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CADTH COMMON DRUG REVIEW

Clinical Review Report

Sucroferric Oxyhydroxide (Velphoro)

(Vifor Fresenius Medical Care Renal Pharma Ltd.)

Indication: For the control of serum phosphorus levels in adult patients with end-stage renal disease on dialysis

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Abbreviations

AE	adverse event
ANCOVA	analysis of covariance
BMI	body mass index
CDR	CADTH Common Drug Review
CI	confidence interval
CKD	chronic kidney disease
CORD	Canadian Organization for Rare Disorders
CT	computed tomography
ESRD	end-stage renal disease
FAS	full analysis set
GI	gastrointestinal
HR	hazard ratio
HRQoL	health-related quality of life
iPTH	intact parathyroid hormone
ITT	intention-to-treat
IVRS	interactive voice response system
JSDT	Japanese Society for Dialysis Therapy
LD	low dose
LOCF	last observation carried forward
LS	least squares
LTSE	long-term safety extension
KDIGO	Kidney Disease Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
MMRM	mixed-effects model for repeated measures
MAR	missing at random
MCID	minimal clinically important difference
MCS	mental component score
MD	maintenance dose
MID	minimum important difference
PCS	physical component score
PB	phosphate binder
PPS	per-protocol set
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
SE	standard error
SF-36v2	Short Form (36) Health Survey version 2
SO	sucroferric oxyhydroxide
TEAE	treatment-emergent adverse event
WDAE	withdrawal due to adverse event

Drug	Sucroferric oxyhydroxide (Velphoro)
Indication	For the control of serum phosphorus levels in adult patients with end-stage renal disease (ESRD) on dialysis
Reimbursement Request	As an alternative to sevelamer for the control of serum phosphorus levels in patients with end-stage renal disease (ESRD) on dialysis
Dosage Form(s)	Chewable tablet, 500 mg iron (equivalent to 2,500 mg sucroferric oxyhydroxide)
NOC Date	January 5, 2018
Manufacturer	Vifor Fresenius Medical Care Renal Pharma Ltd.

Executive Summary

Introduction

Chronic kidney disease (CKD) is defined as, "abnormalities in structure or function, present for more than three months."[1] CKD affects 5% to10% of the world population.[2] Almost 48,000 patients in Canada are being treated for kidney failure, and 58.4% of them are undergoing routine dialysis.[3] As kidney function declines, abnormalities in serum phosphorus, calcium, and bone mineral metabolism occur as mineral homeostasis is challenged.[1] Hyperphosphatemia occurs in the majority of patients with end-stage renal disease (ESRD) and may be associated with increased mortality and morbidity.[4-6]

Dialysis and dietary restriction alone are usually not sufficient for controlling hyperphosphatemia in patients requiring maintenance dialysis and the vast majority of patients will require pharmacologic treatment with a phosphate binder (PB). PBs decrease serum phosphorus levels by decreasing intestinal absorption from dietary sources. PBs currently available in Canada are either calcium-based (calcium carbonate, calcium acetate), or non–calcium-based (sevelamer hydrochloride, sevelamer carbonate, and lanthanum carbonate). Though widely used, calcium carbonate does not have a Health Canada–approved indication for controlling hyperphosphatemia. According to the clinical expert consulted by CADTH Common Drug Review (CDR), the optimal use of PBs (i.e., how low a phosphorus concentration should be targeted) is controversial. However, when PB treatment is appropriate, calcium-based PBs are most often used in Canada, mainly due to cost and accessibility.

Sucroferric oxyhydroxide (SO; Velphoro) is a chewable tablet, available as 500 mg iron (equivalent to 2,500 mg SO), indicated for the control of serum phosphorus levels in adult patients with ESRD on dialysis.[7] SO is not authorized for use in the pediatric population (i.e., patients < 18 years of age) and is contraindicated in patients with hemochromatosis or any other iron accumulation disorders.

The objective of this report was to perform a systematic review of the beneficial and harmful effects of SO to control serum phosphorus levels in adult patients with ESRD on dialysis.

Results and Interpretation

Included Studies

Four unique randomized controlled trials were included in the CDR systematic review: one phase II dose-finding study, which was considered pivotal in the Health Canada review; two phase III noninferiority studies of SO versus sevelamer; and one switch study designed to compare SO with continued lanthanum treatment. All four trials were conducted in patients with CKD on maintenance dialysis who were currently taking another PB prior to study enrolment. No comparative studies of SO versus calcium-based PBs or placebo-controlled studies were identified.

Study PA-CL-03A[8] was a randomized, open-label, active-controlled, dose-ranging, pivotal phase II study to evaluate the effect of different doses of SO on lowering serum phosphorus levels in 154 patients. After a two-week washout period, patients were randomized to one of five different doses of SO (250 mg, 1,000 mg, 1,500 mg, 2,000 mg, or 2,500 mg iron/day) or sevelamer hydrochloride 4.8 mg/day for six weeks. No dose titration was permitted during the treatment phase of the study. The primary end point was change from baseline in serum phosphorus at the end of treatment. Other end points of interest included the proportion of patients achieving controlled serum phosphorus, serum calcium, and serum intact parathyroid hormone (iPTH) levels. No adjustments for multiplicity were considered — these analyses were based on observed cases with no consideration for imputing missing data, which could be concerning, given the high attrition rate in each treatment group (ranging from 20.0% in the SO 1,500 mg iron/day group to 44.4% in the 2,000 mg iron/day group) and may have compromised randomization. This study was not designed to evaluate the effects of SO versus sevelamer, and results of this study are therefore of limited relevance to this review.

Study PA-CL-05A[9] was an open-label, randomized, active-controlled, pivotal phase III noninferiority study. Patients were randomized in a 2:1 ratio to treatment with either SO (n = 710) or sevelamer carbonate (n = 349). The study consisted of two stages. The primary objective of Study PA-CL-05A was to compare a maintenance dose of SO against switching to a low dose of SO (250 mg iron/day) in a superiority analysis and was based on Stage 2. The 250 mg iron strength of SO is not approved by Health Canada, the dose is not available to Canadian patients, and the results of PA-CL-05A presented in this review are therefore restricted to Stage 1 only. In Stage 1, the dose of both drugs was titrated based on individual patient levels of serum phosphorus during the first eight weeks of treatment. Patients continued on their maintenance dose (SO dose range: 1,000 to 3,000 mg iron/day; sevelamer dose range: 2.4 g/day to 14.4 g/day) to week 24. The key secondary objective, and of relevance to the current review, was to establish noninferiority of SO versus sevelamer based on change from baseline in serum phosphorus at week 12. Other end points of interest to this review included achievement of serum phosphorus control (as per the Kidney Disease Improving Global Outcomes and Kidney Disease Outcomes Quality Initiative [KDOQI] guidelines), duration of serum phosphorus control, serum calcium, iPTH, and health-related quality of life (HRQoL).

Study PA1301[10,11] was an open-label, comparative phase III trial that investigated noninferiority of SO versus sevelamer in Japanese patients with hyperphosphatemia, based on the primary end point of serum phosphorus concentration at the last evaluation (week 12). Patients were randomized either to treatment with SO (n = 108) at a starting dosage of 750 mg iron/day, or to sevelamer (n = 103) at a starting dosage of either 3,000 or 6,000 mg

per day depending on baseline serum phosphorus (1,000 or 2,000 mg/dose three times daily) for 12 weeks. Other end points of interest included achievement of target phosphorus levels, serum calcium, iPTH, and safety.

The study by Otsuki et al.[12] was a phase III switch study of SO in 68 adult patients currently taking lanthanum carbonate hydrate. Patients were randomized to either switch to SO 750 mg iron daily (n = 34) or continue taking lanthanum (n = 34). The dose of PB could be adjusted every two weeks up to a maximum daily dose of 3,000 mg iron SO or 2,250 mg lanthanum. End points of interest included transferrin saturation, and serum phosphorus, calcium, ferritin, and iPTH levels. All results described within this review were obtained from a published report, and the level of detail provided in this publication was not adequate to draw any conclusions pertaining to the efficacy of SO versus lanthanum.

Key limitations identified in the trials included in this review are the open-label design of each study, high frequency of study withdrawals, handling of missing data, and lack of control for multiplicity in statistical testing.

Studies PA-CL-05A and PA1301 are noninferiority phase III studies that provide the most relevant evidence for this CDR review as both evaluated noninferiority versus sevelamer for lowering serum phosphorus, which is aligned with the manufacturer's reimbursement request of SO as an alternative to sevelamer for the control of serum phosphorus levels in patients with ESRD on dialysis.

Efficacy

All-Cause Mortality, Cardiovascular Mortality, Cardiovascular Events, Health-Related Quality of Life, Bone Fractures

Although identified as key efficacy outcomes of interest in this review, none of the included studies assessed all-cause mortality, cardiovascular mortality, cardiovascular events, or bone fractures as efficacy end points. According to the clinical expert, these outcomes are ultimately the most important from a clinical perspective. Findings pertaining to each of these outcomes were assessed as part of the safety evaluations in the included trials.

In Study PA-CL-03A, one patient assigned to the SO 1,000 mg/day group died following gastrointestinal hemorrhage and cardiac arrest.[8] Six patients (4.7%) across SO groups experienced a cardiac disorder treatment-emergent adverse event (TEAE); no such events were reported in the sevelamer group. One patient in the SO 1,000 mg/day group experienced a serious adverse event (SAE) of rib fracture.

In Study PA-CL-05A, a total of 20 patients experienced a fatal TEAE during Stage 1 of the study. Of these, 13 (1.8%) occurred in the SO group and seven (2.0%) occurred in the sevelamer group.[9] Most deaths were due to cardiac disorders, which occurred in six (0.8%) patients in the SO group and in five (1.4%) patients in the sevelamer group. A similar proportion of patients experienced non-fatal cardiac events in the SO and sevelamer groups — 68 (9.6%) and 33 (9.5%), respectively. Eight patients (1.1%) in the SO group and eight patients (2.3%) in the sevelamer group reported an adverse event (AE) related to a bone fracture during Stage 1 of the study.

No deaths were observed in Study PA1301.[10,11] Two patients in the SO group experienced SAEs that were cardiovascular in nature during the treatment period and one bone fracture was reported by one patient in the sevelamer group.

All-cause mortality, cardiovascular mortality, cardiovascular events, and bone fractures were not identified as pre-specified efficacy outcomes in any of the trials included in the review. However, the short duration of the phase III trials (12 to 24 weeks) was likely insufficient to evaluate the efficacy of PBs on all-cause and cardiovascular mortality. Given that none of these outcomes were formally assessed in any of the studies included in the CDR review, no conclusion can be drawn regarding the effect of SO on all-cause mortality, cardiovascular mortality, cardiovascular events, or bone fractures in patients with ESRD.

HRQoL was considered in this review and was identified as important by both patients and the clinical expert contracted by CDR for this review. Only one Study, PA-CL-05A, evaluated HRQoL. In this study, HRQoL was assessed using the Short Form (36) Health Survey (version 2). Change from baseline in the mental and physical component scores was negligible in both the SO and sevelamer groups at week 24.

Serum Phosphorus – Change From Baseline

In the full analysis set (FAS) of Study PA-CL-03A after six weeks of study treatment, the mean change from baseline in serum phosphorus was –0.042 mmol/L in the SO 250 mg iron group, –0.35 mmol/L in the SO 1,000 mg iron group, –0.40 mmol/L in the SO 1,500 mg iron group, –0.64 mmol/L in the SO 2,000 mg iron group, –0.55 mmol/L in the 2,500 mg iron group, and –0.34 mmol/L in the sevelamer group. Reductions from baseline serum phosphorus were reported to be statistically significantly greater in all SO dose groups compared with the SO 250 mg iron group. However, no adjustment was made for multiple testing and no statistical comparison was conducted for any dose of SO compared with sevelamer.

Noninferiority to sevelamer was demonstrated at week 12 in the phase III studies PA-CL-05A and PA1301 based on change from baseline serum phosphorus at week 12.[9,10] In Study PA-CL-05A, the mean (standard deviation [SD]) change from baseline at week 12 was –0.7 (0.62) mmol/L in the SO group and –0.8 (0.67) mmol/L in the sevelamer group in the per-protocol set (PPS).[9] The least squares (LS) mean (standard error) between-groups treatment difference was 0.08 (0.03) mmol/L and the upper bound of the 97.5% confidence interval (CI) was below 0.19 mmol/L, thus SO was considered noninferior to sevelamer. Results in the FAS were consistent with those in the PPS supporting the noninferiority of SO to sevelamer in terms of lowering serum phosphorus levels. Results from the pre-planned superiority analyses were produced using the same model, revealing a statistically significant difference in favour of sevelamer (P = 0.011). At week 12, more patients in the sevelamer group (54.7%) achieved serum phosphorus levels within the KDOQI target compared with patients in the SO group (44.8%).

In the PPS of Study PA1301, the mean serum phosphorus concentration at the end of treatment (week 12) was 1.62 mmol/L in patients treated with SO and 1.72 mmol/L in patients treated with sevelamer, with a difference of –0.11 mmol/L (95% CI, –0.20 mmol/L to –0.02 mmol/L). The upper bound of the 95% CI was below the predefined noninferiority margin of 0.32 mmol/L, thus SO was considered noninferior to sevelamer.[10] At the end of treatment, in the FAS, 79.2% of patients in the SO group and 68.0% of patients in the sevelamer group had achieved target serum phosphorus based on the Japanese Society for Dialysis Therapy target (≥ 1.13mmol/L and ≤ 1.94mmol/L).[13]

Key limitations concerning the noninferiority objective in studies PA-CL-05A and PA1301 include the open-label study design and methods for imputing missing data. It is unlikely that change from baseline in serum phosphorus would be affected by the open-label design

as it is an objective physiological measure. In both studies the last observation carried forward approach was used to handle missing data, which is not conservative in noninferiority trials. However, in Study PA-CL-05A two sensitivity analyses (observed cases and the missing-at-random approach) supported the results.

In the trial by Otsuki et al. there were no appreciable changes in serum phosphorus level from baseline to week 24 between patients treated with SO and those who continued treatment with lanthanum (P = 0.866).[12] In the SO group, mean (SD) serum phosphorus was 1.87 (0.42) mmol/L at baseline and 1.91 (0.52) mmol/L at week 24. In the lanthanum control group, mean (SD) serum phosphorus was 1.84 (0.52) mmol/L at baseline and 1.87 (0.39) mmol/L at week 24. The level of detail provided in this publication is not adequate to draw any conclusions pertaining to the efficacy of SO versus lanthanum.

Serum Calcium

Serum total calcium was a secondary end point in studies PA-CL-03A and PA-CL-05A, while corrected serum calcium was reported in Study PA1301. This information is not specified in Otsuki et al. Mean baseline calcium levels were within the normal range in each of the phase III trials included in this review.

In Study PA-CL-03A, serum total calcium levels at baseline were comparable across the six treatment groups, ranging from 2.10 mmol/L to 2.16 mmol/L in the FAS.[8] Mean change from baseline at the end of treatment ranged from a mean (SD) of –0.06 (0.31) in the SO 250 mg iron/day group to 0.06 (0.14) in the sevelamer group.

In Study PA-CL-05A, the mean serum total calcium levels did not differ at baseline between the SO (2.2 mmol/L) and sevelamer
(2.2 mmol/L) treatment groups. There was no appreciable change in serum total calcium from baseline to week 24 within either the SO or the sevelamer groups (mean [SD] of 0.02 [0.01] and 0.0 [0.20], respectively), and no statistically significant difference between the SO and sevelamer groups, with a mean treatment difference of 0.00 (95% CI, –0.02 to 0.02).[9]

In Study PA1301, the mean (SD) corrected serum calcium levels were similar at baseline in the SO (2.24 [0.14] mmol/L), and sevelamer (2.23 [0.14] mmol/L) treatment groups. Similar mean (SD) changes from baseline at week 12 were also observed in the SO group (0.05 [0.13] mmol/L) and sevelamer group (0.01 [0.14] mmol/L).[10]

In the study by Otsuki et al., there were no appreciable changes in calcium from baseline (mean ± SD SO: 2.25 ± 0.11 mmol/L; lanthanum: 2.25 ± 0.13 mmol/L) to end of treatment at week 24 (SO: 2.25 ± 0.13 mmol/L; lanthanum: 2.23 ± 0.15 mmol/L) between patients treated with SO versus those who continued treatment with lanthanum.[12]

Regardless of specific calcium measures reported, change from baseline was negligible in all groups in all studies, as were between-groups differences. Overall, treatment with SO does not appear to have an effect on serum calcium levels.

Serum Intact Parathyroid Hormone

In Study PA-CL-03A, mean serum iPTH levels at baseline ranged from 23.58 pmol/L in the SO 2,500 mg iron/day group to 28.80 pmol/L in the SO 1,500 mg iron/day group in the FAS.[8] At the end of treatment, mean serum iPTH was generally lower in all treatment groups except in the SO 250 and 1,500 mg iron/day groups.

In Study PA-CL-05A, mean (SD) iPTH was 46.2 (31.87) pmol/L in the SO group and 42.9 (28.89) pmol/L in the sevelamer group.[9] The between-groups difference in the change from baseline in serum iPTH was not statistically significant (least squares mean difference: –1.62 [95% CI, –4.78 to 1.54, *P* = 0.314]).

In Study PA1301, mean (SD) serum iPTH levels generally decreased from baseline (28.31 [16.02] pmol/L, 31.59 [17.48] pmol/L) to end of treatment (21.74 [12.17] pmol/L, 26.57 [17.59] pmol/L) in both the SO and sevelamer groups, respectively.[10] Mean (SD) change from baseline was –6.76 (8.69) pmol/L in the SO group and –5.10 (9.47) pmol/L in the sevelamer group.

In the study by Otsuki et al., there were no significant changes in iPTH from baseline (median [interquartile range] SO: 17.50 [9.33 to 23.65] pmol/L; lanthanum: 16.01 [11.13 to 20.25] pmol/L) to end of treatment at week 24 (SO: 12.94 [8.48 to 18.03] pmol/L; lanthanum: 13.04 [10.60 to 19.62] pmol/L) between patients treated with SO versus those who continued treatment with lanthanum (*P* = 0.689).[12]

Overall, serum iPTH levels varied throughout the duration of each of the studies, but were lower than baseline in both treatment groups at the various end points in PA-CL-03A, PA-CL-05A, and PA1301. There was no change in iPTH levels from baseline in the study by Otsuki et al., likely due to the fact that patients did not discontinue their current PB prior to the baseline assessment. There was no treatment difference between groups in any of the studies.

Harms

Safety results from studies PA-CL-05A and PA1301 are considered the most relevant for the purposes of this review. No dose titration was permitted in Study PA-CL-03A, and safety events of hypophosphatemia and hyperphosphatemia were therefore frequently reported. Based on input from the clinical expert, these events are easily managed via dose titration in clinical practice. A detailed description of safety results is not included in the published report by Otsuki et al.

In Study PA-CL-05A, the proportion of patients reporting AEs was 83.2% and 76.1% in the SO and sevelamer groups, respectively.[9] More patients in the SO group (more than 2%) reported TEAEs of diarrhea, discoloured feces, hyperphosphatemia, and abnormal product taste than in the sevelamer group. In Study PA1301, the incidence of AEs was 78.7% and 66.7% in the SO and sevelamer groups, respectively.[10] The most frequently reported AE in the SO groups was diarrhea (25.0%), followed by nasopharyngitis (22.2%) and discoloured feces (16.7%). In the sevelamer group, the most frequently reported AE was nasopharyngitis (22.9%), followed by constipation (18.1%).

In Study PA-CL-05A, the incidence of SAEs was similar between the SO (18.2%) and sevelamer groups (19.8%).[9] In study PA1301, 5.6% and 4.8% of patients in the SO and sevelamer groups, respectively, experienced an SAE.[10] No SAE was reported in more than one patient in either group. No clear pattern of SAEs emerged in either the SO or sevelamer groups across PA-CL-05A and PA1301.

In Study PA-CL-05A, a higher proportion of patients in the SO group withdrew from Stage 1 of the study due to AEs than in the sevelamer group (15.7% versus 6.6%, respectively).[9] In Study PA1301, 5.6% of patients in the SO group and 6.7% of patients in the sevelamer group withdrew from the study due to AEs.[10] The most common reason for withdrawals due

to AEs was diarrhea (four patients) in the SO group and constipation (three patients) in the sevelamer group.

Gastrointestinal (GI) symptoms were identified as a notable harm of interest for this review and were the most common AEs in the SO and sevelamer groups in PA-CL-05A and PA1301. GI symptoms were also identified as a specific concern in the patient input submission. In Study PA-CL-05A, GI disorders were the most common TEAE and were reported more often in patients receiving SO than sevelamer (45.1% versus 33.6%, respectively).[9] This difference was primarily due to increased reports of diarrhea and discoloured feces in the SO group. The increased incidence of discoloured feces in the SO group was anticipated due to the iron in SO. Constipation, nausea, and abdominal pain/discomfort were reported less often in the SO group compared with the sevelamer group. In Study PA1301, the most common GI symptoms in the SO group were diarrhea (25%), discoloured feces (16.7%), and stomatitis (3.7%).[10] In the sevelamer group, the most common GI symptoms were constipation (18.2%) and abdominal discomfort (4.8%).

Serum ferritin and transferrin saturation were identified as notable harms, given the composition of SO. In Study PA-CL-05A, the difference in serum ferritin and transferrin saturation at week 24 was greater in the SO group than in the sevelamer group.[9] In Study PA1301, mean serum ferritin levels were 207.62 pmol/L and 304.4 pmol/L in the SO group at baseline and week 12, respectively. Transferrin saturation in the SO group was 22.89% and 29.86% at baseline and week 1, respectively.[10] No increase in either of these measures was observed in the sevelamer group. It is unlikely that the open-label nature of the study design influenced either of these parameters as they are objective measures. Overall, these results suggest that iron absorption occurs with SO treatment, although the Health Canada reviewer's report states that the risk of iron overload with long-term SO treatment is minimal.[14]

Potential Place in Therapy[a]

Phosphate retention resulting in hyperphosphatemia is ubiquitous in patients with ESRD who require chronic dialysis.[15,16] Basic science data[17-20] and large observational studies[5,6,21] have implicated serum phosphate as a cardiovascular toxin. As a result, dialysis recipients are counselled to restrict dietary phosphate intake and are prescribed drugs that bind phosphate in the GI tract as a means of limiting phosphate absorption. **Though prescribed to nearly 90% of patients receiving dialysis and supported by guidelines that call for the normalization of serum phosphate, there is no compelling evidence that PBs reduce cardiovascular mortality and morbidity.**[22-24] This is especially concerning given the possibility that PBs may promote vascular calcification and other adverse events.[25] Furthermore, the pill burden associated with phosphate binding significantly impairs quality of life.[26] Finally, phosphate binding is costly, accounting for an ever-increasing proportion of prescriptions given to dialysis patients,[27] with an annual expenditure of > $1.5 billion dollars in the US.[28]

Disordered phosphate metabolism is a nearly universal finding in progressive CKD.[29,30] Until the advanced stages of CKD, serum phosphate is tightly regulated in the normal range of 0.80 mmol/L to 1.50 mmol/L as a result of the complex interplay of the gut, parathyroid gland, bone, and kidneys.[15] As kidney function declines, phosphate retention is mediated by a reduction in the filtered load of this anion. Hyperphosphatemia has long been viewed as a

[a] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

toxic consequence of advanced CKD that should be targeted for correction.[29] The adversity of phosphate was initially attributed to its musculoskeletal effects.[31,32] Subsequently, basic science and translational research have emphasized the putative cardiovascular toxicity of hyperphosphatemia[19,20,33] with data that exposure to high phosphate concentrations induces a phenotypic "switch" in vascular smooth muscle cells that assume the phenotype of osteoblasts.[34]

Current Strategies for Serum Phosphate Control in the Dialysis Population

Dialysis: Adequate dialysis is crucial for serum phosphate control. A typical four-hour dialysis session using a conventional high-flux dialyzer removes 800 mg to 1,000 mg of phosphate.[15] Because the phosphate content of a typical Western diet is approximately 1,000 mg per day (7,000 mg per week),[35] a conventional three-times-weekly dialysis regimen alone cannot maintain phosphate balance.

Dietary restriction of phosphate: Phosphate features prominently in the Western diet, particularly in protein-containing foods such as dairy products, meat, and fish, but also in food additives and taste enhancers.[36,37] Guidelines recommend "limiting dietary phosphate intake" in dialysis recipients, although specific parameters are not provided and no randomized trials have evaluated the impact of dietary phosphate restriction on patient-centred outcomes.[22]

Phosphate binders: The limitations of conventional dialysis regimens and dietary manoeuvres have made intestinal binding of phosphate indispensable to the management of hyperphosphatemia. Taken with meals, PBs prevent the absorption of phosphate, resulting in phosphate excretion via stools. In a study of nearly 24,000 prevalent hemodialysis recipients from 12 countries, 88% of patients were prescribed PBs.[38] *However, despite their pervasive use, the efficacy of any PB in reducing mortality, cardiovascular events, fractures, or any other clinical event has never been tested against placebo/no therapy in a randomized trial.* **In a recent meta-analysis encompassing the spectrum of phosphate binders, Palmer et al. found no evidence that phosphate binding lowered mortality or cardiovascular events compared with placebo.[39]**

Calcium-based products are the leading PBs used around the world, with calcium carbonate being the most widely prescribed binder for Canadian dialysis recipients.[38] Calcium carbonate is effective at reducing serum phosphate[40,41] and is modestly priced.[15] However, the potential for calcium absorption and the subsequent exacerbation of vascular calcification prompted questions about the safety of these agents,[42-47] spurring the emergence of non–calcium-based phosphate binders such as sevelamer and lanthanum.[48,49] Although a recent meta-analysis suggested lower mortality among recipients of non–calcium-based binders, these findings were based on results of small trials at high risk of bias.[39] In the largest trial conducted comparing sevelamer and calcium, sevelamer failed to improve clinical outcomes[50] and non–calcium-based binders are significantly more expensive than calcium-based binders.[15,51] As a result, calcium-based binders continue to be the main pharmacologic agents to lower phosphate in Canadian dialysis recipients. Although alternatives to calcium-based binders may be of interest, the fundamental question of whether PBs modify clinically relevant outcomes seems to be more important than how phosphate is lowered.

Conclusions

Overall, evidence from the four randomized controlled trials included in this CDR review demonstrates that SO is efficacious at lowering serum phosphorus in patients receiving maintenance dialysis, but the impact on mortality and cardiovascular outcomes remains unknown. All-cause mortality, cardiovascular mortality, cardiovascular events, and bone fractures were not identified as pre-specified efficacy outcomes in any of the trials included in the review. However, the short duration of the phase III trials (12 to 24 weeks) was likely insufficient to evaluate the efficacy of PBs on all-cause and cardiovascular mortality. Treatment with SO did not appear to affect patient HRQoL. SO was noninferior to sevelamer in terms of lowering serum phosphorus after 12 weeks of treatment in the two phase III studies (PA-CL-05A and PA1301). These studies provide the most relevant evidence for this CDR review as both evaluated noninferiority versus sevelamer for lowering serum phosphorus, which is aligned with the manufacturer's reimbursement request of SO as an alternative to sevelamer for the control of serum phosphorus levels in patients with ESRD on dialysis. In the pivotal phase III trial (PA-CL-05A), more SO patients withdrew compared with sevelamer patients, and the primary reason for withdrawal was AEs. GI symptoms, specifically diarrhea and discoloured feces, were the most common AEs reported with SO treatment. Findings related to iron parameters suggest that SO may be associated with iron absorption, which may or may not be of clinical relevance. Monitoring of iron parameters is suggested in the product monograph.

All studies, with the exception of Otsuki et al., included sevelamer as a comparator. However, according to the clinical expert, calcium-based PBs are the most appropriate comparators in Canada. As none of the studies included calcium-based PBs as comparators, how SO compares with the standard of care in Canada remains uncertain. Further, there are no placebo-controlled trials to demonstrate the benefit of SO versus standard care in the absence of a PB.

Table 1: Summary of Key Results

Outcome	PA-CL-05A		PA1301		Otsuki et al. (2018)	
	SO	Sevelamer	SO	Sevelamer	SO	Sevelamer
All-cause mortality (SS)	N = 707	N = 348	N = 108	N = 105	NR	NR
N (%)	13 (1.8)	7 (2.0)	0	0		
Cardiovascular mortality (SS)	N = 707	N = 348	N = 108	N = 105	NR	NR
N (%)	6 (0.8)	5 (1.4)	0	0		
Cardiovascular event (SS)	N = 707	N = 348	N = 108	N = 105	NR	NR
N (%)	68 (9.6)	33 (9.5)	2 (1.9)	0		
HRQoL (FAS)	N = 694	N = 347	NR		NR	
Mental component						
Baseline, mean (SD)	49.0 (10.1) n = 690	49.0 (9.8) n = 347				
Week 24 end point, mean (SD)	48.4 (9.8) n = 503	49.1 (9.9) n = 289				
Change from baseline at week 24 end point, mean (SD)	–1.3 (9.6) N = 500	–0.1 (9.0) N = 289				
Treatment difference (95% CI)	0.7 (–0.7 to 2.2)					
Physical component						
Baseline, mean (SD)	42.6 (9.0) n = 690	43.5 (8.6) n = 347				
Week 24 end point, mean (SD)	43.3 (8.9) n = 503	43.3 (8.9) n = 289				
Change from baseline at week 24 end point, mean (SD)	0.0 (7.3) n = 500	–0.3 (6.6) n = 289				
Treatment difference (95% CI)	–0.0 (–1.3 to 1.2)					
Bone fracture (SS)	N = 707	N = 348	N = 108	N = 105	NR	NR
N (%)	8 (1.1)	8 (2.3)	0	1		
Serum phosphorus (PPS)	N = 461	N = 224	N = 100	N = 92	N = 31[a]	N = 32
Baseline, mean (SD)	2.5 (0.59)	2.4 (0.62)	2.51 (0.45)	2.45 (0.39)	1.87 (0.42)	1.84 (0.52)
Week 12 end point, mean (SD)	1.8 (0.43)	1.7 (0.42)	1.62 (0.33)	1.72 (0.33)	NR	NR
Change from baseline at Week 12 end point, mean (SD)	–0.7 (0.62)	–0.8 (0.67)	–0.90 (0.53)	–0.73 (0.45)		
Treatment difference at week 12, LS mean (SE)	0.08 (0.03) 97.5% upper CI, –Inf to 0.15		–0.11 95% CI, –0.20 to –0.02			
Week 24 end point, mean (SD)	1.8 (0.50)	1.6 (0.43)	NR	NR	1.91 (0.52)	1.87 (0.39)
Change from baseline at week 24 end point, mean (SD)	–0.7 (0.66)	–0.8 (0.63)			NR	NR
Treatment difference at week 24, LS mean (SE)	NR				NR	NR

Outcome	PA-CL-05A		PA1301		Otsuki et al. (2018)	
	SO	Sevelamer	SO	Sevelamer	SO	Sevelamer
Serum phosphorus (FAS)	N = 694	N = 347	N = 106	N = 103		
Baseline, mean (SD)	2.5 (0.59)	2.4 (0.57)	2.51 (0.44)	2.45 (0.38)	NR	NR
Week 12 end point, mean (SD)	1.8 (0.47)	1.7 (0.42)	1.63 (0.33)	1.72 (0.34)		
Change from baseline at week 12 end point, mean (SD)	–0.7 (0.63)	–0.7 (0.64)	–0.88 (0.53)	–0.73 (0.46)		
Treatment difference at Week 12, LS mean (SE)	0.10 (0.03) 97.5% upper CI, –Inf to 0.50		NR			
Week 24 end point, mean (SD)	1.8 (0.51)	1.7 (0.45)	NR	NR	NR	NR
Change from baseline at week 24 end point, mean (SD)	–0.7 (0.66)	–0.7 (0.63)				
Treatment difference at week 24, LS mean (SE)	0.05 (0.03) 95% CI, –0.02 to 0.12					
Adverse Events	**SO (N = 707)**	**Sevelamer (N = 348)**	**SO (N = 108)**	**Sevelamer (N = 105)**	**SO (N = 34)**	**Sevelamer (N = 34)**
Patients with > 0 AEs, N (%)	588 (83.2)	265 (76.1)	85 (78.7)	70 (66.7)	NR	NR
Patients with > 0 SAEs, N (%)	129 (18.2)	69 (19.8)	6 (5.6)	5 (4.8)	NR	NR
WDAEs, N (%)	111 (15.7)	23 (6.6)	6 (5.6)	7 (6.7)	3	NR
Notable harms(s)						
GI symptoms[b]						
Diarrhea	142 (20.1)	26 (7.5)	27 (25.0)	3 (2.9)	4	NR
Discoloured feces	109 (15.4)	1 (0.3)	18 (16.7)	1 (1.0)	NR	NR
Constipation	27 (3.8)	25 (7.2)	2 (1.9)	19 (18.2)	NR	NR
Nausea	51 (7.2)	39 (11.2)	2 (1.9)	3 (2.9)	NR	NR
Vomiting	31 (4.4)	19 (5.5)	2 (1.9)	0	NR	NR

AE = adverse event; CI = confidence interval; FAS = full analysis set; GI = gastrointestinal; HRQoL = health-related quality of life; Inf = infinity (as reported by the manufacturer); LS = least squares; PPS = per-protocol set; SAE = serious adverse event; SD = standard deviation; SE = standard error; SO = sucroferric oxyhydroxide; SS = safety set; WDAE = withdrawal due to adverse event.

[a] Although analysis sets are not defined in the Otsuki et al. publication, it is stated that only the remaining patients (31 in the SO group and 32 in the lanthanum group) were included in the analysis.

[b] Occurring in at least 5% of patients in at least one treatment group.

Sources: Study PA-CL-03A Clinical Study Report;[8] Study PA-CL-05A Clinical Study Report;[9] PA1301 Clinical Study Report Synopsis;[10] Koiwa (2017);[11] Otsuki et al. (2018).[12]

Introduction

Disease Prevalence and Incidence

Chronic kidney disease (CKD) is defined as "abnormalities in structure or function, present for > 3 months."[1] CKD affects 5% to 10% of the world population.[2] As of 2018, an estimated one in 10 Canadians were identified as having or being at risk for kidney disease, with the most common cause identified as diabetes, which accounted for 38% of new cases.[3] CKD is classified based on cause, glomerular filtration rate, and albuminuria category. CKD often progresses to end-stage renal disease (ESRD; also termed G5 or kidney failure), where there is minimal to no kidney function remaining. Those with ESRD are classified as having a glomerular filtration rate of < 15 mL/min/1.73m^2).[1] Almost 48,000 patients in Canada are being treated for kidney failure, and 58.4% of these are undergoing routine dialysis.[3] Approximately 47% of Canadians newly diagnosed with renal failure are under the age of 65.

As kidney function declines and mineral homeostasis is challenged, abnormalities in serum phosphorus, calcium, and bone mineral metabolism occur.[1] Hyperphosphatemia occurs in a majority of patients with ESRD and may be associated with increased mortality and morbidity.[4-6] Prolonged elevation of serum phosphorus levels causes soft tissue and vascular calcification and cardiovascular disease, and leads to elevated parathyroid hormone secretion.[52] Secondary hyperparathyroidism may lead to renal bone disease and symptoms of bone and muscular pain, increased incidence of fracture, and abnormalities of bone and joint morphology. Although phosphorous overload itself is usually asymptomatic, some patients may experience symptoms such as itching, tingling sensations on skin or extremities, fatigue, shortness of breath, nausea, muscle pain, muscle cramping, and "pain in the bone."

Some evidence suggests that high serum phosphorus concentration could be related to worse outcomes in patients with CKD.
For example, in one study, every 0.33 mmol/L increase in serum phosphorus concentration was accompanied by an 18% increase in the risk of death (relative risk 1.18; 95% confidence interval [CI], 1.12 to 1.25).[6] In another study, the same 0.33 mmol/L increase in serum phosphorus was associated with an increased prevalence of vascular and valvular calcification.[53] However, to date there are no randomized controlled trials (RCTs) demonstrating that improving metabolic control affects survival.[54,55] The Kidney Disease Improving Global Outcomes (KDIGO) 2017 Guideline Update acknowledges that the body of evidence demonstrating an increased risk of all-cause mortality associated with increased serum phosphorus levels mostly contains a moderate level of bias and is of low quality.[23] See Appendix 5 for further details regarding the relationship between serum phosphorus levels and mortality and cardiovascular comorbidity.

Standards of Therapy

Dialysis and dietary restriction alone are usually not sufficient for controlling hyperphosphatemia in patients requiring maintenance dialysis and the vast majority of patients will require pharmacologic treatment with a phosphate binder (PB). PBs decrease phosphorus levels by decreasing intestinal absorption from dietary sources. Current PBs available in Canada include those that are calcium-based (calcium carbonate, calcium acetate) or non–calcium-based (sevelamer hydrochloride, sevelamer carbonate, and

lanthanum carbonate). According to the clinical expert, not all patients will require treatment with a PB. However, when PB treatment is appropriate, calcium-based PBs are most often used in Canada, mainly due to accessibility.

The most recent Canadian guidelines for the management of CKD that include recommendations for the treatment of abnormalities of mineral metabolism were published in 2008.[55] These guidelines state that serum phosphorus and calcium levels should be maintained within normal levels, but that intact parathyroid hormone (iPTH) may be above normal values. Dietary management is recommended for the treatment of hyperphosphatemia. Calcium-based PBs (calcium carbonate or calcium acetate) are recommended if dietary management alone is insufficient and if hypercalcemia is not present, with a dose-reduction in calcium-based PB if hypercalcemia develops. At the time that these guidelines were published, the panel stated that there was insufficient evidence for recommending treatment with non–calcium-based PBs.

The most recent full guideline by the National Kidney Foundation in the US, the Kidney Disease Outcomes Quality Initiative (KDOQI), was published in 2003.[52] These guidelines recommend that serum phosphorus levels in patients with ESRD on dialysis should be maintained between 1.13 mmol/L and 1.78 mmol/L, and that corrected total calcium should be maintained within a normal range of 2.10 mmol/L to 2.37 mmol/L. The target range recommended for serum iPTH is 16.5 pmol/L to 33.0 pmol/L. Dietary phosphorus should be restricted, and if dietary management alone is insufficient to control serum phosphorus or iPTH, patients should be prescribed PBs. Specific recommendations for patients with ESRD state that either calcium-based or other non-calcium, non-aluminum, or non–magnesium-containing PBs may be used as initial PB treatment. Patients who remain hyperphosphatemic despite treatment with a single PB may receive treatment with an additional PB.

A clinical practice guideline update including recommendations for treatment of CKD with mineral and bone disorder was issued by KDIGO in 2017.[23] Similar to the Canadian and KDOQI 2003 guidelines discussed previously, the KDIGO guidelines recommend lowering serum phosphorus toward the normal range, avoiding hypercalcemia, and maintaining calcium levels within a normal range, but a range of two to nine times the upper limit of normal is acceptable for patients with ESRD. Phosphorus levels should be managed by limiting dietary phosphorus alone or in combination with additional treatment. For patients who require treatment with a PB, it is recommended that the dose of calcium-based binders should be restricted. Long-term use of aluminum-based PBs should be avoided. In patients with persistent hyperphosphatemia, increasing dialytic phosphorus removal is recommended.

The recommendation to restrict the use of calcium-based PBs was based on new evidence from three RCTs that observed higher morbidity/mortality in patients treated with calcium-based PBs versus those treated with non–calcium-based PBs.[25,56,57] A commentary on the KDIGO 2017 guidelines update was published by the KDOQI US working group.[54] Although the group acknowledged that evidence supporting this recommendation is lacking for all calcium-based PBs, they supported limiting the use of calcium-based binders *when possible*. However, some patients may not tolerate the gastrointestinal (GI) events associated with non–calcium-based binders, which could present a challenge in implementing a shift away from using calcium-based binders in clinical practice.

According to the clinical expert consulted by CADTH Common Drug Review (CDR), the use of any PBs to lower serum phosphate toward the normal range has never been rigorously

evaluated with respect to relevant clinical outcomes (e.g., mortality and cardiovascular morbidity or mortality). The clinical expert also stated that calcium-based PBs are the most widely used form of PB treatment in Canada. However, calcium-based PBs may be associated with hypercalcemia and with worsened vascular and other extraskeletal calcification.[25,48,52,58,59] Aluminum-based PBs are also associated with safety concerns, specifically accumulation of systemic aluminum, and their use should be avoided.[23,52] Lanthanum carbonate is associated with a lower pill burden than the other non–calcium-based PBs currently available in Canada (i.e., sevelamer), but also with GI adverse events (AEs) and potentially harmful long-term effects, such as decreased bone quality and risk of fracture, resulting from accumulation of lanthanum.[60] Sevelamer is a calcium- and metal-free PB also associated with GI AEs and a relatively high pill burden, as noted in the patient input submission for the current drug under review.[61-63] The approved indication, recommended dose, and key safety issues for PBs available in Canada are summarized in Table 2.

Drug

Sucroferric oxyhydroxide (SO; Velphoro) is a chewable tablet, containing 500 mg iron (equivalent to 2,500 mg SO), approved by Health Canada for the control of serum phosphorus levels in adult patients with ESRD on dialysis.[7] SO is not approved for use in the pediatric population (i.e., patients < 18 years of age) and is contraindicated in patients with hemochromatosis or any other iron accumulation disorders. The recommended starting dosage is three tablets (1,500 mg iron) per day administered as one tablet (500 mg iron) three times daily with meals. The dosage of SO should be titrated in 500 mg increments per day every two to four weeks until an acceptable serum phosphorus level is reached. Serum phosphorus levels require regular monitoring, and the total daily dose should be divided across meals throughout the day. Optimal serum phosphorus levels are usually achieved at dosages of 1,500 mg to 2,000 mg iron (three to four tablets) per day. The maximum recommended dosage is 3,000 mg iron (six tablets) per day.[7]

SO is a mixture of polynuclear iron(III)-oxyhydroxide (pn- FeOOH), sucrose, and starches.[7] Phosphate binding takes place by ligand exchange between hydroxyl groups and/or water and the phosphate ions throughout the physiological pH range of the GI tract. Both serum phosphorus levels and calcium-phosphorus product levels are reduced as a consequence of the reduced dietary phosphate absorption.[7]

Table 2: Key Characteristics of Phosphate Binders Used in Canada

	Sucroferric Oxyhydroxide[7]	Sevelamer[61-63] (hydrochloride, carbonate)	Lanthanum Carbonate[60]	Calcium-Based PBs (calcium carbonate, calcium acetate)[a64]
Mechanism of action	Iron-based PB	Polymer PB; may also bind bile acids *Note: sevelamer carbonate and sevelamer hydrochloride tablets bind phosphate in a similarly rapid manner*	PB; inhibits the absorption of phosphorus by the formation of highly insoluble lanthanum phosphate complexes	NR
Indication[b]	For the control of serum phosphorus levels in adult patients with ESRD on dialysis	For the control of hyperphosphatemia in patients with ESRD undergoing dialysis	As a phosphate binding agent in patients with ESRD on dialysis	NR
Route of administration	Oral	Oral	Oral	Oral

Recommended dosage range
 	
(All total daily doses should be divided and taken with meals)
	Starting Dosage: 1,500 mg iron (3 tablets) per day
	
	Maintenance Dosage: 1,500 mg to 3,000 mg iron (3 to 6 tablets) per day
	
	Most patients require 1,500 mg to 2,000 mg iron (3 to 4 tablets) per day
		Starting Dosage:
		For patients not using another PB (based on initial serum phosphorus)
		• *1.8 and < 2.4 mmol/L:*
		  ○ 2.4 grams (3 tablets) per day
		• ≥ *2.4 mmol/L:*
		  ○ 4.8 grams (6 tablets) per day
		
		Sevelamer HCl: For patients switching from calcium-based PBs, an equivalent starting dose on a mg/weight basis should be prescribed
		
		Sevelamer carbonate: gram-for-gram basis for patients previously on sevelamer HCl
		
		Maintenance Dosage:
		Sevelamer HCl
		7.1 g to 13 g
		(9 to 17 tablets) per day
		
		Sevelamer carbonate
		6 g to 14.4 g (8 to 18 tablets) per day
			Starting dosage: 750 mg to 1,500 mg (3 tablets) per day
			
			Maintenance dosage: up to 4,500 mg (3 to 6 tablets) per day
			
			Most patients require 1,500 mg to 3,000 mg (3 tablets) per day
				Calcium carbonate
				• 500 mg elemental (1,250 mg tab) t.i.d.
				• Tums: 200 to 400 mg elemental t.i.d.
				• Tums ES: 300 to 600 mg elemental b.i.d. or t.i.d.
				• Ultra: 400 mg elemental t.i.d.
				• Caltrate: 600 mg elemental b.i.d.
				
				Calcium acetate
				• PhosLo, Eliphos 667 (1 tab) to 2,668 mg (4 tab) t.i.d.
				
				As per KDOQI 2003 Guidelines: The total dose of elemental calcium provided by the calcium-based phosphate binders should not exceed 1,500 mg/day

Serious side effects and safety issues	Not approved for use in patients < 18 years of age **Warnings:** • Patients with peritonitis, significant GI disorders, who have undergone major GI surgery, with	**Serious Warnings and Precautions:** Serious cases of dysphagia, bowel obstruction, and perforation have been associated with sevelamer use, some requiring hospitalization and surgery	Safety and efficacy not established in patients < 18 years of age) **Warnings:** • GI obstruction, ileus, subileus, GI perforation and fecal impaction • Constipation • Not established for use	Hypercalcemia, peritonitis, pruritis, xerostomia, muscle cramping, extraskeletal calcification, concomitant OTC antacids use, GI AE, possible ectopic calcification

	Sucroferric Oxyhydroxide[7]	Sevelamer[61-63] (hydrochloride, carbonate)	Lanthanum Carbonate[60]	Calcium-Based PBs (calcium carbonate, calcium acetate)[a64]
	significant hepatic disorders were not included in clinical trials • Can cause discoloured (black) stool, which may visually mask GI bleeding **Contraindications:** • Hypersensitivity to this drug or to any ingredient in the formulation • Hemochromatosis or any other iron accumulation disorders	**Warnings:** • Patients with renal insufficiency may develop hypocalcemia • Difficulty swallowing the tablet • Prevents cholesterol absorption • Not studied in patients not undergoing dialysis • Dysphagia and esophageal tablet retention • Bowel obstruction and perforation • Safety and efficacy of sevelamer carbonate in patients with dysphagia, swallowing disorders, severe GI motility disorders including severe constipation, or major GI tract surgery have not been established • Inflammatory disorders of the GI tract associated with sevelamer crystals have been reported, but causality not demonstrated **Contraindications:** • Hypophosphatemia • Bowel obstruction, known active mucosal injury • Hypersensitivity to sevelamer or one of the other ingredients in the product	in patients with acute peptic ulcer, ulcerative colitis, Crohn's disease, hepatic impairment • Tissue deposition of lanthanum has been demonstrated; rising levels of lanthanum in bone have been noted over time, clinical trials were too short to conclude that lanthanum does not affect bone quality or the risk for fracture or mortality beyond 3 years **Contraindications:** • Hypophosphatemia • Bowel obstruction, ileus and fecal impaction • Hypersensitivity to lanthanum carbonate or one of the other ingredients in the product	
Other (monitoring requirements)	**Serum phosphorus:** Must be monitored during titration as needed until an acceptable serum phosphorous level is reached, with regular monitoring thereafter **Iron:** The formulation of SO gives a product that contains approximately 20% iron by weight. Iron uptake with SO was	• Serum calcium, bicarbonate and chloride levels • Monitor for reduced vitamins D, E, K, and folic acid levels	Serum phosphate levels should be monitored and the dose titrated every 2 to 3 weeks until an acceptable serum phosphate level is reached, with regular monitoring thereafter	Hypercalcemia (in up to 50% of patients) especially if co-administered with calcitriol, vitamin D analogues, PTH over-suppression, development of adynamic bone

	Sucroferric Oxyhydroxide[7]	Sevelamer[61-63] (hydrochloride, carbonate)	Lanthanum Carbonate[60]	Calcium-Based PBs (calcium carbonate, calcium acetate)[a64]
	generally low in patients with CKD; regular monitoring of iron levels should follow standard clinical practice in patients with ESRD on dialysis			

AE = adverse event; b.i.d. = twice daily; CI = confidence interval; CKD = chronic kidney disease; ESRD = end-stage renal disease; GI = gastrointestinal; HCl = hydrochloride; KDOQI = Kidney Disease Outcomes Quality Initiative; NR = not reported; OTC = over the counter; PB = phosphate binder; PTH = parathyroid hormone; SO = sucroferric oxyhydroxide; t.i.d. = three times a day.

[a] No product monographs are available for calcium carbonate or calcium acetate. Calcium carbonate is an over-the-counter medication and is available in Canada as Tums. Calcium acetate was previously available as PhosLo, but is no longer marketed in Canada.

[b] Health Canada indication.

Sources: Velphoro product monograph;[7] Renvela product monograph;[62] Renagel product monograph;[63] Accel-sevelamer product monograph;[61] Fosrenol product monograph;[60] www.RXFiles.ca.[64]

Objectives

To perform a systematic review of the beneficial and harmful effects of SO chewable tablet, 500 mg iron (equivalent to 2,500 mg SO), for the control of serum phosphorus levels in adult patients with ESRD on dialysis.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the manufacturer's submission to CDR and Health Canada, as well as those meeting the selection criteria presented in Table 3.

Table 3: Inclusion Criteria for the Systematic Review

Patient population	Adult patients with ESRD on dialysis **Subgroups:** Age (≥ 65 vs. < 65 years of age) Dialysis status (PD vs HD) PB-naive vs PB-experienced Prior response to PBs
Intervention	SO chewable tablet, 500 mg iron (equivalent to 2,500 mg SO) at the Health Canada–recommended dosage: • *Starting dosage*: 1,500 mg iron (3 tablets) per day • *Maximum recommended dosage*: 3,000 mg iron (6 tablets) per day

Comparators	• *Calcium-based PBs*
	  ○ calcium carbonate
	  ○ calcium acetate
	• *Non-calcium-based PBs*
	  ○ sevelamer hydrochloride
	  ○ sevelamer carbonate
	  ○ lanthanum carbonate
	• *Placebo*
	
	Note: Evidence for each comparator as monotherapy or in combination with other PBs will be considered

Outcomes	**Efficacy outcomes:** • All-cause mortality • Cardiovascular mortality • Cardiovascular events • HRQoL[a] • Bone fracture • Serum phosphate level[a] • Serum calcium • PTH levels **Harms outcomes:** AEs, SAEs, WDAEs, notable harms (GI symptoms,[a] serum ferritin, transferrin saturation)
Study design	Published and unpublished phase III and IV RCTs

AE = adverse events; ESRD = end-stage renal disease; GI = gastrointestinal; HD = hemodialysis; PB = phosphate binder; PD = peritoneal dialysis; PTH = parathyroid hormone; HRQoL = health-related quality of life; RCT = randomized controlled trial; SAE = serious adverse events; SO = sucroferric oxyhydroxide; WDAE = withdrawal due to adverse event.

[a] These outcomes were identified as being of particular importance in the input received by CADTH from patient groups.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was the drug name: sucroferric oxyhydroxide (Velphoro).

No methodological filters were applied to limit retrieval. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on July 23, 2018. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on November 21, 2018. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters):

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4, and excluded studies (with reasons) are presented in Appendix 3.

Results

Findings from the Literature

Four studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4. A list of excluded studies is presented in Appendix 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

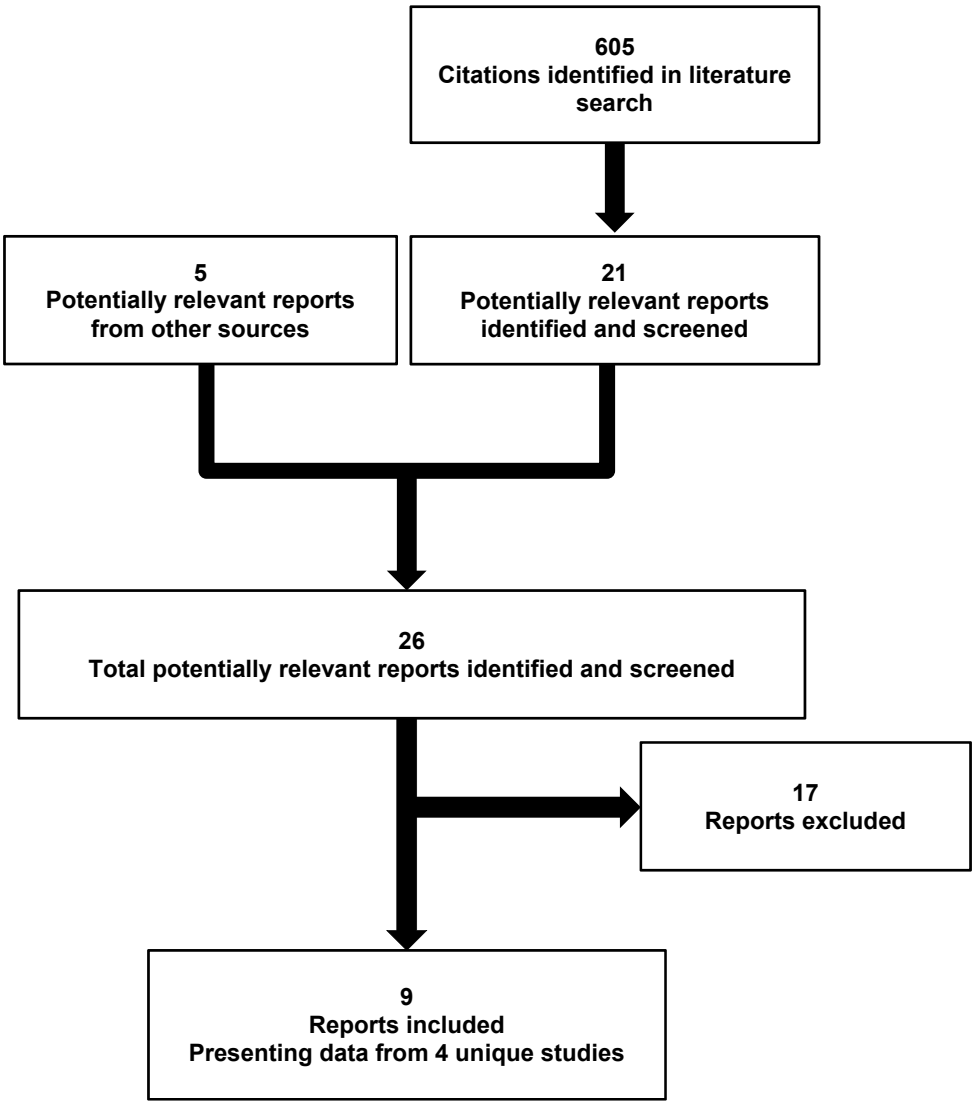


Table 4: Details of Included Studies

		PA-CL-03A	PA-CL-05A[a]	PA1301	Otsuki et al. (2018)
Designs and Populations	**Study design**	OL, active-controlled, phase II RCT	OL, active-controlled, phase III RCT (noninferiority for key secondary end point)	OL, active-controlled, noninferiority, phase III RCT	OL, active-controlled RCT
	Locations	44 sites in Europe, 6 sites in US	56 sites in Europe, 66 sites in US, 52 sites in ROW (Croatia, Russia, Serbia, South Africa, Ukraine)	31 sites in Japan	NR
	Randomized (N)	154	1,059	213	68
	Inclusion criteria	• Adults ≥ 18 years of age • Stable maintenance HD 3 times a week for ≥ 3 months before screening • Following a restricted phosphate diet • Receiving stable doses of PB for at least 1 month • Constant dose of Vitamin D, Vitamin D metabolites, or calcimimetics, for at least 1 month prior to screening, if receiving • Stable calcium content in dialysate for at least 1 month prior to screening • Stable dose of erythropoietin for at least 1 month, if receiving • Serum phosphorus levels > 1.78 mmol/L	• Adults ≥ 18 years of age • Stable maintenance HD 3 times a week • Kt/V of ≥ 1.2 or PD with a Kt/V of ≥ 1.7 for ≥ 3 months before screening (no home or nocturnal HD) • Receiving stable doses of PB for at least 1 month • Serum phosphorus levels ≥ 1.94 mmol/L during washout	• Chronic renal failure on dialysis 3 times/week for at least 12 weeks prior to washout • Stable dose of PB ≥ 4 weeks prior to washout • Predialysis serum phosphorus concentration > 1.94mmol/L and ≤ 3.23mmol/L at week –1 • No change in vitamin D receptor activator, calcimimetic, or osteoporosis drug ≥ 4 weeks prior to washout • Able to discontinue PB for duration of washout • ≥ 20 years of age	• ≥ 20 and ≤ 85 years of age • HD duration > 6 months • Currently taking lanthanum carbonate hydrate
	Exclusion criteria	• Uncontrolled hyperphosphatemia (> 2.5 mmol/L) while on PBs • Hypercalcemia (serum calcium > 2.5 mmol/L) • Serum calcium < 1.9 mmol/L • Severe hyperparathyroidism (iPTH levels > 600 ng/L) • Known history of non-response to PBs • Iron deficiency anemia defined as hemoglobin < 10 g/dL and (ferritin	• iPTH levels > 84.84 pmol/L (iPTH > 63.63 pmol/L could be considered) • Planned parathyroidectomy • Major GI surgery or significant GI or hepatic disorders within 3 years of screening • Unstable angina, hypertension, uncontrolled diabetes, estimated life expectancy < 12 months, anticipated	• Corrected serum calcium ≤ 1.88 mmol/L or > 2.75mmol/L, 1 week prior to baseline • iPTH > 84.84 pmol/L at start of washout • History of hemochromatosis or iron accumulation disorder, serum ferritin > 1,797.60 pmol/L, TSAT	• History of severe heart failure, angina, myocardial infarction, or stroke within the previous 6 months • Concomitant hemorrhagic disease, infectious disease, liver dysfunction, thyroid disease, or malignancy, or treatment with steroids or immunosuppress-ants

		PA-CL-03A	PA-CL-05A[a]	PA1301	Otsuki et al. (2018)
		< 224.7 pmol/L or TSAT < 20%) • History of hemochromatosis, or other iron storage disorders • Significant (based on Investigator's judgment) GI disorder • Treatment with sevelamer within 3 months • Treatment with lanthanum carbonate at any time	renal transplant • History of hemochromatosis, or history of other iron storage disorders, serum ferritin > 4,494 pmol/L • Patients on non–calcium-based PBs with hypercalcemia (serum total calcium > 2.60 mmol/L) at screening • Patients with hypocalcemia (serum total calcium < 1.9 mmol/L) at screening • Patients taking more than 2 PBs concomitantly prior to screening or subjects who are PB-naive prior to screening	> 50% at start of washout • Severe GI disorders, as determined by the investigator • History of digestive tract procedure	• Current hospitalization • Treatment with SO or ferric citrate hydrate within the previous 6 months
DRUGS	**Intervention**	SO chewable tablets containing 250 mg iron, t.i.d. with meals for 6 weeks; no dose titration was permitted • 250 mg/day (1 tablet with largest meal) • 1,000 mg/day (4 tablets) • 1,500 mg/day (6 tablets) • 2,000 mg/day (8 tablets) • 2,500 mg/day (10 tablets)	SO chewable tablets containing 500 mg iron Starting dosage of 1,000 mg iron/day (2 tablets) titrated for efficacy and tolerability up to a maximum of 3,000 mg iron/day (6 tablets); divided with meals	SO chewable tablets containing 250 mg iron Starting dosage of 750 mg iron/day (3 tablets) titrated up to a maximum of 3,000 mg/day) based on serum phosphorus concentration; divided with meals	SO starting dosage of 750 mg iron/day titrated up to a maximum of 3,000 mg iron/day based on serum phosphorus level
	Comparator(s)	Sevelamer HCl 4.8 mg/day (6 tablets) for 6 weeks; no dose titration was permitted	Sevelamer carbonate 800 mg tablet Starting dosage of 2.4 g/day (3 tablets) titrated for efficacy and tolerability up to a maximum of 14.4 g/day (18 tablets); divided with meals	Sevelamer HCl 250 mg tablet Starting dosage of either 3,000 or 6,000 mg/day depending on serum phosphorus concentration and titrated up to 9,000 mg/day; divided with meals	Current dosage of lanthanum carbonate hydrate at enrolment titrated up to 2,250 mg daily based on serum phosphorus level
DURATION	**Phase**				
	Screening	1 week	NR	NR	NR
	Run-in (washout)	2 weeks	2 to 4 weeks	3 weeks	NR
	Treatment	6 weeks	24 weeks	12 weeks	Patients were

		PA-CL-03A	PA-CL-05A[a]	PA1301	Otsuki et al. (2018)
					monitored for 24 weeks
	Follow-up	2 weeks	Option to enrol in PA-CL-5B for up to 52 weeks	NR	NR
Outcomes	**Primary end point**	Change from baseline in serum phosphorus levels at the end of treatment	NA[a]	Adjusted serum phosphorus concentration at the end of treatment	Change in FGF-23 levels *(outcome not included in the current review based on the systematic review protocol)*
	Other end points	*Secondary end points:* • Change from baseline in serum phosphorus levels at each time point • Proportion of patients achieving controlled serum phosphorus levels (i.e., ≥ 1.13 mmol/L to ≤ 1.78 mmol/L) after 1, 2, 3, 4, 5, and 6 weeks of treatment • Time to reach the first controlled serum phosphorus level • Serum phosphorus at each time point • Serum iPTH levels at each time point • Change in serum iPTH levels from baseline at each time point *Safety:* • AEs, SAEs WDAEs	*Secondary end points:* • Change from baseline in serum phosphorus levels at week 12 • Change from baseline in serum phosphorus levels at week 1 through to week 8, weeks 12, 16, 20, and 24 • Proportion of patients achieving controlled serum phosphorus levels within KDOQI target (i.e., ≥ 1.13 mmol/L to ≤ 1.78 mmol/L) at week 12 and week 24 • Proportion of patients achieving controlled serum phosphorus levels within KDIGO target 0.81 mmol/L to 1.45 mmol/L • Duration of serum phosphorus levels in the KDIGO normal range 0.81 mmol/L to 1.45 mmol/L • Duration of serum phosphorus levels in the KDOQI target range of 1.13 mmol/L to 1.78 mmol/L *Secondary end points related to both efficacy and safety:* • Serum calcium at each time point and change from baseline • Serum iPTH at each time point and change from baseline *Safety:*	*Secondary end points:* • Corrected serum calcium concentration • Serum iPTH concentration *Additional evaluations* • Change in serum phosphorus concentration from baseline to end of treatment • Achievement of target serum phosphorus of both 1.13 mmol/L to 1.94 mmol/L (JSDT) and 1.13 mmol/L to 1.78 mmol/L (KDOQI) *Safety* AEs, TSAT, ferritin	• Changes in serum phosphate, serum calcium, iPTH, serum ferritin, TSAT • Safety

		PA-CL-03A	PA-CL-05A[a]	PA1301	Otsuki et al. (2018)
			• Iron status (TSAT, ferritin) *Additional end points:* • Component and domain scores on the SF-36 (version 2)		
NOTES	**Publications**	Wüthrich et al. (2013)[65]	Floege et al. (2014)[66]	Koiwa et al. (2017)[11]	Otsuki et al. (2018)[12]

AE = adverse event; t.i.d..= three times a day; CI = confidence interval; FGF-23 = fibroblast growth factor 23; GI = gastrointestinal; HD = hemodialysis; iPTH = intact parathyroid hormone; JSDT = Japanese Society for Dialysis Therapy; KDIGO = Kidney Disease Improving Global Outcomes; KDOQI = Kidney Disease Outcomes Quality Initiative; Kt/V = dialyzer clearance of urea × time divided by volume of body water; NR = not reported; OL = open-label; PB = phosphate binder; PD = peritoneal dialysis; PO = oral administration; RCT = randomized controlled trial; ROW = rest of world; SAE = serious adverse event; SF-36 = Short Form (36) Health Survey; SO = sucroferric oxyhydroxide; TSAT = transferrin saturation; WDAE = withdrawal due to adverse event.

Note: Two additional reports were included: CADTH Common Drug Review submission[67] and Health Canada reviewer's report.[14]

[a] Details of Study PA-CL-05A summarized in this table pertain to Stage 1 only as this is the focus of the clinical review. The primary objective of Study PA-CL-05A was to compare a maintenance dose of SO with the low dose of SO 250 mg iron/day in a superiority analysis and was based on Stage 2. See Description of Studies section for further details.

Sources: Study PA-CL-03A Clinical Study Report;[8] Study PA-CL-05A Clinical Study Report;[9] PA1301 Clinical Study Report Synopsis;[10] Koiwa (2017);[11] Otsuki et al. (2018).[12]

Included Studies

Description of Studies

Four unique studies were included in the CDR systematic review. Two of the studies were considered pivotal by Health Canada: PA-CL-03A and PA-CL-05A.

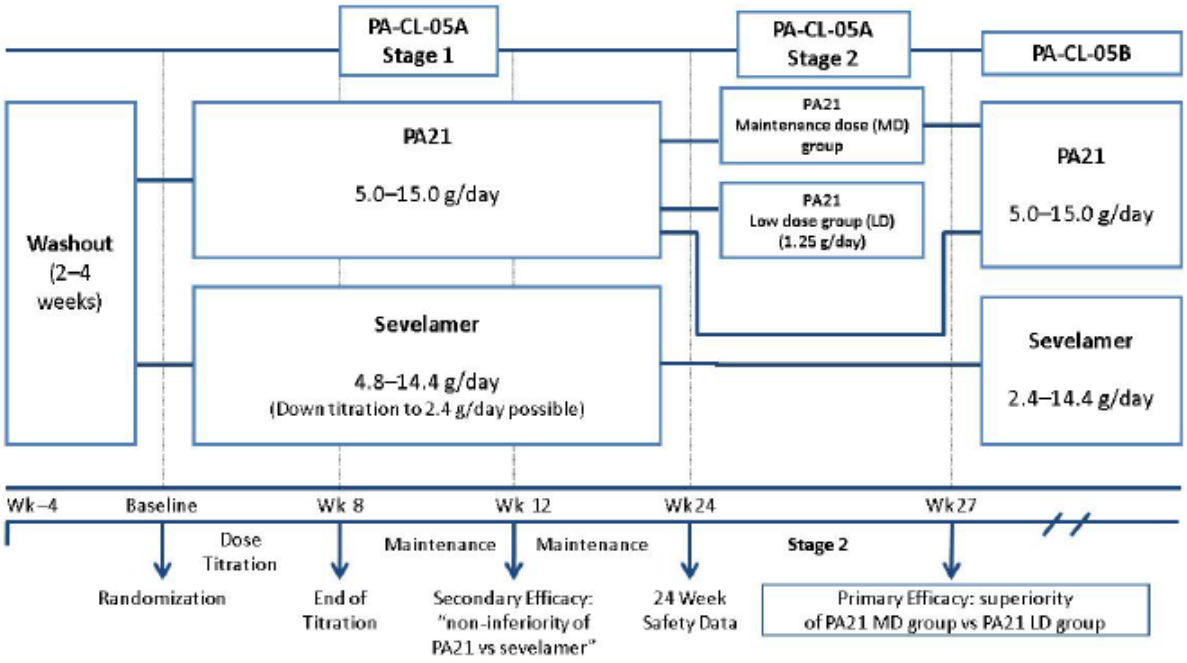
Study PA-CL-03A[8] (N = 154) was a randomized, open-label, active-controlled, dose-ranging, pivotal phase II study to evaluate the effect of different doses of SO on lowering serum phosphorus levels in patients with CKD on maintenance hemodialysis. After a two-week washout period during which patients discontinued treatment with their current PB, patients were randomized on a 1:1:1:1:1:1 basis using a central interactive voice response system (IVRS) to one of five different dosages of SO (250 mg, 1,000 mg, 1,500 mg, 2,000 mg, or 2,500 mg iron/day) or sevelamer hydrochloride 4.8 mg/day for six weeks. Randomization was stratified by geographic region. No dose titration was permitted during the treatment phase of the study for either study drug. The six-week treatment phase was followed by a two-week runout phase during which no study treatment was received.

Study PA-CL-05A[9] (N = 1,059) was an open-label, randomized, active-controlled pivotal phase III study to evaluate the efficacy and safety of SO versus sevelamer in patients with CKD on maintenance hemodialysis. All patients who were eligible for participation discontinued treatment with their previous PB during a two- to four-week washout period. The study consisted of two stages (Figure 2). In Stage 1, patients were randomized in a 2:1 ratio stratified by dialysis status and country to treatment with either SO at a starting dosage of 1,000 mg iron/day or sevelamer carbonate at a starting dosage of 4.8 g/day. The dose of both drugs was titrated based on individual patient level of serum phosphorus during the first eight weeks of treatment. Patients continued on their maintenance dosage (SO dosage range: 1,000 mg to 3,000 mg iron/day; sevelamer dosage range: 2.4 g/day to 14.4 g/day) to week 24. At week 24 (start of Stage 2), a subgroup of patients (n = 99) who were initially

assigned to the SO treatment group and who had a controlled serum phosphorus level of < 1.78 mmol/L (< 5.5 mg/dL) at week 20 were re-randomized to either continue on their maintenance dose of SO or were assigned to the SO low-dose group (250 mg iron/day, the sub-therapeutic dose of SO used in PA-CL-03A) for three weeks. All patients who completed Stage 1 (except those who were re-randomized to Stage 2) had the option of continuing their assigned treatment with either SO or sevelamer for an additional 28 weeks in the PA-CL-05B extension study. Results of PA-CL-05B are presented in Appendix 6.

Note that the primary objective of Study PA-CL-05A, which was based on Stage 2, was to compare a maintenance dosage of SO against the low dosage of SO 250 mg iron/day in a superiority analysis. The 250 mg iron strength of SO is not approved by Health Canada and this dose will not be available to Canadian patients. The results of PA-CL-05A presented in this review are therefore restricted to Stage 1 only. The key secondary objective, and focus of the current CDR review, was to establish noninferiority of SO with sevelamer.

Figure 2: PA-CL-05A Study Design



LD = low-dose; MD = maintenance dose; Wk = week.

Source: PA-CL-05A Clinical Study Report.[9]

Study PA1301[10,11] (N = 213) was an open-label, comparative phase III noninferiority trial designed to test for noninferiority of SO versus sevelamer in Japanese patients with hyperphosphatemia on hemodialysis. After a three-week washout period during which patients were required to stop using their current PB, patients were randomized in a 1:1 ratio to either treatment with SO at a starting dosage of 750 mg iron/day (maximum dosage: 3,000 mg iron/day), or sevelamer at a starting dosage of either 3,000 or 6,000 mg per day depending on baseline serum phosphorus (1,000 or 2,000 mg/dose three times daily) for 12 weeks. No details are provided regarding whether randomization was stratified.

The study by Otsuki et al.[12] (N = 68) was an open-label phase III trial of SO in adult patients with CKD on dialysis currently taking lanthanum carbonate hydrate. No washout period was included in this study. Patients were randomized to either switch to SO 750 mg iron daily (maximum dose 3,000 mg iron/day) or to continue taking lanthanum (maximum dose 2,250 mg/day). Patients were randomized by an independent investigator using the dynamic balancing method accounting for age, sex, duration of hemodialysis, phosphate levels, and hemoglobin concentration. The primary end point in this study was change in fibroblast growth factor 23 levels, which is beyond the scope of this review.

None of the studies were conducted at any sites in Canada.

Populations

Inclusion and Exclusion Criteria

Table 4 provides a list of key inclusion and exclusion criteria for each included trial.

Studies PA-CL-03A, PA-CL-05A, and PA1301 were all conducted in adult patients with CKD on stable maintenance dialysis three times a week for at least three months and who were required to be on a stable dose of PBs for at least one month. Patients previously naive to PB treatment were not included. In general, patients were excluded if it was considered unlikely that treatment with a PB would have an effect on serum phosphorus. Specifically, patients were excluded from PA-CL-03A if they had uncontrolled hyperphosphatemia while on PBs, and all three studies excluded patients with high iPTH levels (> 63.63 pmol/L [600 ng/mL] in PA-CL-03A and > 84.84 [800 ng/mL] in PA-CL-05A and PA1301).

In the Otsuki et al. study, patients ≥ 20 and ≤ 85 years of age with CKD were eligible for participation if they had been on dialysis for more than six months and were currently taking lanthanum. Of note, patients were excluded if they had a history of severe heart failure, angina, myocardial infarction, or stroke within the previous six months, or were currently hospitalized.

Baseline Characteristics

Key differences in patient demographics, specifically body weight and dialysis status, are apparent in the PA-CL-03A and PA-CL-05A studies versus PA1301 and Otsuki, which were conducted exclusively in Japan. Body weight in PA1301 and Otsuki is lower than in PA-CL-03A and PA-CL-05A. Study PA1301 and Otsuki did not include patients on peritoneal dialysis, but did include patients undergoing hemodiafiltration. Despite this, the majority of patients in each of the studies was undergoing hemodialysis. The primary underlying causes of ESRD — glomerulonephritis and diabetes mellitus — were similar across studies, although hypertension was also common in patients included in PA-CL-05A. In the phase III studies, the most common prior PB was a calcium-based PB followed by sevelamer.

The demographic characteristics were generally similar across groups in Study PA-CL-03A (Table 5).[8] Most patients were male (approximately 60%) and white (approximately 95%). The most common cause of CKD was “other” (42.1%) and glomerulopathy (23.9%). The mean duration of CKD differed across the groups, with the shortest mean duration (59.1 months) in the SO 250 mg iron group and the longest mean duration (118.3 months) in the sevelamer group.

In Study PA-CL-05A, almost half the patients (48.4%) in the study population were from the US and 22.3% were from the EU.[9] The majority of the patients were male (57.8%), white (76.8%), and undergoing hemodialysis (91.8%). Baseline characteristics were generally

similar between the SO and sevelamer treatment groups (Table 6). There was a higher proportion of male patients in the SO group than in the sevelamer group (44.8% versus 36.9%, respectively). The most common reason for ESRD was diabetes mellitus (27.9%). The average time of ESRD was 65 months. A total of 14.6% of patients was previously taking more than one PB; the remainder were on one PB prior to washout. Most patients (63%) were previously taking a calcium-based PB (carbonate or acetate) and approximately one-third (33%) were taking sevelamer (hydrochloride or carbonate).

Study PA1301 was conducted only in hemodialysis centres in Japan.[10] There were no notable differences in the majority of demographics and baseline disease characteristics (see Table 6), with the exception that there were more males than females in the SO arm. Approximately two-thirds of patients included in the study were previously taking a calcium-based PB (71% to 79%), approximately one-third were previously taking sevelamer (33%), and almost half had previously taken lanthanum (47%). Previous treatment with these different types of PBs was similar between groups.

In the study by Otsuki et al.,[12] demographics and baseline disease characteristics did not differ significantly between the SO and lanthanum groups (Table 7). The mean ± standard deviation (SD) age of patients was 63.2 ± 12.8 years and 64.3 ±10.8 years in the SO and lanthanum groups, respectively. In both groups, most patients were male (64.5% in the SO group and 68.8% in the lanthanum group) and the duration of dialysis was 49 months. Hemodialysis was the dialysis mode in most patients (SO: 29/31, 93.5%; lanthanum: 29/32, 90.6%), with hemodiafiltration in the remaining patients. Cardiovascular comorbidity and previous medication was similar between groups. Calcium carbonate was being taken by 74.2% and 78.1% of patients and sevelamer was being taken by 38.7% and 43.8% of patients in the SO and lanthanum groups, respectively.

Table 5: Summary of Baseline Characteristics (Full Analysis Set) for Study PA-CL-03A

	250 mg iron (1.25 g SO)/day N = 26	1,000 mg iron (5.0 g SO)/day N = 26	1,500 mg iron (7.5 g SO)/day N = 25	2,000 mg iron (10.0 g SO)/day N = 25	2,500 mg iron (12.5 g SO)/day N = 24	Sevelamer HCl N = 24
Age						
Mean (SD)	60.1 (12.29)	59.7 (13.80)	61.9 (13.71)	60.8 (13.21)	59.3 (12.32)	61.6 (11.22)
Height (cm)						
Mean (SD)	169.5 (10.93)	169.3 (8.97)	168.6 (11.65)	166.8 (7.29)	170.0 (9.45)	166.4 (9.70)
Sex						
Male	17 (65.4%)	19 (73.1%)	16 (64.0%)	15 (60.0%)	13 (54.2%)	14 (58.3%)
Female	9 (34.6%)	7 (26.9%)	9 (36.0%)	10 (40.0%)	11 (45.8%)	10 (41.7%)
Race						
White	24 (92.3%)	26 (100.0%)	24 (96.0%)	22 (88.0%)	24 (100.0%)	23 (95.8%)
Black	2 (7.7%)	0 (0.0%)	0 (0.0%)	2 (8.0%)	0 (0.0%)	0 (0.0%)
Asian	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	1 (4.2%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)
Weight (kg)						
n	26	26	25	27	24	26
Mean (SD)	78.03 (19.19)	77.92 (13.02)	71.70 (16.42)	80.37 (15.06)	81.06 (17.67)	74.84 (13.53)
Reason for CKD						
Glomerulopathy	7 (26.9%)	4 (15.4%)	6 (24.0%)	8 (32.0%)	5 (20.8%)	7 (29.2%)
Vascular nephropathy	7 (26.9%)	4 (15.4%)	5 (20.0%)	7 (28.0%)	3 (12.5%)	3 (12.5%)
Interstitial nephropathy	2 (7.7%)	2 (7.7%)	4 (16.0%)	3 (12.0%)	4 (16.7%)	3 (12.5%)
Other	9 (34.6%)	16 (61.5%)	9 (36.0%)	7 (28.0%)	12 (50.0%)	11 (45.8%)
Missing	1 (3.8%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Duration of CKD (months)						
n	25	26	24	24	24	24
Mean (SD)	59.1 (79.29)	64.6 (56.56)	87.2 (71.75)	90.7 (111.04)	85.2 (66.95)	118.3 (140.29)
Prior PB use, n (%)						
Calcium acetate	5 (19.2)	7 (26.9)	4 (16.0)	7 (28.0)	4 (16.7)	4 (16.7)
Calcium carbonate	17 (65.4)	15 (57.7)	17 (68.0)	17 (68.0)	18 (75.0)	18 (75.0)
Sevelamer	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.0)	0 (0.0)	0 (0.0)

CKD = chronic kidney disease; SO = sucroferric oxyhydroxide; SD = standard deviation.

Source: Study PA-CL-03A Clinical Study Report.[8]

Table 6: Summary of Baseline Characteristics for PA-CL-05A Stage 1 and PA1301 (Full Analysis Set)

	PA-CL-05A		PA1301	
	SO (N = 694)	Sevelamer (N = 327)	SO (N = 106)	Sevelamer (N = 103)
Age (years)				
n	694	347	106	103
Mean (SD)	56.3 (13.40)	55.8 (14.60)	61.1 (11.9)	60.7 (11.9)
Sex, n (%)				
Male	383 (55.2)	219 (63.1)	76 (71.7)	61 (59.2)
Female	311 (44.8)	128 (36.9)	30 (28.3)	42 (40.8)
Race, n (%)				
White	536 (77.2)	263 (75.8)	NR	NR
Black/African-American	127 (18.3)	75 (21.6)		
Asian	9 (1.3)	6 (1.7)		
American Indian/Alaska Native	1 (0.1)	0 (0.0)		
Native Hawaiian/Other Pacific Islander	6 (0.9)	1 (0.3)		
Other	15 (2.2)	2 (0.6)		
Ethnicity, n (%)				
Hispanic or Latino	88 (12.7)	38 (11.0)	NR	NR
Non-Hispanic or Latino	606 (87.3)	309 (89.0)		
Weight (kg)				
n	694	347	106	103
Mean (SD)	83.1 (20.91)	84.0 (20.79)	61.03 (13.27)	59.35 (14.37)
Dialysis status, n (%)				
Hemodialysis	638 (91.9)	318 (91.6)	93 (87.7)	93 (90.3)
Peritoneal dialysis	56 (8.1)	29 (8.4)	—	—
Hemodiafiltration	—	—	13 (12.3)	10 (9.7)
Length of time on dialysis (months)				
Mean (SD)	—	—	103.3 (78.3)	107.7 (97.6)
Reason for ESRD, n (%)				
N	694	347	106	103
Hypertension	158 (22.8)	88 (25.4)	—	—

	PA-CL-05A		PA1301	
	SO (N = 694)	Sevelamer (N = 327)	SO (N = 106)	Sevelamer (N = 103)
Glomerulonephritis	155(22.3)	87 (25.1)	44	45
Diabetes mellitus	196 (28.2)	94 (27.1)	35	23
Pyelonephritis	27 (3.9)	13 (3.7)	0	0
Polycystic kidney disease	66 (9.5)	21 (6.1)	3	7
Interstitial nephritis	18 (2.6)	10 (2.9)	—	—
Hydronephrosis	9 (1.3)	4 (1.2)	—	—
Congenital	9 (1.3)	5 (1.4)	—	—
Nephrosclerosis	—	—	14	10
Other	56 (8.1)	25 (7.2)	5	4
Unknown	—	—	8	14
Time from start of ESRD (months)[a]				
n	692	347	NR	NR
Mean (SD)	63.7 (61.78)	67.7 (69.43)		
Median (range)	44.4 (3.1-445.5)	45.5 (0.4-407.2)		
Prior PB use, n (%)[b]				
n	694	347	100	92
Calcium carbonate	251 (36.2)	127 (36.6)	71 (71.0)	73 (79.3)
Calcium acetate	190 (27.4)	92 (26.5)	—	—
Sevelamer hydrochloride	77 (11.1)	44 (12.7)	33 (33.0)	30 (32.6)
Sevelamer carbonate	149 (21.5)	72 (20.7)	—	—
Lanthanum carbonate	45 (6.5)	14 (4.0)	47 (47.0)	43 (46.7)

ESRD = end-stage renal disease; NR = not reported; PB = phosphate binder; SD = standard deviation; SO = sucroferric oxyhydroxide.

[a] Time from start of ESRD was the difference between the date of screening and the date of end-stage renal disease diagnosis.

[b] Prior PBs listed are restricted to comparators identified in the protocol of the current review. Previous PB use includes PBs stopped after screening date and before the beginning of the washout period. Some patients did not report any relevant prior PB use.

Sources: PA-CL-05A Clinical Study Report;[9] PA1301 Clinical Study Report Synopsis;[10] Koiwa (2017).[11]

Table 7: Baseline Characteristics of Patients who Completed Otsuki et al. (2018)

	Sucroferric oxyhydroxide group ($n = 31$)	Control group ($n = 32$)	p value
Gender, male	20 (64.5)	22 (68.8)	0.727
Age, years	63.2±12.8	64.3±10.8	0.717
Duration of hemodialysis, months	49 (19–88)	49 (14–83)	0.985
Diabetes mellitus	13 (41.9)	14 (43.7)	0.887
Systolic BP, mm Hg	142±17	144±15	0.710
Diastolic BP, mm Hg	80±13	80±11	0.861
Heart rate, bpm	78±14	75±12	0.312
Body mass index	22.5±4.6	22.7±4.3	0.888
Kt/V	1.35±0.16	1.37±0.19	0.509
Dialysis mode			0.673
Hemodialysis	29 (93.5)	29 (90.6)	
Hemodiafiltration	2 (6.5)	3 (9.4)	
Vascular access			0.321
Arteriovenous fistula	29 (93.5)	28 (87.5)	
Arteriovenous graft	2 (6.5)	3 (9.4)	
Catheter	0	1 (3.1)	
Cardiovascular comorbidity			
Ischemic heart disease	5 (16.1)	4 (12.5)	0.687
Cerebrovascular disease	1 (3.2)	2 (6.3)	0.578
Peripheral artery disease	2 (6.5)	2 (6.3)	0.974
Medication			
Calcium carbonate	23 (74.2)	25 (78.1)	0.719
Sevelamer	12 (38.7)	14 (43.8)	0.690
Vitamin D receptor activator	20 (64.5)	22 (68.8)	0.726
Cinacalcet	9 (29.0)	10 (31.3)	0.851

Data are expressed as the number (percentage), mean ± SD, or median (interquartile range).
BP, blood pressure.

Kt/V = dialyzer clearance of urea × time divided by volume of body water; SD = standard deviation.

Source: Permission obtained from the publisher to use Table 1 from Effect of Sucroferric Oxyhydroxide on Fibroblast Growth Factor 23 Levels in Hemodialysis Patients by Otsuki et al. (2018).[12]

Interventions

SO was provided as chewable tablets in all four of the studies included in the CDR review. However, tablet strength differed across studies. SO 250 mg iron tablets were used in Study PA-CL-03A, PA1301, and Otsuki et al., while SO 500 mg tablets (the strength available in Canada) were used in PA-CL-05A. Sevelamer was the comparator in three of the included trials; sevelamer hydrochloride was the comparator in PA-CL-03A and PA1301 while sevelamer carbonate was the comparator in PA-CL-05A. SO was compared with lanthanum carbonate in the trial by Otsuki et al. The total daily dose of all study treatments was to be divided and taken with meals. None of these trials permitted use of an additional PB other than the assigned study treatment during the trial.

Patients in Study PA-CL-03A were randomized to one of five total daily doses of SO or sevelamer hydrochloride. SO was provided as chewable tablets each containing 250 mg iron. Sevelamer was provided as tablets to be swallowed whole, each containing 800 mg of sevelamer HCl (Renagel). No dose titration was employed and the administration regimen for each group was as follows:

- SO 250 mg iron (1.25 g): one tablet with the largest meal of the day
- SO 1,000 mg iron (5.0 g): four tablets per day; two tablets with the largest meal and one tablet with each of the two smaller meals
- SO 1,500 mg iron (7.5 g): six tablets per day; two tablets with each meal
- SO 2,000 mg iron (10.0 g): eight tablets per day; four tablets with the largest meal and two tablets with each of the two smaller meals
- SO 2,500 mg iron (12.5 g): 10 tablets per day; four tablets with the largest meal and three tablets with each of the two smaller meals
- Sevelamer hydrochloride 4.8 g: six tablets per day; two tablets with each meal.

No dose adjustments to study treatment were permitted throughout the study. As specified in the inclusion criteria, patients were permitted to continue treatment with vitamin D, vitamin D metabolites, or calcimimetics if they were on a stable dose for at least one month prior to screening.

In Study PA-CL-05A, SO was provided as chewable tablets containing 500 mg iron (2,500 mg SO). The active control was sevelamer carbonate (Renvela) tablets containing 800 mg sevelamer. In Stage 1, patients were randomized on a 2:1 ratio to treatment with either SO at a starting dosage of 1,000 mg iron/day (two tablets/day) or sevelamer carbonate at a starting dosage of
4.8 g/day (six tablets per day). Doses were titrated every two weeks based on each patient's tolerability and serum phosphorus level. The dose of SO was titrated in increments of 500 mg iron (2.5 g/day) up to a maximum total daily dose of 3,000 mg iron
(six tablets/day).The minimum SO dosage was 1,000 mg iron/day. The dose of sevelamer was titrated in increments of 2.4 g/day
(three tablets) down to a minimum of 2.4 g/day (three tablets/day) and up to a maximum of 14.4 g/day (18 tablets/day). As depicted in Figure 2, the dose titration period was defined as the first eight weeks of the study. During this time, doses were titrated when serum phosphorus levels were outside the target levels of 0.81 to 1.78 mmol/L or for tolerability concerns. During the maintenance period from weeks 8 to 12, dose adjustments were permitted for tolerability reasons only. After the noninferiority assessment of SO versus sevelamer occurred at week 12, the maintenance period continued for another 12 weeks to week 24, during which dose adjustments were made for both tolerability and efficacy reasons. Concomitant medications (including vitamin D, vitamin D analogues, and calcimimetics), dietary restrictions, and dialysis regimens did not change throughout the study unless required for safety reasons.

In Study PA1301, patients received treatment with either SO provided as a chewable tablet containing 250 mg iron, or sevelamer hydrochloride provided as a tablet containing 250 mg sevelamer. The starting dose of SO was a total daily dose of 750 mg iron (three tablets titrated in 750 mg iron increments up to a maximum daily dose of 3,000 mg iron). The starting dosage of sevelamer was based on serum phosphorus concentration: 1,000 mg/day if serum phosphorus was lower than 2.58 mmol/L or 2,000 mg/day if serum phosphorus was ≥ 2.58 mmol/L, and then increased in increments of either 750 or 1,500

mg/day up to a maximum daily dose of 9,000 mg. Dose adjustments occurred during weeks 2 to 8 of treatment and were titrated based on serum phosphorus level of the previous week: if serum phosphorus was above 1.94 mmol/L the doses were increased, doses were decreased if serum phosphorus was below 1.13 mmol/L, and maintained if serum phosphorus was between 1.13 mmol/L and 1.94 mmol/L. Doses were maintained from weeks 8 to 12. Both treatments were administered three times a day, divided with each meal. Other PBs, any drugs that could affect serum phosphorus, and oral iron agents were prohibited. Use of intravenous iron, vitamin D receptor activators, and calcimimetics were permitted throughout the study.

In the study by Otsuki et al., patients taking lanthanum were randomized to either switch to SO or continue taking lanthanum.[12] In the SO group, treatment was initiated at 750 mg iron/day. PB dosage was adjusted every two weeks, up to a maximum of 3,000 mg iron/day of SO and 2,250 mg lanthanum, if serum phosphate was not within the target range identified in the study of 3.50 mg/dL to 6.0 mg/dL (1.13 mmol/L to 1.94 mmol/L). Patients continued their current treatment with calcium carbonate, sevelamer, vitamin D receptor activator, or cinacalcet for the duration of the study.

Outcomes

Refer to Appendix 5 for more information on the validity of outcome measures described in this section.

Short Form (36) Health Survey (Version 2)

Health-related quality of life (HRQoL) was assessed in Study PA-CL-05A using the Short Form (36) Health Survey version 2 (SF-36v2) at week 12 and 24.

The SF-36v2 is a 36-item, general health status instrument that has been used extensively in clinical trials in many disease areas.[68] It was developed in 1996 based on the original SF-36, which required some substantial changes to address its shortcomings.[68] Like the SF-36, the SF-36v2 consists of eight health domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health.[68] Each of the eight domains is scored on a domain-specific scale, with higher scores corresponding to better health.[68] A principal components analysis of the eight domains is also used to create a physical component summary and a mental component summary.[68] Each score from the eight domains is converted to a scale ranging from 0 to 100, which is then transformed to a T-score (mean of 50 and SD of 10) that is standardized to the US general population. A score of 50 on any scale would be at the average or norm of the general US population and a score 10 points lower (i.e., 40) would be one standard deviation below the norm. The domain scores are then aggregated using a weighted formula to score the summary scores, which are also transformed to a T-score.[68]

The validity of the widely used SF-36v2 was also reviewed. The generic health status instrument has been well validated previously. A study by Erez et al. (2016)[69] reported a minimal clinically important difference (MCID) of 5.7 for the physical component summary and 9.2 for the mental component summary using an anchor-based approach for patients with CKD undergoing conservative (non-dialysis) management of their disease. Distribution-based methods were also applied and determined an MCID of 1.63 and 2.46 for the physical component summary and the mental component summary, respectively, based on a magnitude of one standard error (SE) of the mean.

Serum Phosphorus

Serum phosphorus level was the primary end point in studies PA-CL-03A, PA1301, the key secondary end point in Study PA-CL-05A, and a secondary end point in the study by Otsuki et al. Serum phosphorus is routinely measured in clinical practice. It is generally measured by automated calorimetric methods and considered relatively precise and reproducible.

In Study PA-CL-03A, the primary end point was change from baseline in serum phosphorus at the end of treatment. Serum phosphorus was measured once weekly from the screening visit until end of treatment. Serum phosphorus was measured weekly for two weeks after treatment terminated (weeks 8 and 9).

In Study PA-CL-05A, the key end point in Stage 1 was change from baseline in serum phosphorus level at week 12 and the basis for the noninferiority analysis of SO versus sevelamer. Serum phosphorus was measured once weekly in patients on hemodialysis and every other week in patients on peritoneal dialysis up to week 12. Measurements were taken once weekly regardless of dialysis status from week 12 to week 16, and then again at week 24.

The primary efficacy outcome in Study PA1301 was serum phosphorus concentration at the last evaluation (week 12).[10,11] In Study PA1301, serum phosphorus was measured at each time point (each week to end of treatment at week 12).[10,11]

Achievement of Target Serum Phosphorus

Achievement of serum phosphorus control was evaluated in three of the studies included in the CDR review: PA-CL-03A, PA-CL-05A, and PA1301. Serum phosphorus control was defined as:

- Within the KDOQI guideline target range (1.13 mmol/L to 1.78 mmol/L) at any given time point
- Within the KDIGO normal range (0.81 mmol/L to 1.45 mmol/L) at any given time point
- Within targets established by the Japanese Society for Dialysis Therapy (JSDT; 1.13 mmol/L to 1.94 mmol/L).

In Study PA-CL-03A, the proportion of patients achieving controlled serum phosphorus was analyzed after one, two, three, four, five, and six weeks of treatment. The definition of controlled serum phosphorus was based on KDOQI guidelines (≥ 1.13 mmol/L to ≤ 1.78 mmol/L).[52] In Study PA-CL-05A, achievement of response (serum phosphorus control) was evaluated at week 12 and 24 and was defined as within the KDOQI guideline target range and KDIGO normal range at any given time point.[9] Duration of serum phosphorus control was also evaluated in Study PA-CL-05A. The range recommended by the JSDT was used to define serum phosphorus control in Study PA1301.

Serum Calcium and Intact Parathyroid Hormone

According to KDIGO guidelines, corrected total calcium should be maintained within a normal range of 2.10 mmol/L to 2.37 mmol/L and the target range recommended for serum iPTH is between 16.5 mmol/L and 33.0 mmol/L.[52]

Serum calcium was routinely measured in each of the studies included in the CDR review. Samples were collected prior to the start of a dialysis session in studies PA-CL-03A and PA-CL-05A. Precise information pertaining to the timing of sample collection is not available

in PA1301 or in the study by Otsuki et al. Total serum calcium was a secondary end point in studies PA1301 and PA-CL-05A, while corrected serum calcium was reported in Study PA1301.

In Study PA-CL-03A, serum total calcium and iPTH were measured once weekly from the screening visit until end of treatment and on the second week of follow-up only (week 9).

In Study PA-CL-05A, serum total calcium was measured at the same time points as serum phosphorus: once weekly in patients in hemodialysis and every other week in patients on peritoneal dialysis up to week 12. Measurements were taken once weekly regardless of dialysis status from week 12 to 16, and then again at week 24. Serum iPTH was measured once every four weeks from baseline to week 12 and once weekly up to week 20, and then again at week 24.

Detailed sampling of corrected serum calcium and iPTH is not provided in Study PA1301, but data for serum calcium are presented for each week of the study, and data for iPTH are presented on a biweekly basis.

In Otsuki et al., serum calcium levels were measured every two weeks and iPTH levels were measured every three months.

Harms

Adverse events (AEs) including treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), withdrawal due to adverse events (WDAEs), and notable AEs (i.e., of interest for this review) were reported in studies PA-CL-03A, PA-CL-05A, and PA1301. A detailed report of AEs was not provided in the study by Otsuki et al.

Definitions of AEs and SAEs were based on definitions established by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use in Study PA-CL-03A. In Study PA-CL-05A, SAEs were considered to be life-threatening events or events that posed a threat to a patient's functioning.[9] No definition for SAEs is included in PA1301. In Otsuki et al., SAEs were defined as events leading to death, hospitalization, significant disability, or incapacity.[12]

Serum ferritin and transferrin saturation were included as laboratory tests. In Study PA-CL-03A, iron parameters were measured at baseline, week 4, and week 9 (follow-up occurring two weeks after termination of study treatment).[8] In Study PA-CL-05A, iron parameters were measured once every four weeks from baseline to week 12, once weekly up to week 20, and then again at week 24.[9] In Study PA1301 laboratory tests were conducted at each evaluation point.[11] In Otsuki et al., serum ferritin and transferrin were measured once per month.[12]

Statistical Analysis

Study PA-CL-03A

The primary efficacy end point was absolute change from baseline in serum phosphorus level at the end of treatment. A sample size of 19 patients per group with at least one post-baseline efficacy measurement was required for an alpha level of 0.05 and 90% power. This was based on an assumed withdrawal rate of 14%, a treatment difference of 0.65 mmol/L, and an SD of 0.81 mmol/L. No rationale was provided for the basis of the assumed treatment difference or SDs. Single sample t-tests were conducted within each of the five SO groups in a hierarchical manner in order of descending dose until either the lowest dose

or a *P* value > 0.05 was reached. A single sample t-test was also conducted on change from baseline in serum phosphorus on the sevelamer group, but this was not included in the hierarchical testing procedure and multiplicity adjustments were therefore not taken into account. A secondary analysis on absolute change from baseline in serum phosphorus compared each of the five SO dose groups using an analysis of covariance (ANCOVA) model with dose group as a fixed effect and baseline serum phosphorus values as covariates. Pairwise comparisons were conducted of the four higher SO dosage groups (1,000 mg, 1,500 mg, 2,000 mg, and 2,500 mg iron/day) and the lowest SO dosage of 250 mg iron/day using Dunnett's test. Missing data for the efficacy analyses on serum phosphorus were imputed using the last operation carried forward (LOCF) approach.

The proportion of patients with controlled serum phosphorus (based on KDOQI guidelines of ≥ 1.13 mmol/L to ≤ 1.78 mmol/L)[52] were analyzed after each week of treatment for a dose effect using a two-sided Cochran–Armitage test and pairwise comparisons were conducted versus the SO 250 mg iron group using a chi-square test. Significance was set at 5%.

Serum calcium and iPTH were measured weekly and descriptive statistics and change from baseline was summarized by treatment group. No methods for handling missing data or accounting for multiplicity are described for these measures.

No subgroup analyses were conducted.

Study PA-CL-05A – Stage 1

The main efficacy outcome of interest for this review included in Study PA-CL-05A was the key secondary objective: noninferiority of SO versus sevelamer in lowering serum phosphorus levels. The sample size for Stage 1 was calculated based on the secondary end point of change from baseline in serum phosphorus. A total of 507 patients was required for the per-protocol set (PPS) to demonstrate 90% power with a noninferiority margin of 0.19 mmol/L. This was based on the assumptions of a mean decrease in serum phosphorus levels of 0.65 mmol/L and an SD of 0.63 mmol/L. The noninferiority margin and anticipated mean decrease in serum phosphorus of approximately 0.65 mmol/L were based on the effect of absolute change in serum phosphorus previously observed in clinical trials of sevelamer.[48,70,71] With a 2:1 randomization ratio, 338 patients were required in the SO group and 169 in the sevelamer group. Considering an assumed 20% dropout rate from each group, 636 patients were planned to be randomized to treatment (424 in the SO group and 212 in the sevelamer group). Enrolment was permitted to continue up to 940 patients to ensure an adequate number of patients in each group for the safety evaluation at six months. This increased enrolment would result in power of 95% for demonstrating noninferiority under similar assumptions. The LOCF rule was applied to all efficacy end points in Stage 1. In the LOCF, the last assessment available post-baseline was carried forward and considered in the between-groups treatment difference. All statistical tests were conducted using a two-sided significance level of 5%.

An ANCOVA was conducted on the PPS to compare the change from baseline in serum phosphorus levels at week 12 between groups, using a mixed model with baseline serum phosphorus level, dialysis status, and region as covariates. Missing data at the end point were imputed using LOCF. Noninferiority of SO versus sevelamer was confirmed if the upper bound of the 97.5% one-sided confidence interval (CI) was below the noninferiority margin of 0.19 mmol/L. The noninferiority margin was based on the effect of absolute change in serum phosphorus observed with sevelamer in previous clinical studies.[48,70,71] If

noninferiority was achieved, a pre-planned superiority analysis was conducted using a similar model. The significance level for this superiority analysis was not provided. A similar analysis in the full analysis set (FAS) population (using LOCF and observed cases) was conducted to support the results. A mixed-effects model for repeated measures–missing at random (MMRM-MAR), including participants as a random effect, week and treatment as fixed effects, and treatment by visit interaction, was used to assess the change from baseline in serum phosphorus levels between groups over time. In this MMRM-MAR, covariates included region, dialysis type, baseline serum phosphorus, and the baseline serum phosphorus by visit interaction. The MMRM-MAR also compared the trend in serum phosphorus change from baseline over time between the SO and sevelamer groups.

Analyses of all other secondary end points of interest were conducted in the FAS. Achievement of serum phosphorus control at week 12 and 24 was defined as the percentage of patients with serum phosphorus within ranges specified by the KDIGO or KDOQI targets and within the normal range at any specified time point. Logistic models with treatment and baseline phosphorus as covariates were used. Duration of serum phosphorus levels within the KDIGO normal range or KDOQI target range was defined as the total number of days that measured serum phosphorus was within the target range. Duration was estimated using a linear extrapolation between visits when a switch from within to outside or vice versa was observed. The following algorithm was applied when a switch occurred between two consecutive visits: t = 1/(V1 − V2) * [T1*(Vu − V2) + T2*(V1 − Vu)]. In this algorithm, t is the switch, T1 is the first visit, T2 is the second visit, V1 is serum phosphorus at T1, V2 is serum phosphorus at T2, and Vu is the upper boundary value of the normal range. Visits occurred once weekly in patients on hemodialysis and every other week in patients on peritoneal dialysis up to week 12. Measurements were taken once weekly regardless of dialysis status from week 12 to week 16, and then again at week 24.

Serum total calcium and iPTH levels were also summarized in the FAS. Serum total calcium was originally the only calcium measure specified in the study protocol (corrected and ionized calcium were added to the study protocol as laboratories usually provide these values as well). Therefore, results reported in the current review are restricted to serum total calcium. Change from baseline at week 24 for serum total calcium was assessed using an ANCOVA model with treatment, baseline level, dialysis status, and region as covariates. iPTH was analyzed in a similar manner.

Pre-specified subgroup analyses were conducted for each of the secondary end points in Stage 1 of the study identified above. Three of these subgroups were identified in the review protocol: dialysis status (hemodialysis, peritoneal dialysis), age (< 65 years, ≥ 65 years), and previous treatment with sevelamer. An interaction of subgroup with treatment was further evaluated when $P < 0.1$ in the ANCOVA.

HRQoL was assessed using the SF-36v2 questionnaire, which was considered an “other” end point. Between-groups differences were evaluated using t-tests and 95% CIs were estimated.

No multiplicity adjustments were made to control for type I error. All analyses pertaining to the secondary efficacy end points should therefore be interpreted with consideration of the risk of type I error.

Serum ferritin and transferrin saturation were identified as safety specific secondary end points. The change from baseline and 95% CI with t-tests were summarized. No multiplicity adjustments were made to control for type I error.

PA1301

Noninferiority of SO versus sevelamer based on adjusted serum phosphorus concentration at end of treatment was the primary efficacy analysis for serum phosphorus. The sample size required to achieve 90% power and a two-sided significance level of 5% was 62 patients per group with an assumed treatment difference of 0 mmol/L and an SD of 0.55 mmol/L. The target sample size was 100 patients per group. Noninferiority of SO versus sevelamer for the primary efficacy analysis for serum phosphorus at the last evaluation was confirmed if the upper limit of the two-sided 95% CI was ≤ 0.32 mmol/L.[10,11] The assumed SD was based on an SD observed in previous phase III trials of sevelamer and similar drugs, which ranged from 0.48 mmol/L to 0.65 mmol/L and a dose-response study in Japanese patients with hyperphosphatemia (no reference provided).

The primary efficacy analysis for serum phosphorus at the last evaluation was conducted using an ANCOVA with group as a fixed effect and serum phosphorus concentration at week 0 as a covariate. Summary statistics for serum phosphorus and change from baseline were calculated at each evaluation time point for each treatment group. Additional analyses conducted on serum phosphorus concentration included achievement rates of target serum phosphorus at each evaluation point for each group and number of days elapsed at the target rate.

Patients with serum phosphorus values between 1.13 mmol/L and 1.94 mmol/L (3.5 mg/dL and 6.0 mg/dL) were considered to have achieved target, as per JSDT guidelines.[13] The achievement rate at each time point and the two-sided 95% CI were derived for each treatment group.

The number of days at target was derived from the date of the first study treatment and the date of evaluation. A Kaplan–Meier estimate of cumulative target achievement rate was conducted. For each secondary end point, summary statistics at each time point and change from baseline (week 0), and 95% CIs were calculated for each treatment group.

No reference to controlling for multiplicity or handling missing data is mentioned for the primary or secondary end points. Multiple analyses were conducted on the primary end point, and these results should be interpreted with consideration of the risk of type I error. Further, missing data may bias the study results.

Otsuki et al.

Patients in the Otsuki et al. trial were randomized to treatment using a dynamic balancing method; the statistical methods applied to account for this are not described. End points of interest in Otsuki et al.[12] were secondary outcomes, including serum phosphorus, calcium, iPTH, serum ferritin, and transferring saturation. Between-group differences were compared using Student's t-test or the Mann–Whitney U test for normal and skewed distributions, respectively. Paired t-tests or the Wilcoxon signed-rank test were used to compare change from baseline within each parameter. Sample size was calculated based on the primary end point of mean per cent change in fibroblast growth factor (not included in the current review) with a power of 80%, assuming an effect size of 30% and SD of 40% (based on previous trials). The assumed dropout rate after randomization was 20%, resulting in a required sample size of 27 patients per group. Statistical significance was set at $P < 0.05$. No methods to control for multiplicity or missing data are described.

Analysis Populations

In Study PA-CL-03A, all efficacy analyses were conducted in the FAS and PPS. The FAS consisted of all randomized patients who included at least one dose of study treatment, and had at least a post-baseline efficacy result. The PPS consisted of all randomized patients who were compliant with the study protocol, and the safety set consisted of all randomized patients who included at least one dose of study treatment.

In Study PA-CL-05A, the secondary efficacy end point of change from baseline in serum phosphorus in Stage 1 was evaluated in the PPS (all patients who completed up to week 12 and have at least one serum phosphorus result for evaluation on or after week 12 without any major protocol violations) and FAS (patients who were randomized, received at least one dose of study treatment, and have at least one efficacy assessment post-baseline). All other efficacy end points in Stage 1 were evaluated in the FAS. Safety analyses for Stage 1 were conducted using the safety set (all patients who were randomized and received at least one dose of study treatment).

Analysis sets are not formally defined in study PA1301; numbers of patients included in each analysis set are presented in Table 9. The primary analysis for the primary end point of mean serum phosphorus concentration at end of treatment was evaluated in the PPS and the FAS. All other analyses on serum phosphorus and secondary end points were conducted in the PPS and FAS.

Analysis sets are not defined in the study by Otsuki et al.

Patient Disposition

In the PA-CL-03A study, 417 patients were screened and 154 were randomized to one of the five SO treatment groups or sevelamer.[8] All patients randomized received at least one dose of study medication. Of the randomized patients, 66.9% completed the study and 33.1% discontinued prematurely. Study discontinuations were highest in the two highest doses of SO (2,000 mg and 2,500 mg iron/day, 44.4% and 37.5%, respectively), and were due primarily to hypophosphatemia (25.9% and 25.0%, respectively). This was not unexpected, as dose titration was not permitted during the study and hypophosphatemia was a predefined withdrawal criterion. Study discontinuations due to hyperphosphatemia were most common in the SO 250 mg iron/day group (15.4%). Patient disposition in the PA-CL-03A phase II study is summarized in Table 8.

In the PA-CL-05A study, 1,840 patients were screened and 1,059 were randomized to receive treatment with either SO (n = 710) or sevelamer (n = 349).[9] Some discrepancies were found upon reconciliation of the IVRS and clinical databases; specifically, 11 patients were incorrectly randomized according to dialysis status. All discrepancies were recorded correctly in the final clinical database and the impact of these misallocations was presumed to be minimal as the overall randomization ratio was preserved. Of those patients randomized, 99.6% received treatment. A total of 808 patients (76.3%) completed Stage 1 (up to week 24). More patients in the SO group (27.5%) withdrew from the study than from the sevelamer group (16.0%). The primary reason for discontinuation in both groups was due to AEs other than phosphorus or calcium and was higher in patients treated with SO than sevelamer (13.2% in the SO group and 6.0% in the sevelamer group). Patient disposition in the pivotal PA-CL-05A study is summarized in Table 9.

In the PA1301 study, 321 patients were screened and 213 were randomized to receive treatment with either SO (n = 108) or sevelamer (n = 105).[11] Discontinuation rates appear to be balanced between the two treatment groups: 13% of patients in the SO group and 17.1% of patients in the sevelamer group discontinued the study prematurely. The primary reason for discontinuation was AEs (seven patients in the SO group and 10 in the sevelamer group). Patient disposition for study PA1301 is summarized in Table 9.

In the study by Otsuki et al., 159 patients were screened and 68 of these were randomized (34 to each group).[12] Three patients (8.82%) in the SO group and two patients (5.88%) in the lanthanum group discontinued the study prematurely. A total of 63 patients were included in the analysis (SO: n = 31; lanthanum: n = 32). Patient disposition is summarized in Table 9.

Table 8: Patient Disposition for Study PA-CL-03A

	250 mg Iron (1.25 g SO)/day N = 26	1,000 mg Iron (5.0 g SO)/day N = 26	1,500 mg Iron (7.5 g SO)/day N = 25	2,000 mg Iron (10.0 g SO)/day N = 27	2,500 mg Iron (12.5 g O)/day N = 24	Sevelamer N = 26
Screened, N	417					
Randomized, N (%)	26 (100)	26 (100.0)	25 (100.0)	27 (100.0)	24 (100.0)	26 (100.0)
Withdrawals, N (%)	8 (30.8)	9 (34.6)	5 (20.0)	12 (44.4)	9 (37.5)	8 (30.8)
Prohibited medication	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.7)
Serum phosphorus below safety limit	1 (3.8)	3 (11.5)	3 (12.0)	7 (25.9)	6 (25.0)	1 (3.8)
Serum phosphorus level above upper safety limit any time as of 2 weeks after start of treatment	4 (15.4)	2 (7.7)	0 (0.0)	2 (7.4)	0 (0.0)	2 (7.7)
Serum calcium above safety limit	2 (7.7)	2 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Protocol violation	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Adverse event	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)	1 (4.2)	2 (7.7)
Withdrawal by subject	1 (3.8)	0 (0.0)	1 (4.0)	2 (7.4)	1 (4.2)	0 (0.0)
Death	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	1 (4.0)	0 (0.0)	1 (4.2)	1 (3.8)
FAS, N	26	26	25	25	24	24
PPS, N	18	21	22	20	19	20
SS, N	26	26	25	27	24	26

FAS = full analysis set; PPS = per-protocol set; SO = sucroferric oxyhydroxide; SS = safety set.

Source: Study PA-CL-03A Clinical Study Report.[8]

Table 9: Patient Disposition for Phase III Studies

	PA-CL-05A		PA1301		Otsuki et al. (2018)	
	SO	Sevelamer	SO	Sevelamer	SO	Lanthanum
Screened, N	1,840		321		159	
Randomized, N (%)	710	349	108	105	34 (21.38)	34 (21.38)
Withdrawals, N (%)	195 (27.5)	56 (16.0)	14 (13)	18 (17.1)	3 (8.82)	2 (5.88)
Death	9 (1.3)	5 (1.43)			—	—
AEs	94 (13.2)	21 (6.0)	7 (6.50)	10 (9.52)	—	—
Hyperphosphatemia	12 (1.7)	0 (0.0)	—	—	—	—
Hypophosphatemia	1 (0.1)	0 (0.0)	—	—	—	—
Hypercalcemia	2 (0.3)	0 (0.0)	—	—	—	—
Calcium decrease	—	—	2 (1.85)	3 (2.86)	—	—
Ferritin increase	—	—	1 (0.93)	0 (0.0)	—	—
Diarrhea	—	—	—	—	1	
Hospital admission	—	—	—	—	2	1
Transferred to another centre	—	—	—	—	—	—
Withdrew consent	32 (4.5)	15 (4.3)	—	—	—	—
Investigator decision	5 (0.7)	1 (10.3)	—	—	—	—
Sponsor decision	5 (0.7)	4 (1.1)	—	—	—	—
Prohibited medication	2 (0.3)	0 (0.0)	—	—	—	—
Protocol deviation	7 (1.0)	0 (0.0)	—	—	—	—
Renal transplant	16 (2.3)	7 (2.0)	—	—	—	—
Other	10 (1.4)	3 (0.9)	6 (5.56)	5 (4.76)	—	—
FAS, N	694	347	106	103	31[a]	32[a]
PPS, N	461	224	100	92		
SS, N	707	348	108	105		

FAS = full analysis set; PPS = per-protocol set; SO = sucroferric oxyhydroxide; SS = safety set.

[a] Analysis sets not specified.

Sources: Study PA-CL-05A Clinical Study Report;[9] PA1301 Clinical Study Report Synopsis;[10] Koiwa (2017);[11] Otsuki (2018).[12]

Exposure to Study Treatments

In Study PA-CL-03A the median treatment duration and average daily dose were aligned with the protocol-specified requirement for each of the treatment groups (Table 10). The average daily dose was slightly lower than that required by the protocol in the SO 2,000 mg and 2,500 mg iron/day groups.[8] Patients were considered compliant to study medication if they were within a range of 80% to 120%. The mean treatment compliance across all SO groups was 94.1% and 92% in the sevelamer group.

As presented in Table 11, in Stage 1 of Study PA-CL-05A the mean duration of exposure was 142.9 days in the SO groups and 155.5 days in the sevelamer group.[9] The mean daily dosage in the SO group was 1,540 mg iron/day and the mean daily dosage in the sevelamer group was 6.5 g/day. The mean (SD) number of tablets (SO 500 mg iron) was lower in the SO group at 3.1 (1.14) tablets/day compared with the sevelamer group at 8.1 (3.15) tablets/day. At the end of Stage 1 (week 24) 31% of patients were being treated with the maximum SO dosage of 3,000 mg iron/day (15 g/day; six tablets) and 11.9% were

being treated with the lowest dosage of 1,000 mg iron/day (5 g/day; two tablets). The rest of the patients were equally distributed across the SO dosages of 1,500 mg to 2,500 mg iron/day (7.5 g/day to 12.5 g/day; three to five tablets). For patients treated with sevelamer, 19.5% received the highest dosage (14.4 g/day) and 2.7% received the lowest (2.4.g/day). The remaining patients in the sevelamer group were equally distributed among the dosages of 2.4 g/day to 12.0 g/day. Overall extent of exposure or dose distribution did not vary by age or dialysis status subgroups. Pill burden was lower in the SO group versus the sevelamer group, with a mean (SD) number of tablets taken daily of 3.1 (1.14) and 8.1 (3.15), respectively. Mean compliance (defined as compliant at 70% to 120% of the number of expected tablets) was 89.0% in the SO group versus 86.2% in the sevelamer group. A greater proportion of patients in the SO group (5.4%) was compliant within the 70% to 120% range, which was defined as compliant compared with the proportion of patients in the sevelamer group (82.6% versus 77.2%, respectively).

In Study PA1301, the mean duration of exposure was similar in both treatment groups: 78.5 days in the SO group and 75.6 days in the sevelamer group (Table 11).[10] The average daily dosage in the SO group was 1,174 mg iron/day (5.87 g/day) and 4.37 g/day in the sevelamer group. The mean (SD) number of tablets (SO 250 mg iron or sevelamer 250 mg) was lower in the SO group at
4.7 (1.7) tablets/day compared with the sevelamer group at 17.5 (6.1) tablets/day. Compliance in the FAS exceeded 90% in both treatment groups (96.2% and 96.1% in the SO and sevelamer groups, respectively).

Details regarding the treatment duration and mean dosage in each treatment group are not provided in the Otsuki et al., report. Patients were questioned about compliance with medication at each study visit, but this information is not reported.

Table 10: Exposure to Study Treatment in PA-CL-03A

	250 mg iron (1.25 g SO)/day N = 26	1,000 mg iron (5.0 g SO)/day N = 26	1,500 mg iron (7.5 g SO)/day N = 25	2,000 mg iron (10.0 g SO)/day N = 27	2,500 mg iron (12.5 g SO)/day N = 24	Sevelamer HCl N = 26
Duration (days)						
n	26	26	25	27	24	26
Mean (SD)	39.2 (8.43)	37.3 (10.56)	38.2 (9.74)	32.1 (14.15)	35.8 (11.42)	35.8 (14.26)
Average daily dose (g)						
n	25	24	24	25	24	26
Mean (SD)	1.2 (0.19)	4.5 (0.78)	7.0 (0.98)	8.5 (2.82)	11.1 (2.93)	4.2 (0.95)

SD = standard deviation; SO = sucroferric oxyhydroxide.

Source: Study PA-CL-03A Clinical Study Report.[8]

Table 11: Summary of Exposure in Phase III Studies (Safety Set)

	PA-CL-05A		PA1301	
	SO (N = 707)	Sevelamer (N = 348)	SO (N = 108)	Sevelamer (N = 105)
Duration (days), mean (SD)	142.9 (51.56)	155.5 (37.41)	78.5 (18.7)	75.6 (22.8)
Average daily dose (g), mean (SD)	7.7 (2.86)	6.5 (2.52)	5.868 (2.169)	4.366 (1.519)

SD = standard deviation; SO = sucroferric oxyhydroxide.

Sources: Study PA-CL-05A Clinical Study Report;[9] PA1301 Clinical Study Report Synopsis;[10] Koiwa (2017).[11]

Critical Appraisal

Internal Validity

PA-CL-03A

Study PA-CL-03A was a phase II exploratory study. Patients were randomized via a central IVRS to minimize selection bias. The treatment groups were imbalanced with regard to sex, race, and duration of CKD. The study population was predominantly male and white. Further, the range for mean duration of CKD was broad, with the shortest mean duration (59.1 months) in the SO 250 mg iron group and the longest mean duration (118.3 months) in the sevelamer group. This could have introduced bias, as duration of CKD may represent different health states. Efficacy analyses were based on the FAS, which is not a true intent-to-treat (ITT) population. However, only four of the 154 patients (less than 3%) randomized to treatment were not included in the FAS (two patients in the SO 2,000 mg iron/day group and two patients in the sevelamer group), thus use of this modified ITT population is unlikely to have a major impact on the interpretation of the results. Use of the FAS may have introduced bias to the study as those patients who withdrew after receiving treatment but prior to providing a post-baseline assessment were excluded from the analysis. Although the study was an open-label trial, it is unlikely that the primary and other efficacy end points of interest to this review (serum phosphorus, calcium, iPTH) were influenced by potential bias because they were all objective, physiological measures. However, safety end points, such as AE reporting, could have been influenced by the open-label design. Implications of the open-label study design are discussed further in the critical appraisal of Study PA-CL-05A. Serum phosphorus is a surrogate outcome measure, and there is conflicting evidence regarding the link to clinical outcomes such as mortality and cardiovascular morbidity; evidence for an association between elevated levels of serum phosphorous and all-cause mortality in patients with CKD is weak and observational in nature.[53,72-75] This study did not include any measures to provide direct evidence of the effect of SO on clinical outcomes in patients with ESRD. A treatment difference of 0.65 mmol/L was assumed for the power calculation even though no rationale was provided for expecting a treatment effect of this magnitude. Further, the clinical relevance of this difference is unclear. A larger proportion of patients within each SO dosage and sevelamer group (ranging from 20% to 44.4%) discontinued the study than the assumed 14% specified in the statistical analysis plan. However, because the primary end point of change from baseline in serum phosphorus at end of treatment was achieved, the study appears to be sufficiently powered despite the withdrawal rate. The high rate of withdrawal may have resulted from the lack of dose titration during the treatment period. Withdrawal rates were highest in the SO 2,000 mg and 2,500 mg iron/day groups, due to AEs. This was anticipated by the investigator but represents a potential source of bias as withdrawals cannot be considered to be MAR. No methods for imputing missing data were implemented in the study; except for the primary end point, an ANCOVA-LOCF model was used to conduct comparisons. This may not be appropriate given the differential rate of withdrawal across the treatment groups. Statistical testing for the primary analysis was conducted in a hierarchical manner in each of the SO groups in order of descending dose. A comparison of changes from baseline serum phosphorus among the four higher SO dose groups versus the SO 250 mg dose group was conducted. The SO 250 mg dose was assumed to be an inactive control, and in the absence of a placebo-control group, there is uncertainty surrounding the effects of the SO 250 mg dose. No adjustments for multiplicity were applied beyond the within-group tests in the aforementioned hierarchy. Although sevelamer was considered the active control, no formal comparisons were conducted with any of the SO

groups. The change from baseline in serum phosphorus for the sevelamer group was not included in the hierarchical testing procedure. Therefore, results of this study are not sufficient to conclude that the serum-phosphorus–lowering effect of SO offers any benefits over no treatment or over sevelamer.

PA-CL-05A

PA-CL-05A is the pivotal phase III trial supporting the efficacy and safety of SO. It was a two-stage, re-randomization study in which the primary efficacy end point was based on comparing a maintenance dose of SO with a low-dose of SO in Stage 2 of the study. Given that the low-dose comparator was not identified as appropriate in the protocol for this review and is not available in Canada, the focus of this review and the critical appraisal of this study are restricted to the methodology and results of Stage 1, for which the key secondary end point was establishing noninferiority of SO versus sevelamer in control of serum phosphorus. Patients were randomized in Stage 1 via an IVRS, thus minimizing selection bias, using a 2:1 ratio for SO: sevelamer. Randomization was stratified by dialysis status and country. It is therefore unlikely that the potential for differences in response to treatment resulting from dialysis status or standard of care across different countries influenced the results of the study. Baseline characteristics were generally similar between groups, but there were more males in the sevelamer group than in the SO group (63.1 versus 55.2, respectively). Although not identified in the CDR review protocol as an outcome of interest, sex was included as a subgroup analysis in this study, and did not appear to affect the serum-phosphorus–lowering effect of SO, and this imbalance is unlikely to be of consequence to the CDR review. However, subgroup analyses may lack statistical power and were not adjusted for multiplicity and should be interpreted with consideration of the risk of type I error. As previously discussed in Study PA-CL-03A, the study did not include a true ITT population, which may be a potential source of bias in the current study. However, of the 1,059 patients randomized to treatment (710 to the SO group and 349 to the sevelamer group), less than 2% were not included in the FAS (16 patients in the SO group and two patients in the sevelamer group), and use of this modified ITT population is unlikely to have a major impact on interpretation of the results.

PA-CL-05A was an open-label study, which may introduce bias. The manufacturer states that blinding was not possible due to the difference in administration of SO and sevelamer (chewable tablets versus those that must be swallowed whole, respectively) and in the number of tablets required to obtain the optimal dosages of SO and sevelamer. Although in theory a double-dummy design could have been implemented, unblinding would have been likely throughout the course of the study as treatment with SO is associated with fecal discoloration. It is unlikely that the key secondary end point of this study (change from baseline in serum phosphorus) and other laboratory parameters of interest (serum calcium and iPTH levels) would be affected by the open-label design as these are objective physiological measures. However, 30% of patients enrolled in the trial had previous experience with sevelamer, and this prior experience may have affected their decision to enrol in the study or to remain in the study once randomization occurred. More patients withdrew from the SO than the sevelamer arm, which could lead to bias in the estimate of the effect for these objective outcomes. In addition, other patient-reported outcomes such as HRQoL and AE reporting could have been affected. Further, some patients in the study had previous experience with sevelamer (approximately 30%) and may have been familiar with the tolerability profile and been more tolerant of some potential adverse events, which may have resulted in an underestimation of the frequency of AEs in the sevelamer group. Compliance in this study was defined as 70% to 120% of the number of expected tablets,

and was similar across treatment groups (89% versus 86.2% in the SO and sevelamer groups, respectively), and was thus unlikely to bias a treatment effect in favour of either treatment.

The sample size for Stage 1 was calculated based on the secondary end point of change from baseline in serum phosphorus. The number of patients randomized to each group exceeded the required 507 patients. No basis for the assumptions surrounding the treatment difference of 0.65 mmol/L and SD of 0.63 mmol/L used in the power calculations was provided. Therefore, the clinical relevance of this treatment difference cannot be interpreted, although Health Canada accepted that 0.65 mmol/L was a clinically meaningful difference. The rationale for selecting the noninferiority margin of 0.19 mmol/L was provided and was based on clinical trials of sevelamer versus calcium acetate/carbonate or placebo.[48,70,71] A dropout rate of 20% was assumed from each treatment group. However, the percentage of patients who discontinued the study was higher in the SO arm (27.5%) than this assumed rate, and was higher than the percentage of patients who withdrew from the sevelamer group (16%). The primary reason for study discontinuation was AEs, and the proportion of patients discontinuing due to AEs was higher in the SO than in the sevelamer group (13.2% versus 6.0%). Given the number of patients who withdrew from the study, it is important to consider how missing data were imputed. Missing data were generated using the LOCF, but this approach is not generally conservative in noninferiority trials. A sensitivity analysis was conducted using the MAR approach. However, the assumption of missingness at random may not be valid, considering that a greater proportion of patients withdrew from the SO arm and that the primary reason for these withdrawals was AEs. Therefore, treatment effects and harms may be over- or underestimated. No multiplicity adjustments were conducted, and all analyses pertaining to the secondary efficacy end points should therefore be interpreted with consideration of the risk of type I error.

PA1301

PA1301 was an open-label study in which patients were allocated to treatment with either SO or sevelamer via an IVRS. It is not clearly described how the randomization was generated, but baseline characteristics were generally balanced across treatment groups, with the exception of a higher proportion of males, most notably in the SO treatment arm. As previously discussed, the open-label nature of the study may have contributed to bias, specifically in reporting safety outcomes, which may favour sevelamer as it is an established PB with a well-known tolerability profile. However, the primary outcome of the study (change from baseline in serum phosphorus at end of treatment) and other secondary end points of interest for this review (serum calcium, iPTH levels) are objective laboratory parameters and unlikely to be affected by the open-label nature of the study. However, as previously noted in the critical appraisal of PA-CL-05A, approximately 30% of patients had previous experience with sevelamer, which could have influenced patients' decisions to enrol in or withdraw from the study after randomization, thus contributing to bias in the treatment effect. Treatment compliance did not differ between treatment groups and was above 90% in both groups. Assumptions surrounding the noninferiority margin and SD were well-defined and based on previous phase III trials of sevelamer and other similar drugs. The noninferiority margin established in this study (≤ 0.32 mmol/L) was higher than that established in PA-CL-05A (0.19 mmol/L), but according to the clinical expert contracted by CDR for this review, this difference is small and the noninferiority margin was appropriate. As with the other studies included in this review, the primary outcome of serum phosphorus levels assessed in PA1301 was a surrogate outcome, and the evidence supporting a link to clinical outcomes is contentious.[53,72-75] Discontinuations were similar between the SO and

sevelamer groups, and sample sizes of the PPS and FAS exceeded the required number of participants within each group established in the statistical analysis plan. However, multiple statistical tests were conducted on predefined primary and secondary end points, and there was no mention of controlling for multiplicity or handling missing data. Therefore, type I error may be inflated, and these results should be interpreted with consideration of the risk of type I error.

Otsuki et al.

No clinical study report was available for Otsuki et al., and all information contained within this review was obtained from a published report. Patients were randomized using the dynamic balancing method to ensure baseline patient characteristics were evenly distributed across treatment groups. Randomization was done by an independent investigator who did not have any previous information pertaining to the study participants, and group assignment was provided to the investigators. The statistical analysis does not describe methods for accounting for this randomization technique, and the results should therefore be interpreted with consideration of type I error. Although this was an open-label study, the primary and key secondary end points were changes in laboratory and biochemical parameters, which are objective measures and unlikely to be influenced by the open-label design. However, as acknowledged in the appraisal of the other studies included in the CDR review, the open-label design may have influenced safety assessments. Further, all patients in the study had previous experience with lanthanum and were likely familiar with the tolerability profile of the drug, which could have biased the results in favour of lanthanum (i.e., patients may not have reported AEs as they were familiar with and had already been tolerating them). However, as a detailed safety analysis is not included in this study, the effects of this potential bias cannot be determined. Potential carry-over effects may exist in patients switched from lanthanum to SO treatment as no washout phase was included in the trial. Therefore, the treatment effect of SO may be biased due to previous lanthanum treatment. Although compliance data were gathered via patient reports throughout the study, no information pertaining to compliance is provided in the published report. Therefore, there is uncertainty regarding the extent of exposure to the study drug and whether there were any differences between groups. In addition, no methodology for controlling multiplicity was provided. Given that multiple statistical tests were conducted to assess a number of secondary end points, rates of type I error may be inflated. The level of detail provided in this publication is not adequate to draw any conclusions pertaining to the efficacy of SO versus lanthanum. Overall, results of this study as reported in this publication pertaining to the outcomes of interest to this review should be interpreted with caution.

External Validity

Based on study sites, baseline characteristics, and prior treatment experience with PBs, the study population included in the trials of SO in this review may not be representative of Canadian patients with ESRD on dialysis. None of the studies included in the CDR review included Canadian patients. PA-CL-03A and PA-CL-05A were conducted at various sites in the US and EU, and PA-CL-05A included other countries such as Croatia, Russia, Serbia, South Africa, and Ukraine. In Study PA-CL-05A, almost half of the patients were from the US. Study PA1301 and the study by Otsuki et al. were conducted exclusively in Japan. Standard of care, available treatment, and patient diet in the countries in which the studies were conducted may not be reflective of current clinical practice in Canada or representative of Canadian patients with ESRD on dialysis. For example, some patients in Study PA1301 were previously taking the PB bixalomer, which is not available in Canada.

The Health Canada reviewer's report states that "populations enrolled in the PA21 studies PA-CL-03A and PA-CL-05A/05B were representative of the adult population with CKD on dialysis."[14] However, based on consultation with the clinical expert, the demographic characteristics of patients with ESRD in Canada differ from that in the phase III pivotal trial in that Canadian patients with ESRD are slightly older and there is a higher representation of the Asian population. Further, the study population in PA-CL-05A appeared to be a healthier subset of dialysis patients based on younger age, lower frequency of diabetes, and longer time on dialysis. The majority of patients were on hemodialysis (approximately 92% of patients in both the SO and sevelamer groups), with only a small proportion of patients (approximately 8% in each group) on peritoneal dialysis. Therefore, whether results are generalizable to the patient population receiving peritoneal dialysis is questionable. Patients with hypercalcemia (defined as serum calcium > 2.5 mmol/L, > 2.6 mmol/L, and > 2.75 mmol/L) were excluded from studies PA-CL-03A, PA-CL-05A, and PA1301, respectively.

Of note, in Study PA-CL-05A, patients on calcium-based PBs with hypercalcemia were eligible for enrolment, but these patients were withdrawn if hypercalcemia persisted during the washout period and could not be controlled with another treatment. However, current listing criteria for sevelamer in some Canadian jurisdictions stipulate that sevelamer will only be reimbursed for patients with hypercalcemia (without specifying an underlying cause), and trial results may not be applicable to a key segment of the target patient population in Canada. Further, in each of the four studies included in this CDR review, a large percentage of patients who were screened were not randomized to study treatment. This large per cent of screening failures questions the generalizability of the study population to the target treatment population in Canada.

The comparators used in the clinical trials of SO may not be the most representative of Canadian clinical practice for serum phosphorus control in patients with ESRD. Based on input from the clinical expert, not all patients with ESRD on dialysis in Canadian practice would be treated with a PB to control serum phosphorus. All of the studies included in the review were active-controlled studies; no placebo-controlled studies supporting the efficacy and safety of SO were identified. There is a lack of evidence supporting superiority of SO in terms of mortality and morbidity compared with no PB treatment.

Sevelamer was the comparator in three of the trials included in this review (PA-CL-03A, PA-CL-05A, and PA1301). Although sevelamer hydrochloride and sevelamer carbonate are available in Canada, according to the expert, access to these drugs is limited and therefore used less often in Canadian practice. According to the clinical expert, calcium-based PBs (specifically calcium carbonate) are most commonly used to treat hyperphosphatemia in patients with ESRD in Canada, and thus would be considered the most appropriate comparator for SO in the Canadian context. As no comparative trials of SO versus calcium-based PBs were identified, the efficacy and safety of SO versus the standard PB treatment in Canada remains unknown. Lanthanum is also available in Canada, and would be considered a comparator for SO. In the trial by Otsuki et al., lanthanum was the active control, but the level of detail provided in this publication is not adequate to draw any conclusions pertaining to the efficacy of SO versus lanthanum. In summary, evidence supporting the serum-phosphorus–lowering effects of SO versus all treatments used in Canadian clinical practice (calcium-based PBs or no PB treatment) is lacking.

In clinical practice, some patients may require treatment with more than one PB to achieve acceptable serum phosphorus levels. In three of the trials (PA-CL-03A, PA-CL-05A, and

PA1301), patients were required to discontinue use of their current PB prior to initiating study treatment, thus the majority of evidence supports SO as a PB monotherapy. In the trial by Otsuki et al., patients were permitted to continue using other PBs including calcium carbonate and sevelamer, but serum phosphorus level was a secondary end point in the study;[12] and evidence supporting the phosphorus-lowering effects and safety of SO when used in addition to other PBs is therefore limited.

The treatment regimen of SO in the trials included in the CDR review differed slightly from that recommended by Health Canada. In Canada, SO is approved as a 500 mg iron tablet containing 2,500 mg SO.[7] The recommended starting dosage of SO is 1,500 mg iron/day, taken as one 500 mg iron tablet with each meal. The dose of SO should be titrated up or down in increments of 500 mg iron until acceptable serum phosphorus level is reached.

In Study PA-CL-03A dose titration was not permitted; this is not reflective of Canadian clinical practice. The starting dosage in PA-CL-05A was lower (1,000 mg iron; two tablets/day) than the recommended starting dose approved by Health Canada (1,500 mg iron; three tablets/day). However, the Health Canada reviewer's report acknowledges that the dosage could be titrated down to 1,000 mg iron/day, as stated in the product monograph. The average daily dose of SO in Study PA-CL-05A was 1,540 mg iron, which is aligned with the anticipated usual daily dose stated in the product monograph of 1,500 mg to 2,000 mg iron/day (three to four tablets/day).[7] In Study PA1301 and Otsuki et al., the starting dosage was 750 mg iron (three 250 mg iron tablets) per day, and this regimen is unlikely to be used in Canada if SO tablets are not scored. The average daily dosage of SO in PA1301 was 1,174 mg iron/day, which is at the lower end of the dosage range approved in Canada. Therefore, dosages of SO in Study PA-CL-05A are representative of the anticipated usage of SO in Canada, but the dosage regimens in PA1301 and Otsuki et al. appear to be different than the anticipated use of SO in Canada.

It is also noteworthy that the starting dosage of sevelamer was at the high end of the Health Canada–recommended dosage. In studies PA-CL-03A and PA-CL-05A treatment with sevelamer was initiated at 4.8 g (six tablets) per day, which is the dosage specified for patients with initial serum phosphorus ≥ 2.4 mmol/L.[61-63] The starting dosage of sevelamer in patients with initial serum phosphorus > 1.8 mmol/L and < 2.4 mmol/L is 2.4 g (three tablets) per day. Therefore, some patients in the sevelamer groups may have received a higher dose than required, and been subject to an unnecessarily higher pill burden and potentially a higher frequency of AEs. This could have affected compliance and introduced bias in favour of SO, although the dose of sevelamer (and SO) was titrated based on individual patient level of serum phosphorus or tolerability in each of these studies.

HRQoL was considered in this review and was identified as important by both patients and the clinical expert. Only one study,
PA-CL-05A, evaluated HRQoL, which was assessed using the SF-36v2. Although reliability and validity of the SF-36v2 has been demonstrated across various conditions, including in patients with Stage 5 CKD who were not receiving dialysis, evidence of validity in patients with ESRD on dialysis was not identified.

All-cause mortality, cardiovascular mortality, cardiovascular events, or bone fractures were not pre-specified efficacy outcomes in any of the trials included in the CDR review. However, the short duration of the phase III trials (12 to 24 weeks) was likely insufficient to evaluate the efficacy of PBs on all-cause and cardiovascular mortality. According to the clinical expert, these outcome measures are most important to patients. Whether SO offers any benefit on any of these outcomes compared with other PBs remains uncertain.

One outcome of interest identified in the review protocol was serum phosphorus. Serum phosphorus level is considered a surrogate outcome measure for mortality and cardiovascular comorbidity, although the evidence supporting the association between high serum phosphorus and improved mortality and cardiovascular comorbidities is conflicting and based primarily on observational studies.[53,72-75] Outcome measures related to serum phosphorus levels were primary end points in studies PA-CL-03A and PA1301 and key secondary end points in studies PA-CL-05A and Otsuki et al. Although some studies have demonstrated an association between levels of serum phosphorous ≥ 6.0 mg/dL (1.9 mmol/L) and all-cause mortality in patients with CKD, the evidence supporting this link is weak.[73,75,76] Other studies have concluded that serum phosphorus level is not predictive of death.[72] The same is true for the evidence demonstrating a link between elevated serum phosphorous levels and an increased risk for cardiovascular mortality and disease.[74,75] To date there are no RCTs demonstrating that an improving serum phosphorus level affects survival.[54,55]

The KDIGO 2017 Guideline Update acknowledges that the body of evidence demonstrating an increased risk of all-cause mortality associated with increased serum phosphorus levels mostly contains a moderate level of bias and is of low quality.[23]

Three of the studies (PA-CL-03A, PA-CL-05A, and PA1301) evaluated the proportion of patients achieving serum phosphorus control according to international and national guidelines, specifically KDOQI, KDIGO, and JSDT. Achieving serum phosphorus control was a secondary end point in studies PA-CL-03A and PA-CL-05A, and an additional end point in Study PA1301. According to the clinical expert, serum phosphorus targets in these guidelines are extrapolated from observational studies suggesting a higher risk of adverse outcomes in patients with higher serum phosphate concentrations. The evidence to support these targets is thus extremely weak according to the clinical expert contracted for this review by CDR.

Duration of the phase III studies included in this review ranged from 12 to 24 weeks, which is likely insufficient to evaluate the efficacy of PBs on all-cause and cardiovascular mortality. While the clinical expert agreed that this time frame is adequate for demonstrating the phosphorus-lowering effect of SO, long-term data are required to provide certainty regarding the safety and tolerability of SO, as well as the long-term effects on mortality and cardiovascular outcomes in patients with ESRD. As previously noted, in Study PA-CL-05A a higher proportion of patients in the SO group discontinued prematurely due to AEs. Given the chronic nature of ESRD and that PBs are a lifelong treatment, it is important to establish tolerability over the long term.

Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Table 3). See Appendix 4 for detailed efficacy data.

All-Cause Mortality

This outcome was not assessed as an efficacy outcome in the clinical trials included in this review; no formal hypotheses were stated or formally tested. Information pertaining to this outcome was reported as deaths in the safety evaluation of studies PA-CL-03A, PA-CL-05A, and PA1301. Deaths were not reported by Otsuki et al.[12] Overall, no deaths reported in any of the studies included in the CDR review were considered related to study treatment

and the proportion of deaths that occurred between treatment groups did not differ substantially.

One patient died during Study PA-CL-03A.[8] The patient was randomized to the SO 1,000 mg iron/day group and died following a gastrointestinal hemorrhage and cardiac arrest. The death was not considered to be related to study treatment.

In Study PA-CL-05A, a total of 20 patients experienced a fatal TEAE during Stage 1 of the study.[9] Of these, 13 (1.8%) occurred in the SO group and 7 (2.0%) occurred in the sevelamer group. Most deaths were due to cardiac disorders. Cause of death did not differ between treatment groups and none of the deaths were considered treatment-related.

No deaths were reported in PA1301.[10]

Cardiovascular Mortality

This outcome was not assessed as an efficacy outcome in the clinical trials included in this review; no formal hypotheses were stated or formally tested. Information pertaining to this outcome was reported as part of the safety evaluation of each study. The number of cardiovascular events leading to death reported during the treatment phase of each study is summarized in Table 1.

As previously noted, one patient died during Study PA-CL-03A and the death occurred following a gastrointestinal hemorrhage and cardiac arrest, but was not considered related to study treatment by the investigator.[8]

Most of the deaths that occurred during Stage 1 of Study PA-CL-05A were due to cardiac disorders.[9] A summary of cardiac disorders leading to death is presented in Table 12.

Table 12: PA-CL-05A: Summary of Cardiac Disorders Leading to Death in Stage 1 (SS)

MedDRA SOC/Preferred Term	SO (N = 707)	Sevelamer (N = 348)
Any cardiac disorder	6 (0.8%)	5 (1.4%)
Acute myocardial infarction	2 (0.3%)	0 (0.0%)
Cardiac arrest	3 (0.4%)	1 (0.3%)
Cardiac tamponade	0 (0.0%)	1 (0.3%)
Cardiorespiratory arrest	1 (0.1%)	1 (0.3%)
Cardiogenic shock	1 (0.1%)	0 (0.0%)
Cardiopulmonary failure	0 (0.0%)	1 (0.3%)
Myocardial infarction	0 (0.0%)	1 (0.3%)

MedDra = Medical Dictionary for Regulatory Activities; SO = sucroferric oxyhydroxide; SOC = system organ class; SS = safety set.

Source: Study PA-CL-05A Clinical Study Report.[9]

No deaths occurring during Study PA1301 were attributed to cardiovascular events.[10] The publication by Otsuki et al. does not contain any information pertaining to this outcome.

Cardiovascular Events

This outcome was not assessed as an efficacy outcome in the clinical trials included in this review; no formal hypotheses were stated or formally tested. Information pertaining to this outcome was reported as part of the safety evaluation of each study. The number of cardiovascular events reported during the treatment phase of each study is summarized in Table 1.

In Study PA-CL-03A, six patients (4.7%) in the SO groups experienced a cardiac disorder TEAE. However, no single cardiac event was reported by more than one patient in any one SO dose group.[8] No cardiac TEAEs were reported in the group treated with sevelamer.

In Study PA-CL-05A, a similar proportion of patients in the SO and sevelamer groups reported cardiac disorders in Stage 1.[9] The most commonly occurring cardiac disorders are presented in Table 13.

Table 13: PA-CL-05A: Summary of Most Commonly Occurring Cardiac Disorders in Stage 1 (SS)

MedDRA SOC/Preferred Term	SO (N = 707)	Sevelamer (N = 348)
Any cardiac disorders	68 (9.6%)	33 (9.5%)
Myocardial infarction (includes acute myocardial infarction and ischemia)	11 (1.6%)	4 (1.1%)
Cardiac failure (includes congestive, acute and chronic)	11 (1.6%)	6 (1.7%)
Atrial fibrillation	9 (1.3%)	5 (1.4%)

MedDra = Medical Dictionary for Regulatory Activities; SO = sucroferric oxyhydroxide; SOC = system organ class; SS = safety set.

Note: Each patient counts only once for each adverse event.

Source: Study PA-CL-05A Clinical Study Report.[9]

In Study PA1301 two patients experienced SAEs that were cardiovascular in nature during the treatment period, both in the SO group: one congestive cardiac failure and one supraventricular tachycardia.[10]

No cardiovascular events were reported in the study by Otsuki et al.[12]

Health-Related Quality of Life

This outcome was not assessed in PA-CL-03A or in PA1301. No information pertaining to this outcome is described in the study by Otsuki et al.

PA-CL-05A is the only study included in this review that evaluated HRQoL, which was measured using the SF-36v2. Overall, change from baseline in component scores was less than what is considered clinically meaningful.[9] No statistically significant differences were observed between the SO and sevelamer treatment groups for any of the component or sub-component scores measured with the SF-36v2. Results of the physical and mental component scores are summarized by treatment group in Table 29 in Appendix 4.

Bone Fractures

This outcome was not assessed as an efficacy outcome in the clinical trials included in this review; no formal hypotheses were stated or formally tested. Information pertaining to this outcome was reported as part of the safety evaluation of each study. The number of fracture events reported during the treatment phase of each study is summarized in Table 1. The publication by Otsuki et al. does not contain any information pertaining to this outcome.

In Study PA-CL-03A, one patient in the SO 1,000 mg iron group experienced a serious AE of rib fracture and consequently withdrew from the study.[8]

As shown in Table 1, in Study PA-CL-05A, eight patients (1.1%) in the SO group and eight patients (2.3%) in the sevelamer group reported an AE related to a bone fracture during Stage 1 of the study.[9]

In Study PA1301, one fracture AE (hand fracture) was reported in the sevelamer group, but was considered mild in severity.[10]

Serum Phosphorus

Change From Baseline

The primary efficacy end point in Study PA-CL-03A was change in serum phosphorus from baseline to end of treatment after six weeks. Mean serum phosphorus at baseline was similar across each of the SO dose and sevelamer groups.[8] In the FAS, the mean change from baseline in serum phosphorus was –0.042 mmol/L in the SO 250 mg iron group, –0.35 mmol/L in the SO 1,000 mg iron group, –0.40 mmol/L in the SO 1,500 mg iron group, –0.64 mmol/L in the SO 2,000 mg iron group, –0.55 mmol/L in the 2,500 mg iron group, and –0.34 mmol/L in the sevelamer group. No statistical comparison was conducted for any dose of SO compared with sevelamer. Reductions from baseline serum phosphorus were reported to be statistically significantly greater in all SO dose groups compared with the SO 250 mg iron group. However, no adjustment was made for multiple testing; see Table 31 in Appendix 4.

The key secondary analysis in Study PA-CL-05A was a noninferiority analysis of SO versus sevelamer in change from baseline of serum phosphorus levels at week 12 (Table 14). In the PPS, the mean (SD) change from baseline at week 12 was –0.7 (0.62) mmol/L in the SO group and –0.8 (0.67) mmol/L in the sevelamer group.[9] The least squares (LS) mean (SE) between-groups treatment difference was 0.08 (0.03) mmol/L and the upper bound of the 97.5% CI was below 0.19 mmol/L, thus SO was considered noninferior to sevelamer. Results in the FAS were consistent with that in the PPS supporting the noninferiority of SO to sevelamer in terms of lowering serum phosphorus levels (Table 14).

The pre-planned superiority analyses was conducted using the same model, revealing a statistically significant difference in favour of sevelamer (P = 0.011).[9]

Table 14: PA-CL-05A: Serum Phosphorus (mmol/L) Change From Baseline to Week 12 in Stage 1

	SO	Sevelamer
PPS (N = 685)	N = 461	N = 224
Baseline, mean (SD)	2.5 (0.59)	2.4 (0.62)
Week 12 end point, mean (SD)	1.8 (0.43)	1.7 (0.42)
Change from baseline, mean (SD)	–0.7 (0.62)	–0.8 (0.67)
Change from baseline, LS mean (SE)[a]	–0.71 (0.03)	–0.79 (0.04)
Treatment difference, LS mean (SE)[a]	0.08 (0.03)	
97.5% upper CI	–Inf to 0.15	
FAS (N = 1,041)	N = 694	N = 347
Baseline, mean (SD)	2.5 (0.59)	2.4 (0.57)
Week 12 end point, mean (SD)	1.8 (0.47)	1.7 (0.42)
Change from baseline, mean (SD)	–0.7 (0.63)	–0.7 (0.64)
Change from baseline, LS mean (SE)[a]	–0.66 (0.03)	–0.76 (0.03)
Treatment difference, LS mean (SE)[a]	0.10 (0.03)	
97.5% upper CI	–Inf to 0.16	

ANCOVA = analysis of covariance; CI = confidence interval; FAS = full analysis set; Inf = Infinity (as reported by the manufacturer); LS = least squares; LOCF = last observation carried forward; PPS = per-protocol set; SD = standard deviation; SE = standard error; SO = sucroferric oxyhydroxide.

[a] ANCOVA analysis on end point results (LOCF) using a mixed model with the maximum likelihood estimation. The model includes treatment, dialysis status, region, and baseline serum phosphorus level as fixed effects. Missing data at week 12 were replaced using the last post-baseline evaluable measurement prior to week 12 (LOCF rule).

Notes: Baseline is defined as the last assessment prior to or on the date of the first dose of study medication. Missing data at week 12 were replaced using the last post-baseline measurement prior to week 12.

Source: PA-CL-05A Clinical Study Report.[9]

Two sensitivity analyses on the ANCOVA-LOCF were conducted on the key secondary end point in the PPS and FAS populations. Both analyses supported noninferiority of SO versus sevelamer for serum phosphorus control at week 12. In sensitivity analyses in the per-protocol and FAS populations, and employing both the ANCOVA–observed cases and MMRM-MAR models, the LS means (SE) of each analysis were within the upper bound of the 97.5% CI of 0.14 mmol/L[9], and were below the predefined noninferiority margin of 0.19 mmol/L. In addition, the MMRM-MAR model compared the trend in serum phosphorus change from baseline over time (Table 15). Full summary statistics for serum phosphorus levels and the change from baseline within each treatment group at each time point are presented in Appendix 4.

Table 15: PA-CL-05A: Analysis of Serum Phosphorus Change from Baseline (MMRM-MAR) (Full Analysis Set; N = 1,041)

Statistic	LS Mean (SE)	95% CI	*P* value[a]
MMRM model[a] (n = 1,033)			
Serum phosphorus (mmol/L)			
Contrasts:			
Week 4: SO vs. sevelamer	0.14 (0.03)	0.08 to 0.20	< 0.001
Week 8: SO vs. sevelamer	0.10 (0.03)	0.04 to 0.16	< 0.001
Week 12: SO vs. sevelamer	0.08 (0.03)	0.02 to 0.14	0.013
Week 16: SO vs. sevelamer	0.06 (0.03)	–0.00 to 0.12	0.069
Week 20: SO vs. sevelamer	0.01 (0.03)	–0.06 to 0.08	0.798
Week 24: SO vs. sevelamer	0.05 (0.03)	–0.02 to 0.12	0.141

CI = confidence interval; FAS = full analysis set; LS = least squares; MAR = missing at random; MMRM = Mixed-effects model for repeated measures; SE = standard error; SO = sucroferric oxyhydroxide.

[a] MMRM-MAR: Assumes the MAR missingness mechanism was used. The model includes subject as a random effect, fixed effects of week, treatment, baseline serum phosphorus, region (US/EU/rest of world), dialysis type, and treatment × week.

Source: PA-CL-05A Clinical Study Report.[9]

Results of the noninferiority analysis for serum phosphorus were further examined in predefined subgroup analyses. Dialysis status, age, and previous PB treatment were identified as subgroups of interest for the CDR review. Results of these analyses are presented in the PPS in Table 16. Results of these analyses suggest that the serum-phosphorous–lowering effects of SO compared with sevelamer are not appreciably different within the aforementioned subgroups and tests for interaction were not statistically significant; see Table 16.[9]

Table 16: PA-CL-05A: Subgroup Analysis of Change in Serum Phosphorus (mmol/L) From Baseline to Week 12 (Per-Protocol Set; N = 685)

Statistic	SO Mean (SD) Serum Phosphorus (mmol/L)				Sevelamer Mean (SD) Serum Phosphorus (mmol/L)				*P Value* for Interaction With Treatment
	N	Baseline	Week 12 End Point	Change From Baseline to Week 12 End Point	N	Baseline	Week 12 End Point	Change From Baseline to Week 12 End Point	
Dialysis status									0.287
PD	41	2.3 (7.1)	1.8 (5.5)	–0.5 (–1.7)	16	2.1 (6.5)	1.5 (4.8)	–0.5 (–1.7)	
HD	420	2.5 (7.7)	1.8 (5.5)	–0.7 (–2.3)	208	2.5 (7.7)	1.7 (5.2)	–0.8 (–2.4)	
Age									0.785
< 65 years	346	2.5 (7.8)	1.8 (5.6)	–0.7 (–2.2)	163	2.5 (7.7)	1.7 (5.3)	–0.8 (–2.4)	
≥ 65 years	115	2.3 (7.2)	1.6 (5.1)	–0.7 (–2.1)	61	2.3 (7.2)	1.6 (4.9)	–0.7 (–2.3)	
Previous treatment with sevelamer									0.355
Yes	148	2.5 (7.7)	1.7 (5.4)	–0.7 (–2.3)	76	2.4 (7.5)	1.7 (5.2)	–0.7 (–2.3)	
No	313	2.5 (7.7)	1.8 (5.5)	–0.7 (–2.2)	148	2.5 (7.6)	1.7 (5.2)	–0.8 (–2.4)	

HD = hemodialysis; PD = peritoneal dialysis; SD = standard deviation; SO = sucroferric oxyhydroxide.

Source: PA-CL-05A Clinical Study Report.[9]

For Study PA1301, in the PPS, the mean serum phosphorus concentration at the end of treatment (week 12) was 1.62 mmol/L in patients treated with SO and 1.72 mmol/L in patients treated with sevelamer, with a difference of –0.11 mmol/L (95% CI, –0.20 mmol/L

to –0.02 mmol/L) (Table 17); and the upper bound of the 95% CI was below the predefined noninferiority margin of 0.32 mmol/L, thus SO was considered noninferior to sevelamer.[10,11]

A similar analysis of serum phosphorus concentration at the last evaluation in the FAS was stated to confirm that SO was noninferior to sevelamer for serum phosphorus control (Table 17). However, details of this analysis were not provided.[10,11] Summary statistics for serum phosphorus levels and change from baseline are summarized in Table 33 in Appendix 4.

Table 17: PA1301: Serum Phosphorus (mmol/L) Change From Baseline

	SO	Sevelamer
PPS	N = 100	N = 92
Baseline, mean (SD)	2.51 (0.45)	2.45 (0.39)
Week 12 end point, mean (SD)	1.62 (0.33)	1.72 (0.33)
Change from baseline		
Mean (SD)	–0.90 (0.53)	–0.73 (0.45)
95% CI	–1.00 to -0.79	–0.82 to -0.63
Treatment difference, LS mean (95% CI)	–0.11 (–0.20 to –0.02)	
FAS	N = 106	N = 103
Baseline, mean (SD)	2.51 (0.44)	2.45 (0.38)
Week 12 end point, mean (SD)	1.63 (0.33)	1.72 (0.34)
Change from baseline		
Mean (SD)	–0.88 (0.53)	–0.73 (0.46)
95% CI	–0.98 to –0.78	–0.82 to –0.64
Treatment difference, LS mean (SE)	NR	

CI = Confidence interval; LS = Least square; NR = not reported; PPS = per protocol set; SD = standard deviation; SE = Standard error; SO = sucroferric oxyhydroxide.

Source: PA1301 Clinical Study Report Synopsis.[10]

In the study by Otsuki et al., there were no statistically significant changes in serum phosphorus from baseline (SO mean [SD]: 5.8 ± 1.3 mg/dL [1.87 ± 0.42 mmol/L]; lanthanum: 5.7 ± 1.6 mg/dL [1.84 ± 0.52 mmol/L]) to end of treatment at week 24 (SO: 5.9 ±1.6 mg/dL [1.91 ± 0.52 mmol/L]; lanthanum: 5.8 ± 1.2 mg/dL [1.87 ± 0.39 mmol/L]) between patients treated with SO versus those who continued treatment with lanthanum.[12]

Proportion of Patients Achieving Target Serum Phosphorus

In Study PA-CL-03A, approximately 25% of patients in the FAS had serum phosphorus levels within KDOQI guidelines.[8] Across groups, the proportion of patients within guidelines ranged from 11.5% in the SO 1,000 mg iron/day group to 32.0% in the SO 2,000 mg iron/day group. The proportion of patients with controlled serum phosphorus varied over time, but the proportion of patients at any time during treatment was highest in the SO 2,500 mg iron/day group (87.5%). The proportion of patients with controlled serum phosphorus at any time in the sevelamer group was 83.3%. The Cochrane–Armitage test showed a statistically significant trend in SO dose for controlled serum phosphorus at any time and also over time. The proportion of patients with controlled serum phosphorus levels in each treatment group over time is presented in Table 34 in Appendix 4.

In Study PA-CL-05A, it is acknowledged that despite the requirement of serum phosphorus ≥ 1.94 mmol/L during the washout phase, some patients were within the KDOQI range at baseline visit (42 [6.1%] in the SO group and 29 [8.4%] in the sevelamer group). At week 12, more patients in the sevelamer group (54.7%) achieved serum phosphorus levels within the KDOQI target than did patients in the SO group (44.8%).[9] This difference between

treatment groups was smaller at week 24. Similar results were observed for the KDIGO normal range: more patients in the sevelamer group were within range at week 12 (27.4%) compared with the SO group (19.2%; *P* = 0.01), but the magnitude of the difference between groups was lower at week 24. The proportion of patients with serum phosphorus within the KDOQI target and KDIGO normal range is presented in Table 18. The duration of control of serum phosphorus (as defined by KDOQI or KDIGO targets) was longer in the sevelamer group than in the SO group (Table 19). On average, patients in the sevelamer group spent more days within the target range established by KDOQI and KDIGO than patients in the SO group.

Table 18: PA-CL-05A: Proportion of Patients who Achieved Serum Phosphorus Levels Within the KDOQI Target and KDIGO Normal Ranges During Stage 1 (Full Analysis Set; N = 1,041)

Time Point	Based on KDOQI Target[a]		Based on KDIGO Normal[b]	
	SO (N = 694)	Sevelamer (N = 347)	SO (N = 694)	Sevelamer (N = 347)
Baseline				
Evaluated, n	694	347	694	347
Controlled, n (%)	42 (6.1)	29 (8.4)	16 (2.3)	4 (1.2)
Week 12				
Evaluated, n	589	318	589	318
Controlled, n (%)	264 (44.8)	174 (54.7)	113 (19.2)	87 (27.4)
OR (95% CI)	0.69 (0.52 to 0.91)		0.65 (0.47 to 0.90)	
P value[c]	0.010		0.010	
Week 24				
Evaluated, n	496	285	496	285
Controlled, n (%)	261 (52.6)	155 (54.4)	119 (24.0)	85 (29.8)
OR (95% CI)	0.99 (0.73 to 1.34)		0.78 (0.56 to 1.08)	
P value[c]	0.949		0.137	

CI = confidence interval; KDIGO = Kidney Disease Improving Global Outcomes; KDOQI = Kidney Disease Outcomes Quality Initiative; OR = odds ratio; SO = sucroferric oxyhydroxide.

[a] Patients with controlled serum phosphorus according to KDOQI target range = 1.13 to 1.78 mmol/L (3.5 to 5.5 mg/dL).

[b] Patients with controlled serum phosphorus according to KDIGO normal range = 0.81 to 1.45 mmol/L (2.5 to 4.5 mg/dL).

[c] Logistic models were used on the full analysis set to derive the odds ratios using treatment and baseline phosphorus value as covariates.

Source: PA-CL-05A Clinical Study Report.[9]

Table 19: PA-CL-05A: Duration (Days) of Serum Phosphorus Levels Within the KDOQI Target and KDIGO Normal Ranges in Stage 1 (Full Analysis Set; N = 1,041)

Statistic	Based on KDOQI Target[a]		Based on KDIGO Normal[b]	
	SO (N = 694)	Sevelamer (N = 347)	SO (N = 694)	Sevelamer (N = 347)
n	599	320	408	237
Mean (SD)	71.8 (47.62)	81.4 (47.45)	40.4 (37.14)	51.0 (42.59)

KDIGO = Kidney Disease Improving Global Outcomes; KDOQI = Kidney Disease Outcomes Quality Initiative; SD = standard deviation; SO = sucroferric oxyhydroxide.

Note: Duration of controlled serum phosphorus level was defined as the total number of days in Stage 1 when measured serum phosphorus was within target range.

[a] KDOQI target range = 1.13 to 1.78 mmol/L (3.5 to 5.5 mg/dL).

[b] KDIGO normal range = 0.81 to 1.45 mmol/L (2.5 to 4.5 mg/dL).

Source: PA-CL-05A Clinical Study Report.[9]

In Study PA1301, target serum phosphorus concentration was based on the range recommended in the JSDT guidelines of ≥ 1.13 mmol/L and ≤ 1.94 mmol/L.[13] At the end of treatment, in the FAS, 79.2% of patients in the SO group and 68.0% of patients in the sevelamer group had achieved target serum phosphorus based on the JSDT target (Table 20).[10]

Table 20: PA1301: Proportion of Patients who Achieved Serum Phosphorus Levels within the JSDT Target (Full Analysis Set)

Time Point	SO (N = 106)	Sevelamer (N = 103)
Baseline		
n (%)	7 (6.6)	10 (9.7)
95% CI	2.7 to 13.1	4.8 to 17.1
Week 12 end point		
n (%)	84 (79.2)	70 (68.0)
95% CI	70.3 to 86.5	58.0 to 76.8

CI = confidence interval; JSDT = Japanese Society for Dialysis Therapy; SO = sucroferric oxyhydroxide.

[a] Target range recommended in the JSDT guidelines is ≥ 1.13mmol/L and ≤ 1.94mmol/L.

Source: PA1301 Clinical Study Report Synopsis.[10]

The proportion of patients achieving target serum phosphorus was not evaluated in the study by Otsuki et al.

Serum Calcium

Serum total calcium was a secondary end point in studies PA-CL-03A and PA-CL-05A, while corrected serum calcium was reported in study PA1301. Mean calcium levels at baseline were within the normal range in each of the phase III trials included in this review.

In Study PA-CL-03A, serum total calcium levels were comparable across the six treatment groups, ranging from 2.10 mmol/L to 2.16 mmol/L at baseline in the FAS.[8] Mean changes from baseline at the end of treatment were negligible and ranged from a mean (SD) of –0.06 (0.31) in the SO 250 mg iron/day group to 0.06 (0.14) in the sevelamer group. Summary statistics for serum calcium at baseline, end of treatment, and change from baseline for each group are presented in Table 35 in Appendix 4.

In Study PA-CL-05A, mean serum total calcium levels did not differ at baseline between the SO (2.2 mmol/L) and sevelamer (2.2 mmol/L) groups.[9] Change from baseline in serum calcium to week 24 was similarly negligible between the SO and sevelamer groups (Table 21). Summary statistics for serum calcium over time for each group are presented in Table 36 in Appendix 4.

Table 21: PA-CL-05A: Serum Total Calcium (mmol/L) Change from Baseline in Stage 1 (FAS)

	SO (N = 694)	Sevelamer (N = 347)
Baseline, mean (SD)	2.2 (0.19)	2.2 (0.20)
Week 24 end point, mean (SD)	2.2 (0.20)	2.2 (0.17)
Change from baseline, mean (SD)	0.0 (0.21)	0.0 (0.20)
Change from baseline, LS mean (SE)[a]	0.02 (0.01)	0.02 (0.01)
Treatment difference, LS mean (SE)[a]	0.00 (0.01)	
95% CI	–0.02 to 0.02	

ANCOVA = analysis of covariance; CI = confidence interval; FAS = full analysis set; LS = least squares; LOCF = last observation carried forward; SD = standard deviation; SE = standard error; SO = sucroferric oxyhydroxide.

[a] ANCOVA analysis on end point results at week 24 (LOCF) using a mixed model with the maximum likelihood estimation. The model includes treatment, dialysis status, region, and baseline serum total calcium as fixed effects. Missing data at week 24 were replaced using the last post-baseline evaluable measurement prior to week 24.

Source: PA-CL-05A Clinical Study Report.[9]

In Study PA1301, the mean corrected serum calcium levels did not differ at baseline between the SO (2.24 mmol/L) and sevelamer (2.23 mmol/L) treatment groups.[10] As shown in Table 22, there was no significant change from baseline in either group. Serum calcium levels across each treatment group are summarized in Table 37, Appendix 4.

Table 22: PA1301: Corrected Serum Calcium (mmol/L) (Full Analysis Set)

	SO (N = 106)	Sevelamer (N = 103)
Baseline, mean (SD)	2.24 (0.14)	2.23 (0.14)
Week 12 end point, mean (SD)	2.28 (0.17)	2.24 (0.18)
Change from baseline, mean (SD)	0.05 (0.13)	0.01 (0.14)
95% CI	0.02 to 0.07	–0.02 to 0.04

CI = confidence interval; SD = standard deviation; SO = sucroferric oxyhydroxide

Source: PA1301 Clinical Study Report Synopsis.[10]

In the study by Otsuki et al., there were no appreciable changes in calcium from baseline (Mean ± SD SO: 2.25 ± 0.11 mmol/L; lanthanum: 2.25 ± 0.13 mmol/L) to end of treatment at week 24 (SO: 2.25 ± 0.13 mmol/L; lanthanum: 2.23 ± 0.15 mmol/L) between patients treated with SO and those who continued treatment with lanthanum.[12]

Intact PTH Levels

In Study PA-CL-03A, mean serum iPTH levels at baseline ranged from 23.58 pmol/L in the SO 2,500 mg iron/day group to 28.80 pmol/L in the SO 1,500 mg iron/day group in the FAS.[8] At the end of treatment, mean serum iPTH was generally lower in all treatment groups except in the SO 250 mg and 1,500 mg iron/day groups. Serum iPTH levels across each treatment group are summarized in Table 38, Appendix 4.

In the FAS, serum iPTH levels varied throughout Stage 1 of Study PA-CL-05A. The between-groups difference in the change from baseline in serum iPTH was not significant (P = 0.314), although decreases were generally larger in the SO group (Table 23).[9]

Summary statistics for serum iPTH over time for each group are presented in Table 39 in Appendix 4.

Table 23: PA-CL-05A: Serum iPTH (pmol/L) Change from Baseline in Stage 1 (Full Analysis Set)

	SO (N = 694)	Sevelamer (N = 347)
Baseline, mean (SD)		
n	694	347
Mean (SD)	46.2 (31.87)	42.9 (28.89)
Week 24 end point,		
n	673	341
Mean (SD)	39.8 (29.83)	39.2 (28.96)
Change from baseline, mean (SD)	–6.6 (29.22)	–3.2 (25.49)
Change from baseline, LS mean (SE)[a]	–4.38 (1.49)	–2.76 (1.76)
Treatment difference, LS mean (SE)[a]	–1.62 (1.61)	
95% CI	–4.78 to 1.54	

ANCOVA = analysis of covariance; CI = confidence interval; iPTH = intact parathyroid hormone; LOCF = last observation carried forward; LS = least squares; SD = standard deviation; SE = standard error; SO = sucroferric oxyhydroxide.

[a] ANCOVA analysis on end point results at week 24 (LOCF) using a mixed model with the maximum likelihood estimation. The model includes treatment, dialysis status, region, and baseline serum iPTH as fixed effects. Missing data at week 24 were replaced using the last post-baseline evaluable measurement prior to week 24.

Source: PA-CL-05A Clinical Study Report.[9]

In Study PA1301, serum iPTH levels generally decreased from baseline to end of treatment in both the SO and sevelamer groups (Table 24), but were variable over time.[10] Serum iPTH levels across each treatment group are summarized in Table 40, Appendix 4.

Table 24: PA1301: Serum iPTH (pmol/L) Change from Baseline (Full Analysis Set)

	SO (N = 106)	Sevelamer (N = 103)
Baseline		
n	106	103
Mean (SD)	28.31 (16.02)	31.59 (17.48)
Week 12 end point		
n	105	102
Mean (SD)	21.74 (12.17)	26.57 (17.59)
Change from baseline		
n	105	102
Mean (SD)	–6.76 (8.69)	–5.10 (9.47)
95% CI	–8.43 to –5.07	–6.96 to –3.23

CI = confidence interval; iPTH = intact parathyroid hormone; SD = standard deviation; SO = sucroferric oxyhydroxide.

Source: PA1301 Clinical Study Report Synopsis.[10]

In the study by Otsuki et al., there were no statistically significant changes in iPTH from baseline median (interquartile range) SO: 17.50 (9.33 to 23.65) pmol/L; lanthanum: 16.01 (11.13 to 20.25) pmol/L) to end of treatment at week 24 (SO: 12.94 (8.48 to 18.03) pmol/L; lanthanum: 13.04 (10.60 to 19.62) pmol/L) between patients treated with SO and those who continued treatment with lanthanum.[12]

Harms

Only those harms identified in the review protocol are reported below. See Table 25 and Table 26 for detailed harms data.

Adverse Events

In Study PA-CL-03A, the proportion of patients with any TEAE was highest in the 2,500 mg iron/day group at 70.8%, followed by the SO 2,000 mg iron/day group at 66.7% (Table 25).[8] The most common TEAEs in the pooled SO group were hypophosphatemia (18%), discoloured feces (11.7 %), and hyperphosphatemia (7.8%). The percentage of patients experiencing a hypophosphatemia AE were highest in the two highest SO dosage groups: 29.6% in the SO 2,000 mg iron/day group and 29.2% in the SO 2,500 mg iron/day group. TEAEs were reported in 57.7% of patients in the sevelamer group with the most common being hypophosphatemia, diarrhea, and hypotension (11.5% for each event).

As shown in Table 26, in Study PA-CL-05A, the most common TEAEs occurring in patients in the SO group were diarrhea (20.1%), discoloured feces (15.4%) hyperphosphatemia (11.2%), nausea (7.2%), and hypertension (6.4%).[9] In the sevelamer group, the most commonly reported TEAEs were nausea (11.2%), hyperphosphatemia (7.8%), diarrhea (7.5%), hypertension (7.5%), constipation (7.2%), and vomiting (5.5%). More patients in the SO group (more than 2%) reported TEAEs of diarrhea, discoloured feces, hyperphosphatemia, and abnormal product taste than in the sevelamer group. More patients in the sevelamer group reported TEAEs of nausea, constipation, anemia, and decreased appetite than in the sevelamer group.

In Study PA1301, the frequency of AEs was 78.7% and 66.7% in the SO and sevelamer groups, respectively (Table 26).[10] The most frequently reported AE in the SO groups was diarrhea, followed by nasopharyngitis and discoloured feces. In the sevelamer group, the most frequently reported AE was nasopharyngitis followed by constipation.

A detailed report of AEs was not included in the study by Otsuki et al. It was reported that four patients in the SO group developed diarrhea but did not withdraw from the study.[12] AEs were not reported for the lanthanum group.

Serious Adverse Events

In Study PA-CL-03A, a total of eight patients (6.3%) across the SO groups experienced an SAE, but there was no dose-dependent trend in SAEs among the SO groups (Table 25).[8] The only SAE that was reported in more than one patient was staphylococcal sepsis, which was reported in one patient (3.8%) in the SO 1,000 mg iron/day group and one patient (4.2%) in the 2,500 mg iron/day group. Two patients (7.7%) in the sevelamer group experienced a total of three SAEs — diabetic retinopathy, pancreatitis, and cholelithiasis.

In Study PA-CL-05A, the incidence of SAEs was similar between the SO and sevelamer groups.[9] The SAEs that occurred in at least 1.0% of patients in either treatment group included pneumonia, acute myocardial infarction, dyspnea, diarrhea, and chest pain (Table 26).

In Study PA1301, 5.6% and 4.8% of patients in the SO and sevelamer groups, respectively, experienced an SAE.[10] As shown In Table 26, no SAE was reported in more than one patient in either group.

No SAEs are reported in the study by Otsuki et al.[12]

Withdrawal Due to Adverse Events

In Study PA-CL-03A, the proportion of patients who withdrew due to AEs was similar in the pooled SO and sevelamer group (21.1% and 23.1%, respectively).[8] As shown in Table 25, withdrawals due to AEs were highest in the SO 2,000 mg iron/day group (29.6%). The most common reason for WDAEs was hypophosphatemia, which accounted for 22.2% of WDAEs in the SO 2,000 mg iron/day group and 16.7% of WDAEs in the SO 2,500 mg iron/day group.

In Study PA-CL-05A, a higher proportion of patients in the SO group withdrew from Stage 1 of the study due to AEs than in the sevelamer group (15.7% versus 6.6%, respectively).[9] GI events were the most common reason for WDAEs in both groups, accounting for 54% of withdrawals in the SO group and 43.5% of withdrawals in the sevelamer group. Other AEs leading to study withdrawal of patients in the SO group included abnormal product taste (1.6 %) and hyperphosphatemia (1.4%).

In Study PA1301, 5.6% of patients in the SO group and 6.7% of patients in the sevelamer group withdrew from the study due to AEs.[10] The most common reason for WDAEs in the SO group was diarrhea (four patients) and constipation in the sevelamer group (three patients).

Otsuki et al. reported that three patients in the SO group withdrew from the study due to AEs: one due to diarrhea, and two patients were admitted to hospital (one for peripheral artery disease and one for coronary angiography).[12] None of these events were deemed related to study treatment. WDAEs were not reported for the lanthanum group.

Notable Harms

GI symptoms, serum ferritin, and transferrin saturation were identified as the notable harms of interest based on the review protocol.

Gastrointestinal Symptoms

In Study PA-CL-03A a total of 29 patients (22.7%) treated with any dose of SO and seven patients (26.9%) treated with sevelamer reported GI TEAEs.[8] Discoloured feces was the most commonly reported GI symptom reported in patients receiving SO (11.7%), but did not appear to be dose-dependent. No patients treated with sevelamer reported discoloured feces. As shown in
Table 25, other common GI symptoms reported in patients treated with SO were constipation (3.1%), vomiting (2.3%), and gastritis (1.6%), none of which were dose-dependent. The most commonly reported GI symptom reported by patients treated with sevelamer was diarrhea (11.5%; two cases led to study discontinuation).

In Study PA-CL-05A, GI disorders were the most common TEAEs, which were reported more often in patients receiving SO than in those receiving sevelamer (45.1% versus 33.6%, respectively).[9] This difference was primarily due to increased reports of diarrhea and discoloured feces in the SO group. Three cases of diarrhea were considered serious (two in the SO group and one in the sevelamer group). In the SO group, the majority of diarrhea events (69%) were mild in severity and 1.4% were considered severe. Conversely, 57.7% of diarrhea events in the sevelamer group were considered mild and 7.7% of events

were considered severe. Constipation, nausea, and abdominal pain/discomfort were reported less often in the SO group compared with the sevelamer group.

In Study PA1301, as presented in Table 26 the most common GI symptoms in the SO group were diarrhea (25%), discoloured feces (16.7%), and stomatitis (3.7%).[10] In the sevelamer group, the most common GI symptoms were constipation (18.2%) and abdominal discomfort (4.8%).

In Otsuki et al. four patients in the SO group reported diarrhea, and one of these reports resulted in study withdrawal.[12] GI symptoms were not reported in the lanthanum group.

Table 25: Harms by Treatment Group for Study PA-CL-03A (Safety Set)

	250 mg Iron (1.25 g SO)/day N = 26	1,000 mg Iron (5.0 g SO)/day N = 26	1,500 mg Iron (7.5 g SO)/day N = 25	2,000 mg Iron (10.0 g SO)/day N = 27	2,500 mg Iron (12.5 g SO)/day N = 24	Sevelamer HCl N = 26
AEs						
Patients with > 0 AEs, N (%)	14 (53.8%)	16 (61.5%)	13 (52.0%)	18 (66.7%)	17 (70.8%)	15 (57.7%)
Most common AEs[a]						
Anemia	0	0	3 (12.0)	0	0	0
Constipation	0	1 (3.8)	1 (4.0)	2 (7.4)	0	0
Diarrhea	1 (3.8)	2 (7.7)	2 (8.0)	1 (3.7)	1 (4.2)	3 (11.5)
Discoloured feces	2 (7.7)	3 (11.5)	3 (12.0)	4 (14.8)	3 (12.5)	0 (0.0)
Vomiting	0 (0.0)	2 (7.7)	0 (0.0)	1 (3.7)	0 (0.0)	1 (3.8)
Nasopharyngitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (8.3)	0 (0.0)
Hypercalcemia	2 (7.7)	2 (7.7)	1 (4.0)	1 (3.7)	1 (4.2)	2 (7.7)
Hyperphosphatemia	5 (19.2)	3 (11.5)	1 (4.0)	1 (3.7)	0 (0.0)	2 (7.7)
Hypophosphatemia	2 (7.7)	4 (15.4)	2 (8.0)	8 (29.6)	7 (29.2)	3 (11.5)
Muscle spasms	1 (3.8)	1 (3.8)	2 (8.0)	1 (3.7)	3 (12.5)	0 (0.0)
Hypertension	1 (3.8)	0 (0.0)	2 (8.0)	0 (0.0)	2 (8.3)	1 (3.8)
Hypotension	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	3 (11.5)
SAEs						
Patients with > 0 SAEs, N (%)	2 (7.7%)	2 (7.7%)	1 (4.0%)	1 (3.7%)	2 (8.3%)	2 (7.7%)
Most common SAEs[b]						
Cardiac arrest	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Myocardial infarction	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diabetic retinopathy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)
Diverticular perforation	1 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal hemorrhage	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pancreatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)
Cholelithiasis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)
Arteriovenous graft site abscess	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)	0 (0.0)
Peritoneal infection	1 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Staphylococcal sepsis	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	1 (4.2)	0 (0.0)
Arteriovenous graft	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)	0 (0.0)

	250 mg Iron (1.25 g SO)/day N = 26	1,000 mg Iron (5.0 g SO)/day N = 26	1,500 mg Iron (7.5 g SO)/day N = 25	2,000 mg Iron (10.0 g SO)/day N = 27	2,500 mg Iron (12.5 g SO)/day N = 24	Sevelamer HCl N = 26
site hematoma						
Rib fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)	0 (0.0)
Fluid overload	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)	0 (0.0)
Ischemic stroke	0 (0.0)	0 (0.0)	1 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asthma	1 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
WDAEs						
WDAEs, N (%)[b]	5 (19.2%)	5 (19.2%)	4 (16.0%)	8 (29.6%)	5 (20.8%)	6 (23.1%)
Cardiac arrest	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea	0 (0.0)	0 (0.0)	1 (4.0)	0 (0.0)	0 (0.0)	2 (7.7)
Pancreatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)
Arteriovenous graft site abscess	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)	0 (0.0)
Staphylococcal sepsis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)	0 (0.0)
Arteriovenous graft site hematoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)	0 (0.0)
Rib fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)	0 (0.0)
Hypercalcemia	2 (7.7)	2 (7.7)	0 (0.0)	1 (3.7)	1 (4.2)	0 (0.0)
Hyperphosphatemia	2 (7.7)	2 (7.7)	0 (0.0)	1 (3.7)	0 (0.0)	1 (3.8)
Hypoglycemia	0 (0.0)	0 (0.0)	1 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypophosphatemia	1 (3.8)	0 (0.0)	2 (8.0)	6 (22.2)	4 (16.7)	2 (7.7)
Deaths						
Number of deaths, N (%)	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Notable Harms						
GI Symptoms[b]						
Constipation	0 (0.0)	1 (3.8)	1 (4.0)	2 (7.4)	0 (0.0)	0 (0.0)
Diarrhea	1 (3.8)	2 (7.7)	2 (8.0)	1 (3.7)	1 (4.2)	3 (11.5)
Discoloured feces	2 (7.7)	3 (11.5)	3 (12.0)	4 (14.8)	3 (12.5)	0 (0.0)
Gastritis	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	1 (4.2)	0 (0.0)
Vomiting	0 (0.0)	2 (7.7)	0 (0.0)	1 (3.7)	0 (0.0)	1 (3.8)

AE = adverse event; GI = gastrointestinal; N = number of patients; SAE = serious adverse event; SO = sucroferric oxyhydroxide; WDAE = withdrawal due to adverse event.

[a] Occurring in at least 5% of patients in at least one treatment group.

[b] Occurring in at least 1% of patients in at least one treatment group.

Source: Source: Study PA-CL-03A Clinical Study Report.[8]

Table 26: Harms for Phase III Studies

	PA-CL-05A (Stage 1)		PA1301		Otsuki et al. (2018)	
	SO (N = 707)	Sevelamer (N = 348)	SO (N = 108)	Sevelamer (N = 105)	SO (N = 34)	Lanthanum (N = 34)
AEs						
Subjects with > 0 AEs, N (%)	588 (83.2)	265 (76.1)	85 (78.7)	70 (66.7)	NR	NR
Most common AEs[a]						
Nasopharyngitis	19 (2.7%)	14 (4.0%)	24 (22.2)	24 (22.9)	—	NR
Diarrhea	142 (20.1)	26 (7.5)	27 (25.0)	3 (2.9)	4	
Discoloured feces	109 (15.4)	1 (0.3)	18 (16.7)	1 (1.0)	—	
Constipation	27 (3.8)	25 (7.2)	2 (1.9)	19 (18.1)	—	
Abdominal discomfort	—	—	1 (0.9)	5 (4.8)	—	
Hyperphosphatemia	79 (11.2)	27 (7.8)	—	—	—	
Nausea	51 (7.2)	39 (11.2)	—	—	—	
Hypertension	45 (6.4)	26 (7.5)	—	—	—	
Vomiting	31 (4.4)	19 (5.5)	—	—	—	
SAEs						
Subjects with > 0 SAEs, N (%)	129 (18.2)	69 (19.8)	6 (5.6)	5 (4.8)	NR	NR
Most common SAEs[b]						
Pneumonia	7 (1.0)	2 (0.6)	—	—	NR	NR
Acute myocardial infarction	9 (1.3)	0 (0)	—	—		
Dyspnea	4 (0.6)	4 (1.1)	—	—		
Chest pain	8 (1.1)	5 (1.4)	—	—		
Colon cancer	—	—	1 (0.9)	0		
Renal cyst ruptured	—	—	1 (0.9)	0		
Acute pulmonary edema,	—	—	1 (0.9)	0		
Cardiac failure congestive	—	—	1 (0.9)	0		
Supraventricular tachycardia	—	—	1 (0.9)	0		
Pulmonary edema	—	—	1 (0.9)	0		
Pneumonia	—	—	1 (0.9)	0		
Gastric cancer	—	—	0	1 (1.0)		
Diverticulitis	—	—	0	1 (1.0)		
Cerebral infarction	—	—	0	1 (1.0)		
Shunt stenosis	—	—	0	1 (1.0)		
Intervertebral disc protrusion	—	—	0	1 (1.0)		
WDAEs						
WDAEs, N (%)[b]	111 (15.7)	23 (6.6)	6 (5.6)	7 (6.7)	3	NR
Diarrhea	20 (2.8)	2 (0.6)	4 (3.7)	1 (1.0)	1	
Gastroenteritis	—	—	1 (0.9)	0	—	
Hemoglobin increased	—	—	1 (0.9)	0	—	
Constipation	7 (1.0)	5 (1.4)	0	3 (2.9)	—	
Hepatic cirrhosis	—	—	0	1 (1.0)	—	
Abdominal pain	—	—	0	1 (1.0)	—	
Nausea	11 (1.6)	2 (0.6)	0	1 (1.0)	—	
Discoloured feces	—	—	0	1 (1.0)	—	
Decreased appetite	—	—	0	1 (1.0)	—	
Abdominal discomfort	—	—	0	1 (1.0)	—	

	PA-CL-05A (Stage 1)		PA1301		Otsuki et al. (2018)	
	SO (N = 707)	Sevelamer (N = 348)	SO (N = 108)	Sevelamer (N = 105)	SO (N = 34)	Lanthanum (N = 34)
Vomiting	7 (1.0)	2 (0.6)	—	—	—	
Product taste abnormal	11 (1.6)	1 (0.3)	—	—	—	
Hyperphosphatemia	10 (1.4)	0	—	—	—	
Admission to hospital	—	—	—	—	2[c]	
Deaths						
Number of deaths, N (%)	13 (1.8)	7 (2.0)	0	0	NR	NR
Notable Harms						
GI Symptoms[b]						
Diarrhea	142 (20.1)	26 (7.5)	27 (25.0)	3 (2.9)	4	NR
Discoloured feces	109 (15.4%)	1 (0.3)	18 (16.7)	1 (1.0)	NR	
Stomatitis	—	—	4 (3.7)	0		
Constipation	27 (3.8)	25 (7.2)	2 (1.9)	19 (18.2)		
Nausea	51 (7.2)	39 (11.2)	2 (1.9)	3 (2.9)		
Dyspepsia	20 (2.8)	11 (3.2)	—	—		
Abdominal pain	18 (2.5)	10 (2.9)	2 (1.9)	1 (1.0)		
Abdominal pain upper	18 (2.5)	7 (2.0)	0	1 (1.0)		
Flatulence	9 (1.3)	8 (2.3)	—	—		
Dental caries	—	—	2 (1.9)	1 (1.0)		
Toothache	—	—	2 (1.9)	0		
Vomiting	31 (4.4%) 36	19 (5.5%) 22	2 (1.9)	0		
Abdominal discomfort	5 (0.7%)	9 (2.6%)	1 (0.9)	5 (4.8)		
Abdominal distension	—	—	0	3 (2.9)		
Gastroesophageal reflux disease	—	—	0	1 (1.0)		
Gastritis	—	—	0	1 (1.0)		
Gingival pain	—	—	0	1 (1.0)		
Lip swelling	—	—	0	1 (1.0)		

AE = adverse event; GI = gastrointestinal; SAE = serious adverse event; SO = sucroferric oxyhydroxide; WDAE = withdrawal due to adverse event.

[a] Occurring in at least 5% of patients in at least one treatment group.

[b] Occurring in at least 1% of patients in at least one treatment group.

[c] Admissions due to peripheral artery disease and coronary angiography.

Sources: Study PA-CL-05A Clinical Study Report[9]; PA1301 Clinical Study Report Synopsis;[10] Koiwa (2017);[11] Otsuki et al. (2018).[12]

Serum Ferritin and Transferrin Saturation

In Study PA-CL-03A, at week 4, mean (SD) change from baseline in serum ferritin in the pooled SO group was 12.42 (287.25) pmol/L and 5.39 (234.96) pmol/L in the sevelamer group and mean (SD) change in transferrin saturation (%) was –0.91 (9.66) in the pooled SO group and –1.34 (6.38) in the sevelamer group.[8] No analysis for either of these parameters was conducted at end of treatment.

In Study PA-CL-05A, patients in both the SO and sevelamer group exhibited elevated serum ferritin at baseline (

Table 27).[9] Increases from baseline in serum ferritin and transferrin saturation at week 24 were greater in the SO than in the sevelamer group.

In Study PA1301, mean serum ferritin level was 207.62 pmol/L and 304.4 pmol/L in the SO group at baseline and week 12, respectively. Transferrin saturation in the SO group was

22.89% and 29.86% at baseline and week 12, respectively (Table 27).[10] No increase in either of these measures was observed in the sevelamer group. In the study published by Otsuki et al.,[12] median (interquartile range) increases in serum ferritin at week 24 were greater in the SO group than in the lanthanum group: –175.3 (98.9 to 310.1) pmol/L) and 141.1 (89.9 to 197.7) pmol/L, respectively. As shown in

Table 27, similar results were observed for **transferrin saturation**: at week 24, **transferrin saturation** % was increased in the SO group compared with the lanthanum group.

Table 27: Serum Ferritin and Transferrin Saturation in Phase III Studies of SO

Statistic	PA-CL-05A (Stage 1)		PA1301		Otsuki et al. (2018)	
	SO (N = 707)	Sevelamer (N = 348)	SO (N = 108)	Sevelamer (N = 105)	SO (N = 31)	Lanthanum (N = 32)
Serum ferritin (pmol/L)						
Baseline						
n	707	348	108	105	31	32
Mean (SD)	1,497.9 (987.7)	1,605.6 (1,172.7)	207.62 (279.2)	229.6 (284.7)	Median (IQR) 65.16 (29.21 to 114.60)	Median (IQR) 107.856 (83.139 to 157.29)
Week 12						
n	595	321	108	105	NR	
Mean (SD)	1,651.7 (1,095.58)	1,668.8 (1,171.16)	304.4 (324.1)	209.2 (267.0)		
Change from baseline, mean (SD)	184.7 (674.75)	52.6 (894.14)	NR			
95% CI	130.4 to 239.0	–45.6 to 150.8				
Week 24 end point						
n	685	344	NR		31	32
Mean (SD)	1,773.3 (1,141.5)	1,691.6 (1,117.6)			Median (IQR) 175.27 (98.87 to 310.09)	Median (IQR) 141.56 (89.88 to 197.74)
Change from baseline, mean (SD)	277.4 (794.5)[a/b]	92.0 (810.9)[a]			NR	
95% CI	217.8 to 337.0	6.0 to 178.0				
P value	NR				0.031	
Transferrin saturation (%)						
Baseline						
n	706	348	108	105	31	32
Mean (SD)	26.6 (13.7)	27.8 (13.8)	22.89 (9.50)	23.31 (10.20)	19.7 (8.1)	18.7 (3.8)
Week 12						
n	595	319	108	105	NR	
Mean (SD)	29.7 (13.81)	27.7 (15.11)	29.86 (13.51)	22.09 (9.96)		
Change from baseline, mean (SD)	3.5 (15.21)	–0.2 (16.88)	NR			

Statistic	PA-CL-05A (Stage 1)		PA1301		Otsuki et al. (2018)	
	SO (N = 707)	Sevelamer (N = 348)	SO (N = 108)	Sevelamer (N = 105)	SO (N = 31)	Lanthanum (N = 32)
95% CI	2.3 to 4.7	–2.1 to 1.6				
Week 24 end point						
n	684	344	NR		NR	
Mean (SD)	31.3 (16.1)	27.3 (15.3)			28.1 (9.7)	21.5 (6.6)
Change from baseline, mean (SD)	4.8 (17.8)[a]/[b]	–0.5 (17.0)			NR	
95% CI	3.5 to 6.1	–2.3 to 1.3				
P value	< 0.0001				0.003	

CI = confidence interval; IQR = interquartile range; SD = standard deviation; SO = sucroferric oxyhydroxide.

[a] Indicates a statistically significant change from baseline to Week 24 end point.

[b] Indicates a statistically significant difference based on Wilcoxon Mann–Whitney test.

Sources: Study PA-CL-05A Clinical Study Report;[9] Floege et al. (2014);[66] PA1301 Clinical Study Report Synopsis;[10] Koiwa (2017);[11] Otsuki et al. (2018).[12]

Discussion

Summary of Available Evidence

A total of four open-label RCTs were included in the CDR review. Study PA-CL-03A was an open-label, randomized, phase II exploratory trial considered pivotal by Health Canada in which 154 patients were randomized to one of five different doses of SO (250 mg, 1,000 mg, 1,500 mg, 2,000 mg, or 2,500 mg iron/day) or sevelamer hydrochloride (4.8 g/day) for six weeks. The primary end point was the within-groups change in serum phosphorus level from baseline to end of treatment. Pairwise comparisons of each SO dose versus the 250 mg iron dose were also conducted. No dose titration was permitted throughout the duration of the study, a protocol that does not reflect the way that SO is administered in clinical practice.[7] Further, no comparison between any SO dose and sevelamer was conducted. Therefore, the relevance of these results to the current review is limited.

Studies PA-CL-05A and PA1301 are noninferiority phase III studies that provide the most relevant evidence for this CDR review as both evaluated noninferiority versus sevelamer for lowering serum phosphorus, which is aligned with the manufacturer's reimbursement request of SO as an alternative to sevelamer for the control of serum phosphorus levels in patients with ESRD on dialysis. Study PA-CL-05A was the pivotal phase III RCT supporting the efficacy and safety of SO, and PA1301 was a phase III supportive study conducted in Japan. Both studies were conducted in adult patients with CKD who were on hemodialysis and stable doses of a PB prior to enrolment and included a washout phase during which patients were required to discontinue their current PB. A key objective included in both studies was establishing noninferiority of SO compared with sevelamer in lowering serum phosphorus after 12 weeks of treatment (key secondary end point in Stage 1 of Study PA-CL-05A and primary end point in Study PA1301), but the noninferiority margins differed between the two studies (0.19 mmol/L in Study PA-CL-05A and 0.32 mmol/L in Study PA1301). A pre-planned superiority analysis was conducted in Study PA-CL-05A. Neither

study assessed all-cause or cardiovascular mortality, cardiovascular events, or bone fractures as efficacy outcomes. Only Study PA-CL-05A assessed HRQoL.

Dosage regimens of SO differed between these two phase III studies. In Stage 1 of Study PA-CL-05A, patients were randomized to treatment with either SO at a starting dosage of 1,000 mg iron/day or sevelamer carbonate at a starting dosage of 4.8 g/day. The dose of both drugs was titrated based on individual patient level of serum phosphorus during the first eight weeks of treatment. Patients continued on their maintenance dosage (SO dosage range: 1,000 to 3,000 mg iron/day; sevelamer dosage range: 2.4 to 14.4 g/day) to week 24, whereas in Study PA1301 patients were randomized either to treatment with SO at a starting dosage 750 mg iron/day (maximum dosage: 3,000 mg iron/day), or to sevelamer at a starting dosage of either 1,000 mg/day or 2,000 mg/day depending on serum phosphorus concentration (maximum dosage: 9,000 mg/day) three times a day for 12 weeks. Evaluation for serum calcium and iPTH end points also differed between the two studies. Serum total calcium and iPTH were evaluated at week 24 in Study PA-CL-05A and corrected serum calcium and iPTH were evaluated at week 12 in Study PA1301.

The phase III RCT by Otsuki et al. differs from the other phase III RCTs included in this review in that patients eligible for participation in the trial were required to be taking lanthanum prior to enrolment and patients were either randomized to continue taking lanthanum or switch to SO treatment; there was no washout period. Another key difference is that patients were permitted to continue treatment with additional PBs (including calcium carbonate and sevelamer) throughout the study. All outcomes of interest to this review were secondary end points, including transferrin saturation, serum phosphorus, calcium, ferritin, and iPTH levels, and were evaluated at week 24 (end of treatment). Paired t-tests or Wilcoxon signed-rank tests were used to compare change from baseline within each parameter, but the level of detail provided in this publication (e.g., handling of missing data or controlling for multiplicity) is not adequate to draw any conclusions pertaining to the efficacy of SO versus lanthanum.

Interpretation of Results

Efficacy

Although identified as key efficacy outcomes of interest in this review, none of the included studies assessed all-cause mortality, cardiovascular mortality, cardiovascular events, or bone fractures as efficacy end points. According to the clinical expert, these outcomes are of greater clinical importance. However, the short duration of the phase III trials (12 to 24 weeks) was likely insufficient to evaluate the efficacy of PBs on all-cause and cardiovascular mortality. All information pertaining to each of these outcomes was assessed as part of the safety evaluation. No deaths reported in any of the studies were deemed to be due to study treatment, and there was no meaningful difference in the proportion of deaths between treatment groups in any of the studies. Similar observations were reported for cardiovascular mortality. No consistent results were observed across studies for the incidence of cardiovascular events or bone fractures. In the studies included in the CDR review, none of these outcomes were formally assessed, which may have been precluded by the short duration of the studies. Further, based on input from the clinical expert consulted for this review, the study population in each trial appeared to be healthier than the typical Canadian patient with ESRD on dialysis. Therefore, no conclusions can be drawn regarding the effect of SO on all-cause mortality, cardiovascular mortality, cardiovascular events, or bone fractures in patients with ESRD.

HRQoL was considered in this review and was identified as important by both patients and the clinical expert. Only one study,
PA-CL-05A, evaluated HRQoL. In this study, HRQoL was assessed using the SF-36v2. Overall, change from baseline in component scores was less than what is considered clinically meaningful. No statistically significant differences between the SO and sevelamer treatment groups were observed for any of the component or sub-component scores measured with the SF-36v2. Although reliability and validity of the SF-36v2 has been demonstrated across various conditions, including in patients with Stage
5 CKD who were not receiving dialysis, evidence of validity in patients with ESRD on dialysis was not identified.

End points relating to serum phosphorus levels were the primary outcomes (studies PA-CL-03A and PA1301) and key secondary outcomes (PA-CL-05A and Otsuki et al.) in each of the studies, and are considered surrogate measures for clinical outcomes such as mortality and cardiovascular comorbidity. Although some studies have demonstrated an association between levels of serum phosphorous ≥ 6.0 mg/dL (1.9 mmol/L) and all-cause mortality in patients with CKD, the evidence supporting this link is weak.[73,75,76] Other studies have concluded that serum phosphorus level is not predictive of death.[72] The same is true for the evidence demonstrating a link between elevated serum phosphorous levels and an increased risk for cardiovascular mortality and disease.[74,75] To date there are no RCTs demonstrating that lowering serum phosphorus affects survival in patients with ESRD.[54,55] The KDIGO 2017 Guideline Update acknowledges that the body of evidence demonstrating an increased risk of all-cause mortality associated with increased serum phosphorus levels mostly contains a moderate level of bias and is of low quality.[23]

Overall, all four studies included in the review provide evidence for SO as efficacious in lowering serum phosphorus levels in patients with ESRD on dialysis. According to the clinical expert, because PBs are relatively fast-acting drugs, the duration of the studies included in this review is adequate to demonstrate serum-phosphorus–lowering effects of SO. Study PA-CL-03A did not conduct any statistical testing to formally evaluate the efficacy of any dose of SO versus sevelamer, but, as noted in the Health Canada reviewer's report, the 4.8 g sevelamer dose appeared to be similar to the SO 10 mg iron dose.[14] Although sevelamer was included as an active control in this study, no formal comparison of SO versus sevelamer was conducted. Therefore, no conclusion regarding the serum-phosphorus–lowering effects of SO versus sevelamer can be drawn.

Studies PA-CL-05A and PA1301 both included end points in change from baseline serum phosphorus at week 12. Studies PA-CL-03A and PA-CL-05A were powered to detect a treatment difference of 0.65 mmol/L. The observed treatment effect in the SO groups in Study PA-CL-03A was less than this value after six weeks of treatment, but was greater than 0.65 mmol/L in both the SO and sevelamer group in Study PA-CL-05A at week 12. Although the Health Canada reviewer's report considers 0.65 mmol/L a clinically relevant change, no rationale or reference was provided to support a reduction in serum phosphorus of this magnitude with respect to important clinical outcomes, such as reduced mortality or cardiovascular events. The clinical expert contracted by CDR considered a reduction of 0.65 mmol/L in serum phosphorus to be expected in the context of treatment with a single PB.

Noninferiority to sevelamer was demonstrated at week 12 in the phase III studies PA-CL-05A and PA1301, based on change from baseline in serum phosphorus level to week 12. In Study PA-CL-05A, a pre-planned superiority analysis demonstrated that the between-

groups difference favoured sevelamer, but the authors state that the point estimate of 0.08 in the PPS or 0.10 in the FAS is not clinically relevant. The noninferiority margins differ between the two studies (0.19 mmol/L in Study PA-CL-05A and 0.32 mmol/L in Study PA1301) but both margins are based on previous studies with sevelamer and, according to the clinical expert, both margins are acceptable.

The proportion of patients achieving controlled serum phosphorus was evaluated in three of the studies included in this review. The definition of control varied across studies: in PA-CL-03A control was defined as within KDOQI guidelines; in PA-CL-05A control was defined as within KDOQI and KDIGO guidelines; and PA1301 used the JSDT guidelines. In Study PA-CL-03A the proportion of patients that achieved controlled serum phosphorus varied over time and between treatment groups, but no clear dose response was observed. In Study PA-CL-05A, a greater proportion of patients in the sevelamer group than in the SO group achieved serum phosphorus control based on KDOQI and KDIGO guidelines at week 12, but this difference was no longer statistically significant at week 24. In Study PA1301 more patients in the SO group achieved control based on JSDT guidelines than in the sevelamer group. One reason for the discrepancy in results between studies is the different definitions of control applied. The target recommended in the JSDT guidelines is wider than those recommended in KDOQI and KDIGO guidelines. However, the clinical relevance of this outcome is questionable given that serum phosphorus targets recommended in these guidelines are extrapolated from observational studies suggesting a higher risk of adverse outcomes in patients with higher serum phosphate concentrations,[52] and the studies are considered to be low quality of evidence by the KDIGO group.[23]

Serum calcium was measured in all studies included in this review (total calcium was identified as the secondary end point in studies PA-CL-03A and PA-CL-05A while corrected calcium was reported in PA1301, and not specified in Otsuki et al.). Regardless of specific calcium measure reported, change from baseline in serum calcium did not differ at end of treatment in any of the studies, nor was there a between-groups treatment difference. Overall, treatment with SO does not appear to have an effect on serum calcium levels.

Serum iPTH levels varied throughout the duration of each of the studies, but generally decreased from baseline across treatment groups at the various end points in PA-CL-03A (except in the SO 250 and 1,500 mg iron/day groups), PA-CL-05A, and PA1301. There was no change in iPTH levels from baseline in the study by Otsuki et al., likely because patients did not discontinue use with their current PB prior to the baseline assessment. There was no treatment difference between groups in any of the studies.

Overall, the studies included in this review demonstrated that SO was efficacious in lowering serum phosphorus and two of the phase III studies suggest that it is noninferior to sevelamer. Although SO was evaluated versus lanthanum in the trial by Otsuki et al., the level of detail provided in this publication is not adequate to draw any conclusions pertaining to the efficacy of SO versus lanthanum. Although sevelamer HCl and sevelamer carbonate are available in Canada, according to the expert, access to these drugs is limited and therefore used less often in Canadian practice. According to the clinical expert, calcium-based PBs (specifically calcium carbonate) are most commonly used to treat hyperphosphatemia in patients with ESRD in Canada, and thus would be considered the most appropriate comparator for SO in the Canadian context. No comparative trials of SO versus calcium-based PBs were identified, and therefore the efficacy and safety of SO versus the standard PB treatment in Canada remains unknown.

The study population is narrower than those eligible for treatment with SO as per the Health Canada–approved indication "for the control of serum phosphorus levels in adult patients with end-stage renal disease (ESRD) on dialysis." The approved indication does not restrict use to patients who are naive or experienced with PB treatment and does not restrict use of SO as a monotherapy in combination with other PBs. Based on the patient population in the clinical trials included in the CDR review, there is evidence supporting SO as a monotherapy in patients experienced with PB treatment. Although patients were permitted to continue treatment with other PBs during the Otsuki trial, the efficacy of SO in combination with other PBs was not tested. Evidence supporting SO in patients naive to PB treatment is lacking.

The study population does not appear to be aligned with the target Canadian patient population identified in the manufacturer's listing request for SO "as an alternative to sevelamer for the control of serum phosphorus levels in patients with end-stage renal disease (ESRD) on dialysis." Current listing criteria for sevelamer in some Canadian jurisdictions stipulate that sevelamer will only be reimbursed for patients in whom treatment with calcium-based PBs is inappropriate, and some include patients with hypercalcemia (but do not specify the underlying cause). Patients with hypercalcemia were excluded from studies PA-CL-03A, and PA1301. In Study PA-CL-05A, patients on calcium-based PBs with hypercalcemia were permitted to enrol in the study, but were withdrawn if hypercalcemia persisted during the washout period despite other treatment to control calcium level. Trial results may therefore not be applicable to a key segment of the target patient population in Canada.

Harms

Safety results from studies PA-CL-05A and PA1301 are considered most relevant for the purposes of this review. No dose titration was permitted in Study PA-CL-03A, and as a result, safety events of hypophosphatemia and hyperphosphatemia were reported frequently. Based on input from the clinical expert, these events are easily managed via dose titration in clinical practice. A detailed description of safety results is not included in the published report by Otsuki et al.

GI symptoms were identified as a notable harm of interest for this review and were the most common AEs in the SO and sevelamer groups in PA-CL-05A and PA1301. GI symptoms were also identified as a specific concern according to the patient input submission. Based on the safety evaluation in studies PA-CL-05A and PA1301, diarrhea and discoloured feces were the most common AEs in the SO group, while constipation and nausea occurred more frequently in the sevelamer group. The increased incidence of discoloured feces in the SO group was anticipated due to the iron in SO. No clear pattern of SAEs emerged in either the SO or sevelamer groups across PA-CL-05A and PA1301. Overall, rates of SAEs did not differ substantially between treatment groups in studies PA-CL-03A, PA-CL-05A, or PA1301. No SAEs were reported in the study by Otsuki et al.

All studies included in the CDR clinical review were open-label trials and may have introduced bias in AE reporting. In studies PA-CL-05A and PA1301 sevelamer was the comparator and some patients enrolled in the trials had previous experience with the drug. In the trial by Otsuki et al., all patients were previously on treatment with lanthanum, and those in the comparator arm continued their treatment, but a detailed presentation of AEs is not included in the report. A greater proportion of patients withdrew from the SO arm due to AEs in Study PA-CL-05A. The clinical expert consulted for this review noted that the

attrition rate in the trials needs to be considered. Given that treatment with PBs is chronic and will likely last the patient's lifetime, it is important that the PB be safe and tolerable.

Calcium-based PBs are associated with hypercalcemia. Meaningful changes in serum calcium levels with SO treatment were not observed in any of the studies included in this review. However, given that no studies of SO versus calcium-based PBs were identified, there is uncertainty regarding the comparative effects of SO versus calcium-based PBs on serum calcium levels in patients with ESRD.

Serum ferritin and transferrin saturation were identified as notable harms given the composition of SO. It is unlikely that the open-label nature of the study design influenced either of these parameters as they are objective measures. In Study PA-CL-05A, patients in both the SO and sevelamer group exhibited elevated serum ferritin at baseline.[9] Increases from baseline in serum ferritin and transferrin saturation at week 24 were greater in the SO than in the sevelamer group. In Study PA1301, mean serum ferritin level was 207.62 pmol/L and 304.4 pmol/L in the SO group at baseline and week 12, respectively. Transferrin saturation in the SO group was 22.89% and 29.86% at baseline and week 12, respectively (Table 27).[10] No increase in either of these measures was observed in the sevelamer group. In the study by Otsuki et al., the increase in both serum ferritin and transferrin saturation from baseline to week 24 was greater in the SO group than in the lanthanum group.

Serum ferritin and transferrin saturation were evaluated in the long-term extension trial PA-CL-05B (see Appendix 6). In this study, the mean (SD) change from the baseline reported at the PA-CL-05B end point (an additional 28 weeks of treatment) was higher for the SO arm, at 102.1 pmol/L (627.65; 95% CI, 39.3 to 164.9), than for the sevelamer arm, at 55.5 pmol/L (851.64; 95% CI, –48.5 to 15.5).[77] The mean (SD) change in transferrin saturation from the PA-CL-05B baseline was minimal at 0.4% (15.97; 95% CI, –1.2 to 2.0) for the SO group and 0.5% (17.34; 95% CI, –1.6 to 2.6) for the sevelamer group.

Overall, these results suggest that iron absorption occurs with SO treatment, although the Health Canada reviewer's report states that the risk of iron overload with long-term SO treatment is minimal.[14] The potential for iron absorption from SO is acknowledged in the product monograph and regular monitoring of iron levels is recommended.[7]

Duration of the phase III studies included in this review ranged from 12 to 24 weeks, which is likely insufficient to evaluate the efficacy of PBs on all-cause and cardiovascular mortality. While the clinical expert agreed that this time frame is adequate for demonstrating the phosphorus-lowering effect of SO, long-term data are required to provide certainty regarding the safety and tolerability of SO, as well as the long-term effects on mortality and cardiovascular outcomes in patients with ESRD. As previously noted, in Study PA-CL-05A a higher proportion of patients in the SO group discontinued prematurely due to AEs.

In Study PA-CL-05B, serious AEs were reported with similar frequency in the SO and sevelamer groups (19.9% and 19.5%, respectively).[77] In terms of GI-related AEs, diarrhea, nausea, and abdominal pain were more common in the SO group, while vomiting, constipation, and dyspepsia were more common in the sevelamer group. Further details regarding the results of study
PA-CL-05B are found in Appendix 6.

Other Considerations

One factor identified by patients as important was pill burden. In general, the mean dose of SO was associated with a lower pill burden than sevelamer, although this did not appear to affect compliance to study medication in the clinical trial setting. In study PA-CL-05A, pill burden was lower in the SO group (3.1 tablets/day) versus the sevelamer group (8.1 tablets/day). Mean compliance (defined as compliant at 70% to 120% of the number of expected tablets) was 89.0% in the SO group versus 86.2% in the sevelamer group. In Study PA1301, the average number of tablets was lower in the SO group (4.7 tablets/day) compared with the sevelamer group (17.5 tablets/day). However, it is important to note that the strength of SO used in this study was a 250 mg iron tablet. Compliance in the FAS exceeded 90% in both treatment groups (96.2% and 96.1% in the SO and sevelamer groups, respectively). If reimbursement of SO is aligned with the manufacturer's request that it be reimbursed "as an alternative to sevelamer for the control of serum phosphorus levels in patients with end-stage renal disease (ESRD) on dialysis," it is likely that most patients would have a reduced pill burden with SO compared with sevelamer.

Whether this difference in pill burden is meaningful in Canadian clinical practice remains uncertain. In Canada, calcium-based PBs, specifically calcium carbonate, are most commonly used when treatment with a PB is deemed appropriate. Based on information from the clinical expert, the usual dose of calcium carbonate is approximately one or two tablets with each meal (three to six tablets per day), which is similar to the dose range of SO specified in the product monograph.

Potential Place in Therapy[a]

Phosphate retention resulting in hyperphosphatemia is ubiquitous in patients with ESRD who require chronic dialysis.[15,16] Basic science data[17-20] and large observational studies[5,6,21] have implicated serum phosphate as a cardiovascular toxin. As a result, dialysis recipients are counselled to restrict dietary phosphate intake and are prescribed drugs that bind phosphate in the GI tract as a means of limiting phosphate absorption. **Though prescribed to nearly 90% of patients receiving dialysis and supported by guidelines that call for the normalization of serum phosphate, there is no compelling evidence that PBs reduce cardiovascular mortality and morbidity.**[22-24] This is especially concerning given the possibility that PBs may promote vascular calcification and other AEs.[25] Furthermore, the pill burden associated with phosphate binding significantly impairs quality of life.[26] Finally, phosphate binding is costly, accounting for an ever-increasing proportion of prescriptions given to dialysis patients[27] and annual expenditures of > $1.5 billion in the US.[28]

Disordered phosphate metabolism is a nearly universal finding in progressive CKD.[29,30] Until advanced stages of CKD, serum phosphate is tightly regulated in the normal range of 0.80 mmol/L to 1.50 mmol/L as a result of the complex interplay of the gut, parathyroid gland, bone, and kidneys.[15] As kidney function declines, phosphate retention is mediated by a reduction in the filtered load of this anion. Hyperphosphatemia has long been viewed as a toxic consequence of advanced CKD that should be targeted for correction.[29] The adversity of phosphate was initially attributed to its musculoskeletal effects.[31,32] Subsequently, basic science and translational research have emphasized the putative *cardiovascular* toxicity of

[a] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

hyperphosphatemia,[19,20,33] based on evidence that exposure to high phosphate concentrations induces a phenotypic "switch" in vascular smooth muscle cells that assume the phenotype of osteoblasts.[34]

Current Strategies for Serum Phosphate Control in the Dialysis Population

Dialysis: Adequate dialysis is crucial for serum phosphate control. A typical four-hour dialysis session using a conventional high-flux dialyzer removes 800 mg to 1,000 mg of phosphate.[15] Because the phosphate content of a typical Western diet is approximately 1,000 mg per day (7,000 mg per week),[35] a conventional three-times-weekly dialysis regimen alone cannot maintain phosphate balance.

Dietary restriction of phosphate: Phosphate features prominently in the Western diet, particularly in protein-containing foods such as dairy products, meat, and fish but also in food additives and taste enhancers.[36,37] Guidelines recommend "limiting dietary phosphate intake" in dialysis recipients, although specific parameters are not provided and no randomized trials have evaluated the impact of dietary phosphate restriction on patient-centred outcomes.[22]

Phosphate binders: The limitations of conventional dialysis regimens and dietary manoeuvers have made intestinal binding of phosphate indispensable to the management of hyperphosphatemia. Taken with meals, PBs prevent the absorption of phosphate resulting in stool phosphate excretion. In a study of nearly 24,000 prevalent hemodialysis recipients from 12 countries, 88% of patients were prescribed PBs.[38] *However, despite their pervasive use, the efficacy of any PB in reducing mortality, cardiovascular events, fractures or any other clinical event has never been tested against placebo/no therapy in a randomized trial.* **In a recent meta-analysis encompassing the spectrum of phosphate binders, Palmer et al. found no evidence that phosphate binding lowered mortality or cardiovascular events as compared with placebo.[39]**

Calcium-based products are the leading PBs used around the world, with calcium carbonate being the most widely prescribed binder for Canadian dialysis recipients.[38] Calcium carbonate is effective at reducing serum phosphate[40,41] and is modestly priced.[15] However, the potential for calcium absorption and the subsequent exacerbation of vascular calcification prompted questions about the safety of these agents,[42-47] spurring the emergence of non–calcium-based phosphate binders such as sevelamer and lanthanum.[48,49] Although a recent meta-analysis suggested lower mortality among recipients of non–calcium-based binders, these findings were based on the results of small trials at high risk of bias.[39] In the largest trial conducted comparing sevelamer and calcium, sevelamer failed to improve clinical outcomes[50] and non–calcium-based binders are significantly more expensive than calcium-based binders.[15,51] As a result, calcium-based binders continue to be the main pharmacological agents for lowering phosphate in Canadian dialysis recipients. Though alternatives to calcium-based binders may be of interest, the fundamental question of whether PBs modify clinically relevant outcomes seems to be more important than how phosphate is lowered.

Conclusions

Overall, evidence from the four RCTs included in this CDR review demonstrate that SO is efficacious at lowering serum phosphorus in patients receiving maintenance dialysis, but the impact on mortality and cardiovascular outcomes remains unknown. All-cause mortality, cardiovascular mortality, cardiovascular events, and bone fractures were not identified as pre-specified efficacy outcomes in any of the trials included in the review. However, the short duration of the phase III trials (12 to 24 weeks) was likely insufficient to evaluate the efficacy of PBs on all-cause and cardiovascular mortality. Treatment with SO did not appear to affect patient HRQoL. SO was noninferior to sevelamer in terms of lowering serum phosphorus after 12 weeks of treatment in two phase III studies (PA-CL-05A and PA1301). These studies provide the most relevant evidence for this CDR review as both evaluated noninferiority versus sevelamer for lowering serum phosphorus, which is aligned with the manufacturer's reimbursement request of SO as an alternative to sevelamer for the control of serum phosphorus levels in patients with ESRD on dialysis. In the pivotal phase III trial (PA-CL-05A), more patients withdrew from the SO arm compared with patients in the sevelamer arm, and the primary reason for withdrawal was AEs. GI symptoms, specifically diarrhea and discoloured feces, were the most common AEs reported with SO treatment. Findings that suggest that SO is associated with iron absorption may or may not be of clinical relevance. Monitoring of iron parameters is recommended in the product monograph.

All studies, with the exception of Otsuki et al., included sevelamer as a comparator. However, according to the clinical expert, calcium-based PBs are the most appropriate comparators in Canada. As none of the studies included calcium-based PBs as comparators, how SO compares with the standard of care in Canada remains uncertain. Further, there are no placebo-controlled trials to demonstrate the benefit of SO versus standard care in the absence of a PB.

Appendix 1: Patient Input Summary

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

One patient group, the Canadian Organization for Rare Disorders (CORD), responded to the patient input request for this review. CORD is a registered charity that provides a voice for those with rare disorders by advocating for changes to health policy and the health care system. CORD also helps meet the needs of patient groups by acting as a source of education and resources.

CORD stated that it did not receive outside help with the completion of its submission. It also did not receive assistance from outside the patient group for the data collection and analysis of this submission. CORD disclosed that it received financial support from the manufacturer of Velphoro within the past two years.

2. Condition-Related Information

CORD collected condition-related information from both patients and caregivers using various sources, including: one-on-one patient interviews, in-person and online focus groups, and correspondence with patients and caregivers via email. A total of 124 persons, including 105 patients with chronic kidney disease (CKD) on dialysis, plus 19 caregivers, provided responses that were included with this patient input response. Ninety-six and 28 responders were from the US and Canada, respectively. Patients from the US were sought for additional feedback about experience with Velphoro as the patient group was not able to identify any Canadian patients who had experience with the drug. The age of patients ranged from 29 to 71 years old, and they had been on dialysis for a range of approximately two to 10 years. The majority (60%) of patients were male and 80% of caregivers were female.

According to patients, managing elevated phosphorous levels (hyperphosphatemia) can be difficult as it tends to be an asymptomatic condition; patients often only become aware of their phosphorous levels when tested. Although all patients were aware that hyperphosphatemia was a potential consequence of CKD, only a few had experienced serious consequences of phosphate overload (such as severe chest pain and muscle cramping), and approximately 20% of patients believed they had experienced symptoms associated with high phosphate levels, including itching, tingling sensations on skin or extremities, fatigue, shortness of breath, nausea, muscle pain, muscle cramping, and “pain in the bone.” It was noted that these symptoms resolve over time with appropriate dietary and medical management (i.e., treatment with phosphate binders [PBs]).

The major burden associated with hyperphosphatemia is related to the actual management of phosphorous levels as opposed to the associated symptoms, as per the patient response. Patient responses concerning the overall burden of managing hyperphosphatemia varied. Approximately 25% of the patient respondents expressed minor concern despite acknowledging the potential for serious complications. Approximately 75% of patients expressed concern with current medication and specifically mentioned the number of pills required.

The patient input response describes living with hypophosphatemia as “analogous to the challenge for patients with diabetes except that patients do not experience any immediate symptoms if they are not adherent and they cannot immediately access their phosphorous numbers to know whether they are in range. This leads to feelings of anxiety and stress but

also feelings of guilt since most acknowledge they are not totally compliant with either diet or pills."

3. Current Therapy-Related Information

Patient input included a summary of the responses from all patients and caregivers participating in the response. The use of PBs for the treatment of hyperphosphatemia was typical among most patients. Approximately 82% of the respondents reported current use of a calcium-based PB, which was either taken independently or in combination with a non-calcium PB. The patient responses provided a list of PBs that had been used previously or currently by respondents, as follows: calcium acetate (PhosLo or EliphosT), calcium carbonate (Tums), sevelamer (Renagel or Renvela), and lanthanum carbonate (Fosrenol), as well as sucroferric oxyhydroxide (Velphoro) and ferric citrate (Auryxia) by patients in the US only, due to availability of the medications.

The key concern for patients regarding management of phosphorous levels is the medication itself. Pill burden is a significant factor, as patients reported that the medication needs to be taken during and throughout meals. For example, a pill (or pills) needs to be taken before the meal, during the meal, and sometimes a third time while eating. This was described as disruptive and annoying. Approximately 90% of patients reported being non-adherent to their PB regimen, with the most frequent reason being "forgetting" to take their pills. One respondent stated, "My husband was taking upwards of 15 pills, two different kinds, three to five per meal, spaced out. If I wasn't right there, I know he just took them randomly and missed most." Another stated that, "If I could just take [the PBs] once or twice a day, same as the diabetes, heart, and other medications, it would be a lot easier to remember." Over half of the respondents reported that at times they deliberately did not take their medications, such as when they just had dialysis or when they were eating foods low in phosphorous. "The good news is that dialysis lowers my phosphorous levels so I don't have to be as careful about what I eat or my medicines on the days when I do dialysis. I don't know if that is really true but that is what I think."

Another challenge with PBs identified by patients is achieving the correct dosage. Inconsistency with the number of pills required over time may be due to variations in their diet or a result of having their phosphorous levels assessed clinically. The challenges of achieving the correct dosage are highlighted by comments from respondents regarding variations in the effectiveness of the pills from month to month, doubling the number of pills taken without lowering phosphorous levels, and gastrointestinal (GI) issues associated with increasing the number of pills per meal.

Symptoms mentioned most often by patients were GI in nature regardless of type of PB. Approximately 20% of respondents on calcium-based PBs reported GI issues, such as constipation and nausea. More than half of the respondents reported GI issues with the use of sevelamer, such as nausea, vomiting, diarrhea, constipation, and stomach bloating; these issues were described as manageable and able to be resolved. According to the patient response, the extent of these issues varies from patient to patient in terms of the type of PB that is used, and the frequency and severity of the GI events.

4. Expectations About the Drug Being Reviewed

As per patient input response, patients are looking for a new medication that is easy to manage (e.g., reduces the pill burden and the stress associated with adherence) and is associated with improved tolerability. Patient input response stated that Canadian patients had no experience with iron-based PBs or Velphoro; patients in the US with experience using Velphoro were therefore included to provide input on this drug.

In general, patients felt their phosphorous levels were more easily managed with Velphoro. Phosphorous levels were reported to be more consistently within target, with a fairly consistent dosage of about three pills per day. They also described an improved relationship with their treating physician while using Velphoro, as the pill burden and adherence issues with previous PBs caused frustration between the patient and doctor.

Significantly fewer pills are required with Velphoro, which was deemed a benefit by all of the patient respondents. One patient noted that it would be ideal to have a pill that is taken once daily either in the morning or evening, along with other pills. “It was so much easier to remember one pill at the beginning of the meal.” “I went from 9 to 12 pills a day to just 3. This I can do!” Patients also expressed a desire to not have to worry so much about what they were eating, i.e., have more freedom with their diet.

With increased confidence in Velphoro, patients highlighted feeling less restricted with what they can and cannot eat, although they must still consider dietary management of the condition. Patients reported an overall increase in their quality of life, feeling “healthier and happier” and “able to enjoy meals with the family again.” With fewer pills to be taken, some patients mentioned that they did not feel as self-conscious when they were dining with others because they did not have to explain why they are taking so many pills throughout meals. Another respondent expressed relief because she did not have to “nag” her husband to adhere to his medications during meals anymore, which was beneficial for both the caregiver and patient.

In terms of tolerability, approximately half of the patients who had experience with Velphoro reported some negative effects, including itching, dry mouth, stools “as black as night,” cramps, and diarrhea. Most of these effects were tolerable or resolved with additional medication.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present Ovid MEDLINE(R) ALL 1946 to present **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	July 23, 2018
Alerts:	Weekly search updates until November 21, 2018
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.po	Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
medall	Ovid database code; MEDLINE ALL; 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY
1. (Colliron* or EINECS 232-464-7 or Encifer* or Fe-back* or Fe-lib* or Feojectin* or Ferijet* or Ferosoft* or Ferplex* or Ferric hydroxide sucrose complex or Ferric oxide or Ferric saccharate or Ferrivenin* or ((Ferrum or ferum) adj2 Hausmann*) or Fesin* or Hippiron* or (Iron adj2 (saccharate or sucrose or sugar)) or Iviron* or Neo-ferrum or P-tol chewable or PA 21 or PA21 or Proferrin* or ((Saccharated or succharated) adj2 (ferric oxide or iron)) or Sucrofer or Sucroferric oxyhydroxide or FZ7NYF5N8L or velphoro* or Venofer* or XI-921 or XI921).ti,ab,ot,hw,rn,nm,kf.
2. exp kidney failure, chronic/
3. exp renal insufficiency, chronic/
4. (renal* or kidney* or dialysis or hemodialysis or haemodialysis or esrd or eskd).ti,ab,kf.
5. or/2-4
6. 1 and 5
7. 6 use medall
8. *sucroferric oxyhydroxide/
9. (Colliron* or EINECS 232-464-7 or Encifer* or Fe-back* or Fe-lib* or Feojectin* or Ferijet* or Ferosoft* or Ferplex* or Ferric hydroxide sucrose complex or Ferric oxide or Ferric saccharate or Ferrivenin* or ((Ferrum or ferum) adj2 Hausmann*) or Fesin* or Hippiron* or (Iron adj2 (saccharate or sucrose or sugar)) or Iviron* or Neo-ferrum or P-tol chewable or PA 21 or PA21 or Proferrin* or ((Saccharated or succharated) adj2 (ferric oxide or iron)) or Sucrofer or Sucroferric oxyhydroxide or velphoro* or Venofer* or XI-921 or XI921).ti,ab,kw,dq.
10. exp end-stage renal disease/
11. exp chronic kidney failure/
12. (renal* or kidney* or dialysis or hemodialysis or haemodialysis or esrd or eskd).ti,ab,kw.
13. or/8-9
14. or/10-12
15. 13 and 14
16. 15 use oemezd
17. 7 or 16
18. conference abstract.pt.
19. 17 NOT 18

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search

Grey Literature

Dates for Search:	July 2018
Keywords:	Drug name
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search

Appendix 3: Excluded Studies

Table 28: Excluded Studies

Reference	Reason for Exclusion
Covic AC, Floege J, Ketteler M, et al. Iron-related parameters in dialysis patients treated with sucroferric oxyhydroxide. *Nephrology Dialysis Transplantation.* 2017;32(8):1330-1338.	Post hoc analysis; does not meet inclusion criteria in protocol
Coyne DW, Ficociello LH, Parameswaran V, et al. Real-world effectiveness of sucroferric oxyhydroxide in patients on chronic hemodialysis: A retrospective analysis of pharmacy data. *Clin Nephrol.* 2017;88(8):59-67.	Not an RCT; does not meet inclusion criteria in protocol
Floege J Covic AC, Ketteler M, et al. One-year efficacy and safety of the iron-based phosphate binder sucroferric oxyhydroxide in patients on peritoneal dialysis. *Nephrology Dialysis Transplantation.* 2017;32(11):1918-1926.	Post hoc analysis; does not meet inclusion criteria in protocol
Floege J Covic AC, Ketteler M, et al. Long-term effects of the iron-based phosphate binder, sucroferric oxyhydroxide, in dialysis patients. *Nephrology Dialysis Transplantation.* 2015;30(6):1037-1046.	Long-term extension; does not meet inclusion criteria in protocol; included in Summary of Other Studies
Isaka Y, Fujii H, Tsujimoto Y, Teramukai S, Hamano T. Rationale, design, and characteristics of a trial to evaluate the new phosphate iron-based binder sucroferric oxyhydroxide in dialysis patients with the goal of advancing the practice of E.B.M. (EPISODE). *Clin Exp Nephrol.* 2018;22(4):967-972.	Study protocol; does not meet inclusion criteria in protocol
Kalantar-Zadeh K, Parameswaran V, Ficociello LH, et al. Real-World Scenario Improvements in Serum Phosphorus Levels and Pill Burden in Peritoneal Dialysis Patients Treated with Sucroferric Oxyhydroxide. *Am J Nephrol.* 2018;47(3):153-161.	Retrospective database study; does not meet inclusion criteria in protocol
Ketteler M, Sprague SM, Covic AC, et al. Effects of sucroferric oxyhydroxide and sevelamer carbonate on chronic kidney disease-mineral bone disorder parameters in dialysis patients. *Nephrology Dialysis Transplantation.* 2018;29:29	Post hoc analysis; does not meet inclusion criteria in protocol
Koiwa F, Yokoyama K, Fukagawa M, Akizawa T. Efficacy and Safety of Sucroferric Oxyhydroxide and Calcium Carbonate in Hemodialysis Patients. *KI Rep.* 2018;3(1):185-192.	Not an RCT; does not meet inclusion criteria in protocol
Koiwa F, Yokoyama K, Fukagawa M, Akizawa T. Long-Term Assessment of the Safety and Efficacy of PA21 (Sucroferric Oxyhydroxide) in Japanese Hemodialysis Patients With Hyperphosphatemia: An Open-Label, Multicenter, Phase III Study. *J Ren Nutr.* 2017;27(5):346-354.	Not an RCT; does not meet inclusion criteria in protocol
Mitsuboshi S, Yamada H, Nagai K, Okajima H. [Low Continuity Rate of Sucroferric Oxyhydroxide among Japanese Hemodialysis Patients with High Phosphate Binder Pill Burden]. *Yakugaku Zasshi - Journal of the Pharmaceutical Society of Japan.* 2018;138(1):135-139.	Not an RCT; does not meet inclusion criteria in protocol
Shima H, Miya K, Okada K, Minakuchi J, Kawashima S. Sucroferric oxyhydroxide decreases serum phosphorus level and fibroblast growth factor 23 and improves renal anemia in hemodialysis patients. *BMC Res Notes.* 2018;11(1):363.	Not an RCT; does not meet inclusion criteria in protocol
Sprague SM, Ketteler M, Covic AC, et al. Long-term efficacy and safety of sucroferric oxyhydroxide in African American dialysis patients. *Hemodialysis International.* 2018;15:15.	Post hoc analysis; does not meet inclusion criteria in protocol
Xie D, Ye N, Li M. A systematic review on the efficacy and safety of PA21 versus sevelamer in dialysis patients. *Int Urol Nephrol.* 2018;50(5):905-909.	Not an RCT; does not meet inclusion criteria in protocol
Sekercioglu N, Angeliki Veroniki A, Thabane L, et al. Effects of different phosphate lowering strategies in patients with CKD on laboratory outcomes: A systematic review and NMA. *PLoS ONE [Electronic Resource].* 2017;12(3):e0171028.	NMA; does not meet inclusion criteria established in the protocol
Sekercioglu N, Thabane L, Diaz Martinez JP, et al. Comparative Effectiveness of Phosphate Binders in Patients with Chronic Kidney Disease: A Systematic Review and Network Meta-Analysis. *PLoS ONE [Electronic Resource].* 2016;11(6):e0156891.	NMA; does not meet inclusion criteria established in the protocol
Sprague SM, Covic AC, Floege J, et al. Pharmacodynamic Effects of Sucroferric	Not an RCT; does not meet

Reference	Reason for Exclusion
Oxyhydroxide and Sevelamer Carbonate on Vitamin D Receptor Agonist Bioactivity in Dialysis Patients. *Am J Nephrol.* 2016;44(2):104-112.	inclusion criteria in protocol
Suzuki D, Ichie T, Hayashi H, Sugiura Y, Sugiyama T. Efficacy of sucroferric oxyhydroxide treatment in Japanese hemodialysis patients and its effect on gastrointestinal symptoms. *Pharmazie.* 2017;72(2):118-122.	Not an RCT; does not meet inclusion criteria in protocol

NMA = network meta-analysis; RCT = randomized controlled trial.

Appendix 4: Detailed Outcome Data

Health-Related Quality of Life

Table 29: PA-CL-05A: Summary of SF-36v2 Component Scores and Change from Baseline (FAS)

Statistic	SO (N = 694)		Sevelamer (N = 347)	
	Actual	Change from Baseline	Actual	Change from Baseline
Mental Component Score				
Screening				
n	690		347	
Mean (SD)	49.0 (10.1)		49.0 (9.8)	
Week 12				
n	575	572	309	309
Mean (SD)	48.7 (9.4)	–0.7 (8.5)	48.9 (9.7)	–0.3 (8.6)
Treatment difference (95% CI)[a]	0.2 (–1.1 to 1.5)			
Week 24				
n	503	500	289	289
Mean (SD)	48.4 (9.8)	–1.3 (9.6)	49.1 (9.9)	–0.1 (9.0)
Treatment difference (95% CI)	0.7 (–0.7 to 2.2)			
Week 24/early discontinuation				
n	120	120	27	27
Mean (SD)	43.9 (11.1)	–2.0 (9.4)	40.1 (10.2)	–6.7 (11.9)
Treatment difference (95% CI)[a]	–3.8 (–8.4 to 0.8)			
Physical Component Score				
Screening				
n	690		347	
Mean (SD)	42.6 (9.0)		43.5 (8.6)	
Week 12				
n	575	572	309	309
Mean (SD)	43.7 (8.7)	0.4 (7.2)	43.1 (8.3)	–0.5 (6.2)
Treatment difference (95% CI)[a]	–0.6 (–1.8 to 0.6)			
Week 24				
n	503	500	289	289
Mean (SD)	43.4 (8.7)	0.0 (7.3)	43.3 (8.9)	–0.3 (6.6)
Treatment difference (95% CI)[a]	–0.0 (–1.3 to 1.2)			
Week 24/early discontinuation				
n	120	120	27	27
Mean (SD)	39.4 (8.4)	–1.1 (5.7)	42.0 (10.5)	–1.6 (8.5)
Treatment difference (95% CI)[a]	2.5 (–1.2 to 6.2)			

CI = confidence interval; FAS = full analysis set; SD = standard deviation; SF-36v2 = Short-Form 36 Health Survey version 2; SO = sucroferric oxyhydroxide.

Note: Week 24 displays ongoing patients (excluding those who discontinued in Stage 1). Week 24/early discontinuation presents patients who discontinued in Stage 1 (but who completed end-of-study assessments as planned in the protocol). Treatment groups were compared using a t-test.

Source: PA-CL-05A Clinical Study Report.[9]

Serum Phosphorus

Change from Baseline

Table 30: PA-CL-03A: Serum Phosphorus (mmol/L): Absolute Change from Baseline at End of Treatment (Primary End Point – Full Analysis Set)

	250 mg Iron (1.25 g SO)/day N = 26	1,000 mg Iron (5.0 g SO)/day N = 26	1,500 mg Iron (7.5 g SO)/day N = 25	2,000 mg Iron (10.0 g SO)/day N = 25	2,500 mg Iron (12.5 g SO)/day N = 24	Sevelamer HCl N = 24
Baseline, mean (SD)	2.203 (0.531)	2.135 (0.348)	2.212 (0.372)	2.186 (0.565)	2.089 (0.383)	2.242 (0.519)
End of treatment, mean (SD)	2.162 (0.661)	1.787 (0.625)	1.808 (0.382)	1.541 (0.620)	1.543 (0.540)	1.901 (0.474)
Change from baseline, mean (SD)	–0.042 (0.650)	–0.348 (0.684)	–0.404 (0.391)	–0.644 (0.551)	–0.547 (0.584)	–0.341 (0.436)
***P* value**	0.7448	0.0157[a]	< 0.001[a]	< 0.001[a]	< 0.001[a]	< 0.001

SD = standard deviation; SO = sucroferric oxyhydroxide.

[a] Two-sided single sample t-test; SO only *P* values ≤ 0.05 flagged [a] according to the hierarchical procedure (descending dose) of SO.

Notes: End-of-treatment values based on value at week 7 or last observation carried forward for missing data.

Source: PA-CL-03A Clinical Study Report.[8]

Table 31: PA-CL-03A: Serum Phosphorus: Absolute Change from Baseline at End of Treatment in SO Groups, ANCOVA (Full Analysis Set)

	Least Squares Mean	*P* Value
SO 2,500 mg iron (12.5 g SO)/day vs SO 250 mg iron (1.25 g SO)/day	–0.564	0.001
SO 2,000 mg iron (10.0 g SO)/day vs SO 250 mg iron (1.25 g SO)/day	–0.612	< 0.001
SO 1,500 mg iron (7.5 g SO)/day vs SO 250 mg iron (1.25 g SO)/day	–0.357	0.063
SO 1,000 mg iron (5.0 g SO)/day vs SO 250 mg iron (1.25 g SO)/day	–0.341	0.078

ANCOVA = analysis of covariance; SO = sucroferric oxyhydroxide.

Note: ANCOVA with dose group as fixed effect and baseline serum phosphorus levels as covariates, *P* value adjusted for multiple comparisons according to Dunnett.

Source: PA-CL-03A Clinical Study Report.[8]

Table 32: PA-CL-05A: Summary of Serum Phosphorus Levels (mmol/L) and Change from Baseline (FAS)

Statistic	SO Mean (SD) Serum Phosphorus (mmol/L) (N = 694)	Sevelamer Mean (SD) Serum Phosphorus (mmol/L) (N = 347)
Stage 1 baseline		
n	694	347
Mean (SD)	2.5 (0.59)	2.4 (0.57)
Week 4		
n	651	334
Mean (SD)	2.0 (0.55)	1.8 (0.48)
Change from baseline, mean (SD)	–0.5 (0.55)	–0.6 (0.57)
Week 8		
n	607	318
Mean (SD)	1.9 (0.49)	1.7 (0.49)
Change from baseline, mean (SD)	–0.6 (0.59)	–0.7 (0.59)
Week 12		
n	589	318
Mean (SD)	1.8 (0.46)	1.7 (0.44)
Change from baseline, mean (SD)	–0.7 (0.62)	–0.7 (0.63)
End point week 12		
n	694	347
Mean (SD)	1.8 (0.47)	1.7 (0.42)
Change from baseline, mean (SD)	–0.7 (0.63)	–0.7 (0.64)
Week 16		
n	549	298
Mean (SD)	1.8 (0.47)	1.7 (0.44)
Change from baseline, mean (SD)	–0.7 (0.62)	–0.7 (0.63)
Week 20		
n	541	299
Mean (SD)	1.7 (0.50)	1.7 (0.45)
Change from baseline, mean (SD)	–0.7 (0.66)	–0.7 (0.63)
Week 24		
n	496	285
Mean (SD)	1.7 (0.47)	1.7 (0.45)

Statistic	SO Mean (SD) Serum Phosphorus (mmol/L) (N = 694)	Sevelamer Mean (SD) Serum Phosphorus (mmol/L) (N = 347)
Change from baseline, mean (SD)	–0.7 (0.65)	–0.7 (0.62)
End point week 24		
n	694	347
Mean (SD)	1.8 (0.51)	1.7 (0.45)
Change from baseline, mean (SD)	–0.7 (0.66)	–0.7 (0.63)

FAS = full analysis set; SD = standard deviation; SO = sucroferric oxyhydroxide.

Notes: Baseline was defined as the last assessment prior to or on the date of the first dose of study medication. Missing data at week 12 were replaced using the last post-baseline measurement prior to week 12. End point was week 24 or includes the latest measurement after baseline prior to withdrawal.

Source: PA-CL-05A Clinical Study Report.[9]

Table 33: PA1301: Serum Phosphorus Levels (mmol/L) (Full Analysis Set)

	SO (N = 106)	Sevelamer (N = 103)
Baseline		
n	106	103
Mean (SD)	2.51 (0.44)	2.45 (0.38)
Week 4		
n	103	97
Mean (SD)	1.81 (0.33)	1.80 (0.34)
Week 8		
n	97	90
Mean (SD)	1.62 (0.29)	1.77 (0.32)
Week 12		
n	93	87
Mean (SD)	1.62 (0.32)	1.71 (0.32)
End point week 12		
n	106	103
Mean (SD)	1.63 (0.33)	1.72 (0.34)
95% CI	1.57 to 1.70	1.66 to 1.79

CI = confidence interval; SD = standard deviation; SO = sucroferric oxyhydroxide.

Source: PA1301 Clinical Study Report Synopsis.[10]

Proportion of Patients Achieving Target Serum Phosphorus

Table 34: PA-CL-03A: Analysis of Proportion of Patients With Controlled Serum Phosphorus Levels (≥ 1.13 to ≤ 1.78 mmol/L) (Full Analysis Set)

	250 mg Iron (1.25 g SO)/day N = 26	1,000 mg Iron (5.0 g SO)/day N = 26	1,500 mg Iron (7.5 g SO)/day N = 25	2,000 mg Iron (10.0 g SO)/day N = 25	2,500 mg Iron (12.5 g SO)/day N = 24	Sevelamer HCl N = 24	Trend Test *P* Value[a]
Baseline n/N' (%)	5/26 (19.2)	3/26 (11.5)	3/25 (12.0)	8/25 (32.0)	6/24 (25.0)	6/24 (25.0)	0.206
P value[b]		0.703	0.703	0.349	0.738	0.738	
Week 2 n/N' (%)	5/26 (19.2)	13/26 (50.0)	12/25 (48.0)	9/24 (37.5)	12/24 (50.0)	10/24 (41.7)	0.109
P value[b]		0.040	0.040	0.211	0.036	0.124	
Week 3 n/N' (%)	1/26 (3.8)	11/25 (44.0)	9/24 (37.5)	12/22 (54.5)	15/21 (71.4)	14/22 (63.6)	< 0.001
P value[b]		< 0.001	0.004	< 0.001	< 0.001	< 0.001	
Week 4 n/N' (%)	4/24 (16.7)	13/23 (56.5)	9/22 (40.9)	7/21 (33.3)	8/21 (38.1)	12/22 (54.5)	0.492
P value[b]		0.006	0.103	0.299	0.176	0.012	
Week 5 n/N' (%)	5/24 (20.8)	11/21 (52.4)	8/21 (38.1)	10/19 (52.6)	13/20 (65.0)	10/20 (50.0)	0.008
P value[b]		0.035	0.323	0.052	0.005	0.059	
Week 6 n/N' (%)	3/22 (13.6)	8/20 (40.0)	9/20 (45.0)	9/16 (56.3)	10/16 (62.5)	8/18 (44.4)	0.001
P value[b]		0.081	0.040	0.012	0.004	0.040	
Week 7 n/N' (%)	4/19 (21.1)	7/17 (41.2)	7/20 (35.0)	6/14 (42.9)	9/15 (60.0)	8/19 (42.1)	0.034
P value[b]		0.281	0.480	0.257	0.034	0.295	
End of treatment n/N' (%)	4/26 (15.4)	12/26 (46.2)	8/25 (32.0)	9/25 (36.0)	11/24 (45.8)	11/24 (45.8)	0.091
P value[b]		0.034	0.199	0.116	0.030	0.030	
Any on-treatment time point n/N' (%)	14/26 (53.8)	21/26 (80.8)	17/25 (68.0)	18/25 (72.0)	21/24 (87.5)	20/24 (83.3)	0.039
P value[b]		0.075	0.393	0.249	0.014	0.035	

SO = sucroferric oxyhydroxide.

[a] Two-sided *P* value of Cochran–Armitage test (trend over SO dose groups only).

[b] Fisher's exact test, pairwise comparison to the lowest SO dose group.

Notes: Controlled serum phosphorus level achieved if serum phosphorus between 1.13 and 1.78 mmol/L (3.5 mg/dL and 5.5 mg/dL). Percentages are based on those having the laboratory parameter tested at the visit (N').

Source: PA-CL-03A Clinical Study Report.[8]

Table 35: PA-CL-03A: Serum Total Calcium (mmol/L) (Full Analysis Set)

	250 mg Iron (1.25 g SO)/day N = 26	1,000 mg Iron (5.0 g SO)/day N = 26	1,500 mg Iron (7.5 g SO)/day N = 25	2,000 mg Iron (10.0 g SO)/day N = 25	2,500 mg Iron (12.5 g SO)/day N = 24	Sevelamer HCl N = 24
Baseline						
n	26	26	25	25	24	24
Mean (SD)	2.13 (0.17)	2.14 (0.18)	2.16 (0.11)	2.10 (0.21)	2.14 (0.14)	2.14 (0.14)
End of treatment						
n	26	26	25	25	24	23
Mean (SD)	2.07 (0.31)	2.17 (0.23)	2.20 (0.15)	2.12 (0.31)	2.10 (0.27)	2.21 (0.14)
Change from baseline						
n	26	26	25	25	24	23
Mean (SD)	–0.06 (0.31)	0.03 (0.20)	0.04 (0.15)	0.02 (0.24)	–0.04 (0.22)	0.06 (0.14)
95% CI	–0.18 to 0.07	–0.05 to 0.11	–0.02 to 0.10	–0.07 to 0.12	–0.13 to 0.05	0.00 to 0.13

SD = standard deviation; SO = sucroferric oxyhydroxide.

Source: PA-CL-03A Clinical Study Report.[8]

Table 36: PA-CL-05A: Serum Total Calcium (mmol/L) (Full Analysis Set)

Statistic	SO (N = 694)	Sevelamer (N = 347)
Baseline		
n	694	347
Mean (SD)	2.2 (0.19)	2.2 (0.20)
Change from baseline, mean (SD)		
Week 4		
n	650	331
Mean (SD)	2.2 (0.19)	2.2 (0.20)
Change from baseline, mean (SD)	0.0 (0.17)	0.0 (0.19)
Week 8		
N	606	319
Mean (SD)	2.2 (0.18)	2.2 (0.18)
Change from baseline, mean (SD)	0.0 (0.18)	0.0 (0.17)
Week 12		
n	589	316
Mean (SD)	2.2 (0.18)	2.2 (0.18)
Change from baseline, mean (SD)	0.0 (0.18)	0.0 (0.17)
Week 16		
n	550	299
Mean (SD)	2.2 (0.20)	2.2 (0.19)
Change from baseline, mean (SD)	0.0 (0.19)	0.0 (0.18)
Week 20		
n	537	299
Mean (SD)	2.2 (0.20)	2.2 (0.20)
Change from baseline, mean (SD)	0.0 (0.20)	0.0 (0.19)
Week 24		
n	496	284
Mean (SD)	2.2 (0.20)	2.2 (0.18)
Change from baseline, mean (SD)	0.0 (0.21)	0.0 (0.20)

Statistic	SO (N = 694)	Sevelamer (N = 347)
End point week 24		
n	694	347
Mean (SD)	2.2 (0.20)	2.2 (0.17)
Change from baseline, Mean (SD)	0.0 (0.21)	0.0 (0.20)

SD = standard deviation; SO = sucroferric oxyhydroxide.

Notes: Baseline was defined as the last assessment prior to or on the date of the first dose of study medication.
End point was week 24 or includes the latest measurement after baseline prior to withdrawal.

Source: PA-CL-05A Clinical Study Report.[9]

Table 37: PA1301: Corrected Serum Calcium (mmol/L) (Full Analysis Set)

	SO (N = 106)	Sevelamer (N = 103)
Baseline		
n	106	103
Mean (SD)	2.24 (0.14)	2.23 (0.14)
Week 4		
n	103	97
Mean (SD)	2.27 (0.16)	2.24 (0.17)
Week 8		
n	97	90
Mean (SD)	2.29 (0.14)	2.24 (0.13)
Week 12		
n	93	87
Mean (SD)	2.29 (0.15)	2.25 (0.14)
End point week 12		
n	106	103
Mean (SD)	2.28 (0.17)	2.24 (0.18)

SD = standard deviation; SO = sucroferric oxyhydroxide.

Source: PA1301 Clinical Study Report Synopsis.[10]

Serum Intact Parathyroid Hormone

Table 38: PA-CL-03A: Serum Intact Parathyroid Hormone (pmol/L) (Full Analysis Set)

	250 mg Iron (1.25 g SO)/day N = 26	1,000 mg Iron (5.0 g SO)/day N = 26	1,500 mg Iron (7.5 g SO)/day N = 25	2,000 mg Iron (10.0 g SO)/day N = 25	2,500 mg Iron (12.5 g SO)/day N = 24	Sevelamer HCl N = 24
Baseline						
n	26	26	25	25	24	24
Mean (SD)	25.2747 (20.0127)	24.1336 (18.0912)	28.8017 (15.6957)	25.9533 (14.7699)	23.5822 (16.0647)	27.7391 (15.3012)
End of treatment						
n	26	26	25	25	24	23
Mean (SD)	26.0583 (20.2418)	22.9714 (17.5355)	28.8091 (20.8388)	23.8494 (16.5355)	17.1516 (9.8568)	23.8462 (14.5642)
Change from baseline to end of treatment						
n	26	26	25	25	24	23
Mean (SD)	0.7837 (7.2609)	–1.1622 (13.5483)	0.0085 (15.0785)	–2.1029 (8.9873)	–6.4316 (11.1951)	–4.1145 (8.4581)
95% CI	–2.1485 to	–6.6352 to	–6.2163 to	–5.8123 to	–11.1559 to	–7.7720 to

	250 mg Iron (1.25 g SO)/day N = 26	1,000 mg Iron (5.0 g SO)/day N = 26	1,500 mg Iron (7.5 g SO)/day N = 25	2,000 mg Iron (10.0 g SO)/day N = 25	2,500 mg Iron (12.5 g SO)/day N = 24	Sevelamer HCl N = 24
	3.7116	4.3054	6.2248	1.6013	–1.6967	–0.456

CI = confidence interval; SD = standard deviation; SO = sucroferric oxyhydroxide.

Source: PA-CL-03A Clinical Study Report.[8]

Table 39: PA-CL-05A: Serum Intact Parathyroid Hormone (pmol/L) (Full Analysis Set)

Statistic	SO (N = 694)	Sevelamer (N = 347)
Baseline		
n	694	347
Mean (SD)	46.2 (31.87)	42.9 (28.89)
Week 4		
n	674	337
Mean (SD)	40.9 (31.52)	37.5 (25.50)
Change from baseline, mean (SD)	–5.4 (25.07)	–5.5 (20.65)
Week 8		
n	625	325
Mean (SD)	38.7 (26.41)	37.4 (26.53)
Change from baseline, mean (SD)	–7.3 (23.24)	–5.6 (20.65)
Week 12		
n	592	315
Mean (SD)	37.9 (26.90)	36.5 (25.69)
Change from baseline, mean (SD)	–8.7 (25.20)	–6.0 (23.56)
Week 16		
n	561	301
Mean (SD)	38.1 (27.05)	38.6 (27.16)
Change from baseline, mean (SD)	–8.5 (25.84)	–4.1 (20.85)
Week 20		
n	542	299
Mean (SD)	38.9 (28.07)	39.6 (29.04)
Change from baseline, mean (SD)	–8.0 (26.36)	–3.5 (22.82)
Week 24		
n	517	291
Mean (SD)	40.3 (30.83)	39.0 (28.22)
Change from baseline, mean (SD)	–7.2 (28.29)	–4.0 (25.82)
End point week 24		
n	673	341
Mean (SD)	39.8 (29.83)	39.2 (28.96)
Change from baseline, mean (SD)	–6.6 (29.22)	–3.2 (25.49)

SD = standard deviation; SO = sucroferric oxyhydroxide.

Notes: Baseline was defined as the last assessment prior to or on the date of the first dose of study medication. End point was week 24 or includes the latest measurement after baseline prior to withdrawal.

Source: PA-CL-05A Clinical Study Report.[9]

Table 40: PA1301: Serum Intact Parathyroid Hormone (pmol/L) (Full Analysis Set)

	SO (N = 106)	Sevelamer (N = 103)
Baseline		
n	106	103
Mean (SD)	28.31 (16.02)	31.59 (17.48)
Week 4		
n	103	97
Mean (SD)	23.27 (13.58)	25.03 (16.04)
Week 8		
n	97	90
Mean (SD)	22.18 (13.65)	26.00 (17.13)
Week 12		
n	93	87
Mean (SD)	22.03 (12.67)	27.18 (18.11)
End point week 12		
n	105	102
Mean (SD)	21.74 (12.17)	26.57 (17.59)

SD = standard deviation; SO = sucroferric oxyhydroxide.

Source: PA1301 Clinical Study Report Synopsis.[10]

Appendix 5: Validity of Outcome Measures

Aim

To summarize the validity of the following outcome measures:

- Serum phosphorous as a predictor of all-cause and cardiovascular mortality
- Short Form (36) Health Survey version 2 (SF-36v2).

Findings

Serum Phosphorous as a Predictor of All-Cause and Cardiovascular Mortality

The primary method of regulating serum phosphorous levels in the body of healthy individuals is through renal excretion by the kidneys.[15] With significant impairment of kidney function, i.e., end-stage renal disease (ESRD), the ability of the kidneys to perform this function is limited, thus leading to a rise in serum phosphorous levels.[15] According to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines, most studies that assess serum phosphate levels in relation to mortality show a link between higher concentrations of serum phosphate that lead to increased risk of all-cause mortality.[23]

All-Cause Mortality

Four studies that evaluated the relationship between serum levels of phosphorous and all-cause mortality in patients with ESRD on dialysis were identified from a targeted literature search.[72,73,75,76] All of the studies were observational in nature and two were specific to Japanese patients.[73,76]

Tentori et al.[75] used the Dialysis Outcomes and Practice Patterns Study, a prospective cohort study, to obtain data for 25,588 patients sampled from dialysis facilities internationally. Values for mean and percentile laboratory values were weighted based on the proportion of patients sampled from the total number of patients per facility in an effort to avoid disproportionate sampling. These data were used to provide evidence for an increase in all-cause mortality associated with higher levels of serum phosphorous based on adjusted hazard ratios (HRs) calculated via Cox proportional hazard models. Adjustments were made for age, sex, race, years with ESRD, body mass index (BMI), and 14 comorbid conditions (including diabetes mellitus, coronary artery disease, congestive heart failure, cancer, and others).[75] Further, 90.2% of patients had a prescription for a phosphate binder (PB) (72.9% calcium-based, 17.1% sevelamer, 21.4% other). Serum phosphorous levels of 6.1 mg/dL to 7.0 mg/dL (2.0 mmol/L to 2.3 mmol/L) ($P < 0.05$) and > 7.0 mg/dL (2.3 mmol/L) ($P < 0.0001$), corresponded to an HR of 1.18 (95% confidence interval [CI], 1.08 to 1.28) and 1.43 (95% CI, 1.32 to 1.56), respectively, compared with a reference phosphorous level of 3.6 mg/dL to 5.0 mg/dL (1.16 mmol/L to 1.62 mmol/L). In the study by Nakai et al.,[76] data were collected from a cross-sectional database (Japanese Society for Dialysis Therapy registry) for 27,404 Japanese dialysis patients on chronic HD who had been on dialysis at least three times per week for more than two years. The effects of bone mineral metabolism on survival were evaluated by Cox's proportional hazard analysis adjusted for possible confounders, which were not explicitly stated in the methodology. This study reported that the risk of death increased along with an increase in serum phosphorous at levels greater than 7.0 mg/dL (2.3mmol/L) ($P < 0.0001$ for serum levels of phosphorous of 7.0 mg/dL to 7.9 mg/dL, 8.0 mg/dL to 8.9 mg/dL, and ≥ 9.0 mg/dL)

in comparison with reference values of 4.0 mg/dL to 4.9 mg/dL. This corresponded to an HR of 1.425 (95% CI, 1.265 to 1.605), 1.893 (95% CI, 1.620 to 2.213), and 1.985 (95% CI, 1.621 to 2.432), for these categories, respectively.

Fukagawa et al.[73] included a sub-cohort of 8,229 chronic kidney disease (CKD) Stage 5D patients, who were originally enrolled in a multi-centre, three-year, prospective cohort study. Patients were randomly selected from the original cohort study at a sampling rate of 40%. Marginal structural models were used to assess the relationship between serum levels of phosphorous and clinical outcomes, including all-cause mortality. A U-shaped relationship between serum phosphorous and all-cause mortality was reported. However, the results were only statistically significant at higher levels of serum phosphorous. Relative to the reference category (5.0 mg/dL to 5.9 mg/dL or 1.61 mmol/L to 1.93 mmol/L) there were 9.40 excess deaths per 100 person-years at phosphorous levels ≥ 9.0 mg/dL (2.9 mmol/L), which corresponded to an estimated relative risk of 2.79 compared with participants in the reference category.

In contrast to the aforementioned studies, Fouque et al.[72] conducted a multi-centre prospective cohort study that sought to evaluate the targets for serum phosphorous set out in the KDIGO guidelines. This included an analysis of clinical data from 5,339 patients (63.7% of enrolment) from voluntary dialysis centres in France, who were receiving intermittent dialysis for a median of
3.0 years at study entry. All patients over the age of 18 were eligible for inclusion, but those who had a parathyroidectomy in the preceding six months were excluded from analysis. Baseline levels of serum phosphorous and the 30-month risk of mortality were assessed using the KDIGO recommendations as a reference point, that is, low serum phosphorous levels were defined as
≤ 2.79 mg/dL (≤ 0.9 mmol/L) and high serum phosphorous levels were defined as > 4.34 mg/dL (1.4 mmol/L). Using these parameters in comparison with the target level of serum phosphorous recommended by KDIGO, an adjusted HR for risk of mortality (by 30 months post–study entry) of 1.15 (95% CI, 0.95 to 1.40) and 1.07 (95% CI, 0.95 to 1.20), respectively, were identified. The authors concluded that based on these results, higher and lower levels of serum phosphorous are not predictive of death. Of note, adjustments were made for gender, age, BMI, diabetes and history of cardiovascular disease, dialysis vintage, serum albumin, and blood hemoglobin concentrations.

Cardiovascular Morbidity and Mortality

Tentori et al.[75] also evaluated and reported an increased risk of cardiovascular mortality associated with an increase of serum phosphorous levels. This was based on a HR of 1.25 (95% CI, 1.09 to 1.44), 1.61 (95% CI, 1.40 to 1.85), and 1.81 (95% CI, 1.57 to 2.09) for categories for serum levels of phosphorous of 5.1 mg/dL to 6.0 mg/dL (1.6 mmol/L to 1.9 mmol/L) ($P < 0.05$), 6.1 mg/dL to 7.0 mg/dL (2.0 mmol/L to 2.3 mmol/L) ($P < 0.0001$), and > 7.0 mg/dL (> 2.3 mmol/L) ($P < 0.0001$), respectively. All were compared with the reference category of 3.6 mg/dL to 5.0 mg/dL (1.2 mmol/L to 1.6 mmol/L).

The association between serum phosphate concentrations and vascular and valvular calcification (cardiovascular morbidity) was evaluated in a community-based cohort study of 439 patients (68.5% of the initial cohort) who had moderate CKD (estimated glomerular filtration rate < 60 mL/min per 1.73 m^2) but no previous diagnosis of clinical cardiovascular disease.[53] The study cohort had an average age of 70 years, 62% were female, and 22% had diabetes. Calcification of the coronary artery, descending thoracic aorta, aortic valve, and mitral valve was assessed using an electron-beam computed tomography (CT) or

multi-detector CT. Participants with phosphate levels > 4.0 mg/dL (1.3 mmol/L) had 42% (95% CI, 1.11 to 1.82; *P* = 0.001) greater prevalence of calcification of the coronary artery, and 80% (95% CI, 1.2 to 2.61; *P* < 0.001) greater prevalence of calcification of the descending thoracic aorta compared with those with serum phosphate levels < 3.0 mg/dL (0.97 mmol/L). Of note, models were adjusted for: age, race, gender, cystatin C, BMI, history of smoking, diabetes, diastolic blood pressure, low-density lipoprotein cholesterol, ln(C-reactive protein), ln(urinary albumin-to-creatinine ratio), serum calcium, and serum 1,23-$OH)_2$D levels. Equivalent values for aortic valve and mitral valve calcification were not statistically significant. A limitation of this analysis was the imprecision associated with CT scanning, as noted by the authors. Further, analyses were based on a single scan for all but the coronary artery, which was based on an average of two scans. An additional limitation is the patient population, which is a small subset of a larger study (N = 6,814) and therefore presents potential for selection bias.

Another study, conducted by Rubel and Milford,[74] used a subset of data from the US Renal Data System and Dialysis Morbidity and Mortality Study, which included data from 12,509 in-centre patients who had been on hemodialysis for at least six months prior to data collection (December 1993). Outcome data were derived from hospital claims records, and patient follow-up ranged from six months to 30 years. This cross-sectional study evaluating cardiovascular outcomes and serum phosphorous levels used “surgical cardiac valvular procedure” as a surrogate outcome for medical valvular disease, as they claimed a medical diagnosis was too inconsistent for use. Based on a univariate analysis, a crude HR of 1.43 (95% CI, 1.02 to 2.02; *P* = 0.037) for phosphate ≥ 5.0 mg/dL (≥ 1.62 mmol/L) in comparison with a serum phosphate level of less than 5.0 mg/dL was determined. A multivariate regression model was also implemented, which determined a similar (adjusted) HR of 1.47 (95% CI, 1.03 to 2.09; *P* = 0.033). Details regarding the adjusted model are unclear, although it was stated that secondary covariates (e.g., data regarding intact parathyroid hormone, parathyroidectomy, blood pressure, cholesterol, race, smoking history, history of comorbidities, as well as other variables) were not adjusted for, which is a major limitation of this evaluation. The date of publication (1993) is another significant limitation of this study as it affects the generalizability of the results, especially considering the change in standards of care over the last 25 years. An additional limitation is the use of claims records due to the potential for issues such as those related to quality control and missing data. Therefore, these results should be carefully considered.

Based on the results presented above, the evidence for an association between elevated levels of serum phosphorous ≥ 6.0 mg/dL (1.9 mmol/L) and all-cause mortality in patients with CKD is weak. The same is true for elevated serum phosphorous levels beyond 5.0 mg/dL (1.62 mmol/L) as an increased risk for cardiovascular mortality and morbidity, which is also subject to a number of limitations and high risk of bias. Moreover, the only data identified regarding this topic were observational in nature, thus the “optimal target” for serum phosphate in terms of reducing all-cause and cardiovascular mortality is not well supported; this was echoed by two reviews on the topic.[6,15] The review by Tonelli et al.[15] noted that hyperphosphatemia may also be due to a lack of adherence to dietary restrictions or insufficient treatment with dialysis, highlighting that the increased risk of mortality could be the result of various other factors and needs further evaluation. Further, because two of the studies discussed were carried out in Japanese patients, the generalizability and applicability of these results to the Canadian context should be taken into consideration due to differences in the demographics of each population, as well as the standard of care in the two countries.

Short Form (36) Health Survey (version 2)

Short Form (36) Health Survey version 2 (SF-36v2) is a 36-item, general health status instrument that has been used extensively in clinical trials in many disease areas.[68] It was developed in 1996 based on the original SF-36, which required substantial changes to address its shortcomings.[68] Like the SF-36, the SF-36v2 consists of eight health domains: physical functioning, role physical, general health, vitality, social functioning, role emotional, and mental health.[68] Each of the eight domains is scored on a domain-specific scale, on which higher scores correspond with better health.[68] A principal components analysis of the eight domains is also used to create two component summaries, the physical component summary (PCS) and the mental component summary (MCS).[68] Each score from the eight domains is converted to a scale ranging from 0 to 100, and then transformed to a T-score (mean of 50 and standard deviation of 10) that is standardized to the US general population. Thus, a score of 50 on any scale would be at the average or norm of the general US population and a score 10 points lower (i.e., 40) would be one standard deviation below the norm. The domain scores are then aggregated using a weighted formula to score the summary scores, which are also transformed to a T-score.[68]

Based on anchor data, the developer of the SF-36v2 proposed the following minimal mean group differences for the individual domain scores: physical functioning, 3; role physical, 3; bodily pain, 3; general health, 2; vitality, 2; social functioning, 3; role emotional, 4; and mental health, 3. These minimal important difference (MID) values were determined as appropriate for groups with mean T-score ranges of 30 to 40. For higher T-score ranges, MID values may be higher.[68] As these MID values were based on clinical and other non–patient-reported outcomes, they do not necessarily identify the smallest difference that patients would consider important. In general, a change of 2 points on the PCS and 3 points on the MCS of the SF-36v2 indicates a clinically meaningful improvement as determined by the patient.[68]

The reliability and validity of the SF-36v2 has been demonstrated across various conditions.[68,78] One study was identified that assessed the validity of the SF-36v2 based on a secondary data analysis using cross-sectional baseline data.[69] The version was not specified, but it was scored according to the manual for the SF-36v2. This study included a convenient sample of 74 patients (72.5% of those invited to participate) with a diagnosis of Stage 5 CKD with a confirmed decision for conservative management, i.e., not receiving dialysis treatment. The average age of participants was 80.7 (± 6.8) years and 68.9% were of white ethnicity. A minimal clinically important difference (MCID) for this population was determined using the Karnofsky performance scale as disease-related criteria for an anchor-based approach; a distribution-based approach was also applied.[69] This analysis reported an MCID of 5.7 and 9.2 for the PCS and MCS, respectively, which is higher than the previously mentioned general recommended MCID for the SF-36v2. Further, the MCIDs based on one standard error of the mean reported for the PCS and MCS were 1.63 and 2.46, respectively.[69] The population included in this study was a limitation due to the small sample size and elderly participants, which affects the generalizability of the results and application of the MCID.

Conclusion

Evidence to support the link between elevated levels of serum phosphorous and increased risk of all-cause and cardiovascular mortality is weak, subject to limitations and bias. The evidence available in support of this relationship is based on observational studies and analyses, which suggest that the risk of all-cause mortality is increased at levels of serum phosphorous ≥ 6.0 mg/dL (1.9 mmol/L), and at levels beyond 5.0 mg/dL (1.62 mmol/L) there is as an increased risk for cardiovascular mortality and morbidity. Some of the studies were carried out in Japanese patients, which was a limitation in terms of generalizability as serum phosphorous is related to dietary factors, which may differ based on ethnicity. The validity of the widely used SF-36v2 was also reviewed. The generic health status instrument has been well validated previously. A study by Erez et al.[69] reported an MCID of 5.7 for the PCS and 9.2 for the MCS using an anchor-based approach for patients with CKD undergoing conservative (non-dialysis) management of their disease. Distribution-based methods were also applied and determined MCIDs of 1.63 and 2.46 for the PCS and the MCS, respectively, based on one standard error of the mean.

Appendix 6: Summary of Other Studies

Objective

To summarize the results of the long-term safety extension (LTSE) of Study PA-CL-05A, which evaluated the long-term safety and efficacy of sucroferric oxyhydroxide (SO) chewable tablets, 500 mg iron (equivalent to 2,500 mg SO) in comparison with 800 mg sevelamer tablets, in patients with end-stage renal disease (ESRD) on dialysis.

Findings

Study Design

The study design characteristics of the open-label, active-controlled, parallel group, multi-centre phase III LTSE (PA-CL-05B or 05B) are summarized in Table 41. The LTSE was conducted in 143 of the 174 centres where the initial phase III study (PA-CL-05A or 05A) was conducted. This included centres in the US (56), EU (43), and 44 sites in other countries, including Croatia, Russia, Serbia, South Africa, and Ukraine. Patients who had completed study 05A, including those who were re-randomized to the maintenance dose (MD) group of Stage 2 and also provided informed consent to participate in PA-CL-05B prior to study-specific procedures, including screening, were eligible for enrolment in study 05B. Patients were ineligible for 05B if they were re-randomized to the low dose (LD) group in Stage 2 of Study 05A, or if they had any of the following at the 05A study visit prior to screening for 05B: hypercalcemia (total serum calcium > 2.75 mmol/L) or hypocalcemia (total serum calcium < 1.9mmol/L), elevated alanine aminotransferase or aspartate aminotransferase (greater than three times the upper limit of the normal range), or elevated serum ferritin (> 4,494 pmol/L). Further, taking medications, which included antacids (containing aluminum, calcium, or magnesium), phosphate binders in addition to SO or sevelamer, and oral iron therapies or supplements, was prohibited. Additionally, being pregnant, breastfeeding, or of childbearing potential without use of contraception, or the presence of any other kind of disorder that compromises the ability to provide consent or comply with study procedures also made patients ineligible for 05B.

Briefly, the original phase III study, 05A, was 24 weeks in length (following a washout period of two to four weeks), during which patients were randomized to receive SO or sevelamer. A titration period of eight weeks was followed by four weeks, during which adjustments could only be made for tolerability, followed by 12 weeks when the dose could be modified for efficacy and tolerability. A subset of patients was re-randomized to a maintenance-dose phase (Stage 2, MD) or low-dose phase (Stage 2, LD) for an additional three weeks after week 24 of 05A.The open-label extension was a continuation of treatment with either SO or sevelamer that was established during 05A or during the Stage 2, MD phase. The minimum and maximum dosage permitted for SO was 1,000 mg iron/day (two tablets/day) and 3,000 mg iron/day (six tablets/day), respectively. As for sevelamer, a minimum of 2.4 g/day (three tablets/day) and a maximum of 14.4 g/day (18 tablets/day) were permitted.

Table 41: Summary of the Study Design and Characteristics of PA-CL-05B

		PA-CL-05B
Designs and Populations	**Study design**	Open-label, extension of 05A
	Participants (N)	659
	Centre locations	US (56), EU (43), other countries (Croatia, Russia, Serbia, South Africa, and Ukraine) (44)
	Eligibility	Patients who had completed PA-CL-05A (including those completing Stage 2 on MD) who also provided informed consent to participate in PA-CL-05B prior to study-specific procedures, including screening
	Primary objective	To assess the long-term safety and tolerability of SO
	Secondary objectives	To compare the long-term serum phosphorous control of SO vs. sevelamer To compare the safety and tolerability of SO vs. sevelamer
Drugs	**Intervention**	SO (2.5 g or 1.25 g chewable tablets) at the established dose provided at week 24 (or week 27 for subjects in Stage 2 MD group) in PA-CL05A; dosages ranged from 1,000 mg to 3,000 mg iron per day (2 to 6 tablets/day or 5 g to 15 g SO/day) Note: dose modifications for tolerability and efficacy reasons were permitted.
	Comparators	Sevelamer (carbonate) tablets, 800 mg; dosages ranged from 2.4 to 14.4 g/day (3 to 18 tablets/day)
Duration	**Main trial: Stage 1 of PA-CL-05A**	24 weeks
	Maintenance-dose phase: Stage 2 of PA-CL-05A	3 weeks
	Open-label extension (PA-CL-05B)	28 weeks
Outcomes	**Primary end points**	Safety: Comparison of the following between SO and sevelamer subjects: TEAE profiles (AEs, SAEs, WDAEs, notable harms)
	Other end points	Safety: Iron status: serum ferritin and transferrin saturation Change in serum calcium from 05B baseline Change in serum iPTH from 05B baseline Efficacy and safety: Change in serum phosphorous from 05B baseline

AE = adverse events; iPTH = intact parathyroid hormone; MD = maintenance dose; SAE = serious adverse event; SO = sucroferric oxyhydroxide; TEAE = treatment-emergent adverse event; WDAE= withdrawal due to adverse events.

Source: Clinical Study Report, Integrated report for PA-CL-05A and PA-CL-05B.[77]

Methods

The primary objective of Study 05B was to assess the long-term safety and tolerability of SO based on the adverse events (AEs) profile for SO in comparison with sevelamer. This included treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and AEs with an outcome of death. Withdrawal due to adverse events (WDAEs) and notable harms (gastrointestinal-related AEs) were also included. TEAEs were defined as AEs that occur or worsen after the first administration of the study drug in 05B. The secondary objectives of the LTSE were to compare the long-term serum phosphorous control by SO against sevelamer, and to compare the safety and tolerability of the intervention and active comparator. Of note, 05B baseline value was defined as the last available value prior to or on the date of the first study drug intake in 05B, and the 05B end point was defined as the

last post-baseline observed value collected no later than seven days after the last dose of the 05B study drug.

Statistical Methods

No sample size calculations were performed for the extension study. The datasets used for analysis are summarized in Table 42. The 05B safety set was used for all safety analyses. The per-protocol set was used for statistical analyses on the efficacy end points of 05B. The full analysis set for 05B was used for the efficacy analyses. Statistical tests were performed using two-sided tests at the 5% significant level, and no adjustments were made for multiplicity. For the efficacy analysis of change in serum phosphorous levels from baseline, missing data were handled following the missing at random (MAR) missingness mechanism and a mixed-effect model for repeated measures (MMRM) was used for consideration of the treatment effect based on the maximum likelihood estimation.

Patient Disposition

Patient disposition is summarized in Table 42. A total of 659 of 1,059 (62.2%) patients randomized to the preceding double-blind trial proceeded to the open-label extension study; 391 were from the arm receiving SO and 268 from the arm receiving sevelamer. A total of 549 (83.3%) patients completed the LTSE study, with 322 (82.4%) from the SO group and 227 (84.7%) from the sevelamer group. Patients from the SO group discontinued the intervention due to AEs other than those relating to serum levels of phosphorous or calcium (4.3%), serum phosphorous > 2.75 mmol/L (3.1%), withdrawal of consent (2.3%), renal transplant (2.8%), the decision of the investigator (1.5%), death (1.5%), violation of protocol (1.3%), serum phosphorous < 0.81 mmol/L (0.5%), or other reasons (0.3%). Patients receiving sevelamer discontinued their intervention due to withdrawal of consent (3.0%), serum phosphorous > 2.75 mmol/L (2.6%), renal transplant (2.6%), death (1.9%), AEs other than those relating to serum levels of phosphorous or calcium (1.5%), the decision of the investigator (1.1%), violation of protocol (1.1%), sponsor decision (1.1%), or other reasons (0.4%). None of the patients receiving sevelamer withdrew due to serum phosphorous < 0.81 mmol/L.

Table 42: Patient Disposition in Study 05B

Disposition, n (%)	SO	Sevelamer	Total
Study 05A	**N = 710**	**N = 349**	**N = 1,059**
Randomized	710 (100)	349 (100)	1,059 (100)
Received treatment	707 (99.6)	348 (99.7)	1,055 (99.6)
Completed	504 (71.0)	293 (84.0)	797 (75.3)
Enrolled in 05B	391 (55.1)	268 (76.8)	659 (62.2)
Study 05B	**N = 391**	**N = 268**	**N = 659**
Received treatment	391 (100)	267 (99.6)	658 (99.8)
Completed	322 (82.4)	227 (84.7)	549 (83.3)
Withdrawn from 05B	69 (17.6)	41 (15.3)	110 (16.7)
Reason for withdrawals from treatment			
Death	6 (1.5)	5 (1.9)	11 (1.7)
AE (other than phosphorus- or calcium-level events)	17 (4.3)	4 (1.5)	21 (3.2)
Pregnancy	0	0	0
Withdrawn consent	9 (2.3)	8 (3.0)	17 (2.6)
Investigator's decision	6 (1.5)	3 (1.1)	9 (1.4)
Serum phosphorus > 2.75 mmol/L[a]	12 (3.1)	7 (2.6)	19 (2.9)

Disposition, n (%)	SO	Sevelamer	Total
Serum phosphorus < 0.81 mmol/L[a]	2 (0.5)	0	2 (0.3)
Serum calcium > 2.75 mmol/L[b]	0	0	0
Subject requires treatment with an additional PB	0	0	0
Prohibited medication	0	0	0
Protocol violation	5 (1.3)	3 (1.1)	8 (1.2)
Sponsor decision	0	3 (1.1)	3 (0.5)
Renal transplant	11 (2.8)	7 (2.6)	18 (2.7)
Other	1 (0.3)	1 (0.4)	2 (0.3)
Data sets			
Safety Set, N (%)	391 (100)	267 (99.6)	658 (99.8)
Full Analysis Set, N (%)	384 (98.2)	260 (97.4)	644 (97.9)
Per Protocol Set, N (%)	314 (80.3)	185 (69.0)	499 (75.7)

AE = adverse event; PB = phosphate binder; SO = sucroferric oxyhydroxide.

[a] Despite appropriate dose adjustments.

[b] Despite appropriate rescue interventions.

Source: Clinical Study Report, Integrated report for PA-CL-05A and PA-CL-05B.[77]

Baseline Characteristics

The LTSE baseline characteristics reported in the study are summarized in Table 43. The age of patients ranged from 21.0 to 88.0 years, with a mean of 55.4 (standard deviation [SD] of 13.77). A greater proportion of the population was male (58.5%), with 41.5% of patients being female. Nearly 80% of patients were white, followed by 16.7% who were black/African-American. Of note, the sevelamer arm had a higher proportion of black/African-American patients (21.7% versus 13.3%). Further, 1.7%, 0.8%, and 0.9% were Asian, Native Hawaiian/Other Pacific Islander, or of another race, respectively. Ethnicity was similar between the two arms, with 11.6% of the total number of patients being Hispanic or Latino. The weight of patients ranged from 40.0 kg to 168.0 kg, with an average of 82.4 kg (SD, 20.28).

Table 43: Baseline Characteristics in Study 05B

Characteristics	SO (N = 391)	Sevelamer (N = 267)	Total (N = 658)
Age, y			
n	391	267	658
mean (SD)	55.2 (13.20)	55.6 (14.58)	55.4 (13.77)
minimum, maximum	22.0, 87.0	21.0, 88.0	21.0, 88.0
Sex, n (%)			
Female	171 (43.7)	102 (38.2)	273 (41.5)
Male	220 (56.3)	165 (61.8)	385 (58.5)
Race, n (%)			
White	324 (82.9)	202 (75.7)	526 (79.9)
Black/African-American	52 (13.3)	58 (21.7)	110 (16.7)
Asian	5 (1.3)	6 (2.2)	11 (1.7)
American Indian/Alaska Native	0	0	0
Native Hawaiian/Other Pacific Islander	5 (1.3)	0	5 (0.8)
Other	5 (1.3)	1 (0.4)	6 (0.9)
Ethnicity, n (%)			
Hispanic or Latino	44 (11.3)	32 (12.0)	76 (11.6)

Characteristics	SO (N = 391)	Sevelamer (N = 267)	Total (N = 658)
Not Hispanic or Latino	347 (88.7)	235 (88.0)	582 (88.4)
Weight (kg)			
n	391	267	658
mean (SD)	81.5 (19.80)	83.8 (20.92)	82.4 (20.28)
minimum, maximum	40.0, 168.0	45.3, 163.9	40.0, 168.0
BMI (kg/m^2)			
n	391	267	658
mean (SD)	28.6 (6.37)	29.4 (7.25)	28.9 (6.75)
minimum, maximum	16.8, 63.7	17.0, 70.8	16.8, 70.8

BMI = body mass index; SD = standard deviation; SO = sucroferric oxyhydroxide.

Source: Clinical Study Report, Integrated report for PA-CL-05A and PA-CL-05B.[77]

The patients were described in terms of the state of their ESRD, which is summarized in Table 44. The most common reason for ESRD among all patients included in Study 05B was diabetic neuropathy (25.5%), followed by glomerulonephritis (24.9%), hypertension (22.8%), polycystic kidney disease (8.8%), pyelonephritis (3.8%), interstitial nephritis (3.3%), congenital (1.7%), hydronephrosis (1.5%), and other (7.6%). Of note, the most common reason for ESRD in each treatment group differs, with hypertension being the most common reason among patients in the sevelamer arm (37.3%) compared with 19.7% in the SO arm. Diabetic neuropathy was the most common reason among patients receiving SO (25.1%). The time from the start of ESRD for all patients ranged from 0.4 months to 396.8 months, with an overall mean of 64.9 months (SD, 65.22). Approximately 91% and 10% of all patients were on hemodialysis and peritoneal dialysis, respectively. The time from the start of first dialysis ranged from 0.7 months to 396.8 months, with an mean of 51.4 months (SD, 51.72) overall.

Table 44: Summary of End-Stage Renal Disease

Parameter	SO (N = 391)	Sevelamer (N = 267)	Total (N = 658)
Reason for ESRD, n (%)			
Hypertension	77 (19.7)	73 (27.3)	150 (22.8)
Glomerulonephritis	97 (24.8)	67 (25.1)	164 (24.9)
Diabetic nephropathy	98 (25.1)	70 (26.2)	168 (25.5)
Pyelonephritis	15 (3.8)	10 (3.7)	25 (3.8)
Polycystic kidney disease	42 (10.7)	16 (6.0)	58 (8.8)
Interstitial nephritis	14 (3.6)	8 (3.0)	22 (3.3)
Hydronephrosis	7 (1.8)	3 (1.1)	10 (1.5)
Congenital	6 (1.5)	5 (1.9)	11 (1.7)
Other	35 (9.0)	15 (5.6)	50 (7.6)
Time from start of ESRD (months)			
n	390	267	657
Mean (SD)	63.1 (61.88)	67.5 (69.85)	64.9 (65.22)
Minimum, maximum	3.1, 381.6	0.4, 396.8	0.4, 396.8
Dialysis, n (%)			
HD	348 (89.0)	249 (93.3)	597 (90.7)
PD	43 (11.0)	18 (6.7)	61 (9.3)

Parameter	SO (N = 391)	Sevelamer (N = 267)	Total (N = 658)
Time from start of first dialysis (months)			
n	391	267	658
Mean (SD)	49.4 (47.59)	54.4 (57.20)	51.4 (51.72)
Minimum, maximum	0.7, 288.3	3.4, 396.8	0.7, 396.8

ESRD = end-stage renal disease; HD = hemodialysis; PD = peritoneal dialysis; SD = standard deviation; SO = sucroferric oxyhydroxide.

Source: Clinical Study Report, Integrated report for PA-CL-05A and PA-CL-05B.[77]

Results

Safety

Adverse Event Profiles

The AE profiles of SO and sevelamer groups are summarized in Table 45. Statistics described in this section include those for patients in the SO arm, followed by those for patients in the sevelamer arm. Approximately three-quarters (73.9% and 76.8%) of patients experienced at least one AE in the LTSE. The most commonly reported AE was hyperphosphatemia (12.0% and 10.9%), followed by hypertension (9.7% and 7.5%), diarrhea (8.2% and 5.6%), muscle spasms (6.6% and 6.0%), nausea (5.9% and 4.1%), hypophosphatemia (5.6% and 5.2%), headache (5.1% and 3.0%), hypotension (4.9% and 7.9%), hyperkalemia (4.3% and 6.0%), anemia (3.8% and 5.6%), and secondary hyperparathyroidism (3.8% and 8.6%).

SAEs were reported in approximately one-fifth of patients (19.9% and 19.5%), with the most common reason being pneumonia (1.5% and 2.2%). Other SAEs that were reported in at least 1% of patients in either treatment arm included fluid overload (1.0% and 2.2%), hematoma (1.0% and 0%), pulmonary edema (0.5% and 1.1%), anemia (0.3% and 1.1%), and atrial fibrillation (0.3% and 1.1%). Gastrointestinal (GI)-related AEs were also included in this review as notable harms, which included diarrhea (8.2% and 5.6%), nausea (5.9% and 4.1%), vomiting (3.6% and 4.5%), constipation (2.6% and 1.9%), abdominal pain (2.0% and 0.7%), dyspepsia (1.5% and 2.2%), abdominal pain upper (1.3% and 0.7%), peritonitis (1.3% and 0.4%), toothache (1.3% and 0.4%), gastritis (1.0% and 1.5%), gastroesophageal reflux disease (1.0% and 1.5%), and gastrointestinal hemorrhage (0% and 1.1%).

As for the WDAEs, 8.2% and 4.9% of patients in the SO arm and sevelamer arm, respectively, reported a WDAE. The most common reasons for a WDAE were hyperphosphatemia (2.8% and 2.6%), followed by diarrhea (0.5% and 0%), hypophosphatemia (0.5% and 0%), the product tasting abnormal (0.5% and 0%), an issue with the product dosage form (0% and 0.4%), and an increase of blood phosphorous (0.3% and 0.4%).

Table 45: Summary of Adverse Events

Adverse Events	SO (N = 391)	Sevelamer (N = 267)
Subjects with > 0 AEs, n (%)	289 (73.9)	205 (76.8)
Subjects with >0 SAEs, n (%)	78 (19.9)	52 (19.5)
Subjects with >0 WDAEs, n (%)	32 (8.2)	13 (4.9)
Deaths		
Number of deaths, n (%)	7 (1.8)	7 (2.6)
AEs reported in ≥ 5% of patients in any group		
Most common AEs, n (%)		
Hyperphosphatemia	47 (12.0)	29 (10.9)
Hypertension	38 (9.7)	20 (7.5)
Diarrhea	32 (8.2)	15 (5.6)
Muscle spasms	26 (6.6)	16 (6.0)
Nausea	23 (5.9)	11 (4.1)
Hypophosphatemia	22 (5.6)	14 (5.2)
Headache	20 (5.1)	8 (3.0)
Hypotension	19 (4.9)	21 (7.9)
Hyperkalemia	17 (4.3)	16 (6.0)
Anemia	15 (3.8)	15 (5.6)
Hyperparathyroidism secondary	15 (3.8)	23 (8.6)
SAEs reported in ≥ 1% of patients in any group		
Most common SAEs, n (%)		
Pneumonia	6 (1.5)	6 (2.2)
Fluid overload	4 (1.0)	6 (2.2)
Hematoma	4 (1.0)	0
Pulmonary edema	2 (0.5)	3 (1.1)
Anemia	1 (0.3)	3 (1.1)
Atrial fibrillation	1 (0.3)	3 (1.1)
GI-related AEs reported in ≥ 1% of patients in any group		
Diarrhea	32 (8.2)	15 (5.6)
Nausea	23 (5.9)	11 (4.1)
Vomiting	14 (3.6)	12 (4.5)
Constipation	10 (2.6)	5 (1.9)
Abdominal pain	8 (2.0)	2 (0.7)
Dyspepsia	6 (1.5)	6 (2.2)
Abdominal pain upper	5 (1.3)	2 (0.7)
Peritonitis	5 (1.3)	1 (0.4)
Toothache	5 (1.3)	1 (0.4)
Gastritis	4 (1.0)	4 (1.5)
GERD	4 (1.0)	4 (1.5)
GI hemorrhage	0	3 (1.1)
WDAEs reported in ≥ 2% of patients in any group		
Most common WDAEs, n (%)		
Hyperphosphatemia	11 (2.8)	7 (2.6)
Diarrhea	2 (0.5)	0

Adverse Events	SO (N = 391)	Sevelamer (N = 267)
Hypophosphatemia	2 (0.5)	0
Product taste abnormal	2 (0.5)	0
Product dosage form issue	0	1 (0.4)
Blood phosphorous increased	1 (0.3)	1 (0.4)

AE = adverse event; GI = gastrointestinal; SAE = severe adverse event; SO = sucroferric oxyhydroxide; WDAE = withdrawal due to adverse event.

Note: GI-related AEs were included as notable harms for this review.

Source: Clinical Study Report, Integrated report for PA-CL-05A and PA-CL-05B.[77]

Clinical Laboratory Values of Interest

Levels of serum calcium and intact parathyroid hormone (iPTH) were included in the evaluation of safety for SO in comparison with sevelamer. Calcium levels were reported as total or corrected. The mean (SD) level of serum calcium (total) for SO was 2.23 mmol/L (0.190) at 05B baseline and 2.25 mmol/L (0.195) at the 05B end point. The corresponding values for sevelamer were similar; at baseline, serum calcium (total) was 2.24 mmol/L (0.175) with an overall change from baseline of 0.02 mmol/L (0.185; 95% confidence interval [CI], 0 to 0.04). Corrected serum levels of calcium were also similar between the two treatment arms. The group receiving SO had a mean (SD) level of serum calcium, corrected, of 2.22 mmol/L (0.186) and a mean change from baseline of 0.02 mmol/L (0.181; 95% CI, 0 to 0.06). For the sevelamer arm, the mean (SD) at corrected serum calcium at baseline was 2.23 mmol/L (0.199), which resulted in a mean (SD) change from baseline at the 05B end point of 0.01 mmol/L (0.165; 95% CI, –0.01 to 0.04).

As for levels of serum iPTH, the mean (SD) at baseline for the SO and sevelamer treatment groups was 39.97 pmol/L (30.02) and 39.32 pmol/L (28.43), respectively. At the 05B end point, the values for serum iPTH were a mean (SD) of 46.08 pmol/L (40.75) and 46.00 pmol/L (34.88).

Table 46: Serum Calcium (Total and Corrected) (mmol/L), Change from Baseline (SS 5B, N = 658)

	SO (N = 391)	Sevelamer (N = 267)
Serum calcium, total (mmol/L)		
05B baseline[a],		
n	391	267
Mean (SD)	2.23 (0.190)	2.24 (0.175)
05B end point[b]		
n	368	258
Mean (SD)	2.25 (0.195)	2.26 (0.180)
Change from baseline[a], mean (SD)	0.02 (0.186)	0.02 (0.185)
95% CI	0 to 0.04	0 to 0.04
Serum calcium, corrected (mmol/L)		
05B baseline[a]		
n	287	200
Mean (SD)	2.22 (0.186)	2.23 (0.199)
05B end point[b]		
n	213	152
Mean (SD)	2.26 (0.190)	2.27 (0.168)

	SO (N = 391)	Sevelamer (N = 267)
Change from baseline[a], mean (SD)	0.02 (0.181)	0.01 (0.165)
95% CI	–0.01 to 0.05	–0.01 to 0.04

CI = confidence interval; SD = standard deviation; SO = sucroferric oxyhydroxide; SS = safety set.

[a] 05B baseline is the last non-missing value prior to or on the date of the first PA-CL-05B study drug intake.

[b] 05B end point is week 28 result or the latest available measurement after 05B baseline when week 28 is missing.

Source: Clinical Study Report, Integrated report for PA-CL-05A and PA-CL-05B.[77]

Table 47: Serum Intact Parathyroid Hormone (pmol/L), Change from Baseline (Safety Set 5B, N = 658)

	SO (N = 391)	Sevelamer (N = 267)
Serum iPTH (pmol/L)		
05B baseline[a]		
n	391	267
Mean (SD)	39.97 (30.02)	39.32 (28.43)
05B end point[b]		
n	383	260
Mean (SD)	46.07 (40.75)	46.00 (34.88)
Change from baseline,[a] mean (SD)	6.13 (29.27)	7.37 (28.77)
95% CI	3.19 to 9.07	3.86 to 10.89

CI = confidence interval; iPTH = intact parathyroid hormone; SD = standard deviation; SO = sucroferric oxyhydroxide.

[a] 05B baseline is the last non-missing value prior to or on the date of the first PA-CL-05B study drug intake.

[b] 05B end point is week 28 result or the latest available measurement after 05B baseline when week 28 is missing.

Source: Clinical Study Report, Integrated report for PA-CL-05A and PA-CL-05B.[77]

Certain iron parameters, including serum ferritin and transferrin saturation, were included in the safety analyses (Table 48). The mean (SD) level of serum ferritin at the 05B baseline for the SO group and sevelamer group was 1,610.7 pmol/L (1,010.82) and 1,718.1 pmol/L (1,113.44), respectively. The mean (SD) change from the 05B baseline reported at the 05B end point was
102.1 pmol/L (627.65; 95% CI, 39.3 to 164.9) for the SO arm and 55.5 pmol/L (851.64; 95% CI, – 48.5 to 15.5) for the sevelamer arm. The mean (SD) change in serum ferritin was also reported from the 05A baseline, which corresponded to a value of 359.2 pmol/L (808.51; 95% CI, 278.3 to 440.1) for the SO group and 148.7 pmol/L (1,024.02; 95% CI, 23.7 to 273.8) for the sevelamer group.

At the 05B baseline, transferrin saturation for the SO arm was a mean (SD) of 30.5% (13.71) and 28.0% (15.54) for the sevelamer arm. The mean (SD) change from the 05B baseline was minimal at 0.4% (15.97; 95% CI, –1.2 to 2.0) for the SO group and 0.5% (17.34; 95% CI, –1.6 to 2.6) for the sevelamer group. The mean (SD) change in transferrin saturation from the 05A baseline to the end of the LTSE (05B end point) was 5.0% (17.50; 95% CI, 3.2 to 6.7) for the SO group and 0.9% (15.85; 95% CI, –1.0 to 2.9) for the sevelamer group.

Table 48: Serum Ferritin (pmol/L) and Transferrin Saturation (%) (Safety Set 5B, N = 658)

	SO (N = 391)	Sevelamer (N = 267)
Serum ferritin (pmol/L)		
05B baseline[a]		
n	391	267
Mean (SD)	1,610.7 (1,010.82)	1,718.1 (1,113.44)
05B end point[b]		
n	386	260
Mean (SD)	1,716.4 (1,053.47)	1,790.4 (1,222.78)
Change from 05B baseline, mean (SD)	102.1 (627.65)	55.5 (851.64)
95% CI	39.3 to 164.9	– 48.5 to 159.5
Change from 05A baseline, mean (SD)	359.2 (808.51)	148.7 (1,024.02)
95% CI	278.3 to 440.1	23.7 to 273.8
Transferrin saturation (%)		
05B baseline		
n	390	267
Mean (SD)	30.5 (13.71)	28.0 (15.54)
05B end point		
n	385	260
Mean (SD)	30.9 (15.12)	28.6 (15.30)
Change from 05B baseline, mean (SD)	0.4 (15.97)	0.5 (17.34)
95% CI	–1.2 to 2.0	–1.6 to 2.6
Change from 05A baseline, mean (SD)	5.0 (17.50)	0.9 (15.85)
95% CI	3.2 to 6.7	–1.0 to 2.9

CI = confidence interval; SD = standard deviation; SO = sucroferric oxyhydroxide.

[a] 05B baseline is the last non-missing value prior to or on the date of the first PA-CL-05B study drug intake.

[b] 05B end point is week 28 results or the latest available measurement after 05B baseline when week 28 is missing.

Source: Clinical Study Report, Integrated report for PA-CL-05A and PA-CL-05B.[77]

Efficacy

Finally, the change from baseline in serum phosphorous levels was included as an efficacy end point using the 5B full analysis data set. For the group receiving the study intervention, SO, the mean (SD) level of serum phosphorous (mmol/L) at the beginning of the LTSE was 1.7 (0.48) and 1.8 (0.54) at the 05B end point. The corresponding baseline and end point values for the group receiving sevelamer was 1.7 (0.46) and 1.8 (0.52), respectively. Based on an analysis of covariance that was conducted for the difference in the change from baseline between the SO and sevelamer groups, a treatment difference of –0.04 mmol/L (0.04; 95% CI, –0.12 to 0.04) was reported, but it was not statistically significant (*P* = 0.293).

Table 49: Serum Phosphorous (mmol/L), Change from Baseline (Full Analysis Set 5B, N = 644)

	SO (N = 384)	Sevelamer (N = 260)
Serum phosphorous (mmol/L)		
05B baseline[a]		
n	384	260
Mean (SD)	1.7 (0.48)	1.7 (0.46)
05B end point[b]		
n	384	260
Mean (SD)	1.8 (0.54)	1.8 (0.52)
Change from baseline[a], mean (SD)	0 (0.52)	0.1 (0.58)
Change from baseline[a], LS mean (SE)	0 (0.04)	0.05 (0.04)
Upper 95% CI	–0.07 to 0.07	–0.04 to 0.13
Treatment difference, LS mean (SE)	–0.04 (0.04), *P* = 0.293	
Upper 95% CI	–0.12 to 0.04	

CI = confidence interval; LS = least squares; SD = standard deviation; SE = standard error; SO = sucroferric oxyhydroxide.

[a] 05B Baseline is the last non-missing value prior to or on the date of the first PA-CL-05B study drug intake.

[b] 05B End point is week 28 result or the latest available measurement after 05B baseline when week 28 is missing.

Source: Clinical Study Report, Integrated report for PA-CL-05A and PA-CL-05B.[77]

Limitations

An important limitation of the LTSE is the loss of a large percentage of patients who were originally randomized in 05A (62.2% of patients were enrolled in 05B), which was also differential between treatments (55.1% of the SO arm and 76.8% of sevelamer arm enrolled in 05B). This may enrich the apparent success of the assessment of safety and efficacy by overstating the efficacy and minimizing the harm of both treatments, as those who remain are more likely to adhere to and tolerate treatment, compared with those who discontinued or did not consent to participate further in the LTSE. Moreover, the differential enrolment may bias between-treatment comparisons, and the uncertainty may be further compounded by missing data due to withdrawals during the LTSE, which ultimately results in an issue with the generalizability of these results.

Another issue with generalizability is the application to the Canadian population based on the distribution of subjects by race, as well as the reasons for ESRD. According to the clinical expert, a greater proportion of patients typically seen in Canada are Asian, older, and have ESRD related to diabetes, compared with the demographics of the patient population in the LTSE.

Summary

The LTSE of the original phase III trial did not reveal any new signals regarding the safety of SO for the treatment of hyperphosphatemia in patients with ESRD on dialysis, based on a 28-week assessment, following the 24-week main trial. Moreover, the profile of AEs for patients treated with SO was similar to that of sevelamer, although 8.2% of patients receiving SO reported experiencing diarrhea compared with 5.6% of patients receiving sevelamer. Of note, the most common reported AE in both treatment arms was hyperphosphatemia (12.0% SO and 10.9% sevelamer). Based on the safety analysis of a change in clinical laboratory values from baseline, serum levels of phosphate, calcium, and iPTH were maintained among those who entered 05B. As for iron parameters, transferrin saturation levels were also maintained, but an increase in serum ferritin was reported at the 05B end point. Finally, the treatment difference between SO and sevelamer, based on a change from baseline, was not statistically significant. Overall, the long-term evaluation of treatment with SO was comparable to that of sevelamer in terms of safety and efficacy; a rise in serum ferritin levels and higher incidence of diarrhea as an AE were noted. The use of SO for treatment of hyperphosphatemia would hypothetically be used for the rest of a patient's life, which should be carefully considered when interpreting the results of a 28-week extension study in addition to the main study (for a total of 52 to 55 weeks) in terms of long-term safety and efficacy.

Appendix 7: Tables for Clinical Reference

Table 50: Conversion Factors of Conventional Units to SI units

	Conventional Unit	Conversion Factor	SI Unit
Phosphate (inorganic)	mg/dL	0.3229	mmol/L
Calcium, total	mg/dL	0.2495	mmol/L
PTH	pg/mL	0.106	pmol/L

PTH = intact parathyroid hormone; SI = Système international.

Note: Conventional unit × conversion factor = SI unit.

Source: KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD)[23]

Table 51: Normal and Target Values for Blood Parameters

	Normal Values[a]	Target Values[b]
Phosphorous (serum)	0.81 mmol/L to 1.45 mmol/L (2.5 mg/dL to 4.5 mg/dL)	1.13 mmol/L to 1.78 mmol/L (3.5 mg/dL to 5.5 mg/dL)
Calcium, total (serum)	2.18 mmol/L to 2.58 mmol/L (8.7 mg/dL to 10.3 mg/dL)	—
Calcium, corrected total (serum)	Should be similar to total serum calcium	*Within normal range, preferably toward the lower end*: 2.10 to 2.37 mmol/L (8.4 mg/dL to 9.5 mg/dL)[c]
PTH[d]	1.6 pmol/L to 9.3 pmol/L (15.1 7 pg/mL to 87.7 pg/mL)	—
iPTH	—	16.5 pmol/L to 33.0 pmol/L (150 pg/mL to 300 pg/mL)[c]

iPTH = intact parathyroid hormone; PTH = parathyroid hormone.

Note: According to the clinical expert consulted for this CDR review, total calcium will vary depending on the albumin concentration. In patients with normal albumin, total and corrected calcium should be the same.

[a] Medical Council of Canada and Clinical Study Report (for phosphorus).

[b] Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease.[52]

[c] For Stage 5 chronic kidney disease patients.

[d] In chronic dialysis recipients, the ranges are different. The Kidney Disease Improving Global Outcomes guidelines recommend targeting iPTH to 2X to 9X the upper limit of normal for the assay in use in the lab.

Sources: PA-CL-05A Clinical Study Report,[9] Medical Council of Canada,[79] Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease.[52]

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