA), and funded by Daiichi Sankyo, Inc. We appreciate Robert Crozier, PhD (Global Medical Affairs, Daiichi Sankyo, Inc.), for his advice on manuscript development.

## SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

**Table S1.** Inclusion and exclusion criteria for part B.

**Figure S1.** Dosing schedules for SAD and MAD studies in healthy volunteers (U101 and U102 studies).

**Figure S2.** Relationship of serum phosphate change from baseline versus AUC from 0 to 24 hours (ratio) from baseline at day 13 of treatment.

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