A Randomized, Controlled, Three-arm, Open-label, Cross-over Bioequivalence Study Comparing Calcium Acetate Oral Solution and Calcium Acetate Gelcaps in Healthy Volunteers

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ABSTRACT

Background/Aim: Hemodialysis (HD) alone does not adequately control serum phosphorus levels. Hyperphosphatemia in end-stage renal disease is treated by a combination of dietary phosphate restriction and administration of phosphate binders. However, the daily pill burden from phosphate binders has been linked to non-adherence, poor serum phosphorus control, and lower quality of life. A novel formulation of calcium acetate oral solution (Phoslyra™) has been developed to address these clinical challenges. This study was conducted to demonstrate bioequivalence between Phoslyra and PhosLo® Gelcaps (calcium acetate gelcaps).

Methods: A controlled, 3-arm, open label, cross-over study included 46 healthy subjects on a controlled diet randomized into three treatment sequences to receive Phoslyra, PhosLo Gelcaps, or calcium citrate (positive control) with a 5–10 day washout period. Serum phosphorus (P), calcium (Ca), glucose, insulin, and 24 hr urine were measured at baseline and at the end of each 3-day treatment period. The primary objective was to demonstrate the bioequivalence

of calcium acetate oral solution to calcium acetate gelcaps with respect to serum phosphorus and urinary calcium excretion. Secondary objectives were to compare changes in urinary phosphorus, serum calcium, serum glucose, and insulin levels.

Results: Thirty-six subjects completed the study. Calcium acetate oral solution was bioequivalent to calcium acetate gelcaps based on the 90% CIs of the serum phosphorus ratios for C_{max} (peak concentration) and AUC_{0-6} (area under the curve from time 0 – 6 hrs). Urinary calcium level with the calcium acetate oral solution was not more than the level with the calcium acetate gelcaps based on the 90% CIs for R_{max} (maximal rate of urinary excretion) and Ae_{0-6} (cumulative urinary excretion from 0-6 hours). Serum glucose and insulin levels did not indicate any effect of maltitol in the liquid formulation on serum glucose control. C_{max}, and average glucose concentration during the 6-hour sampling interval remained within the strict bioequivalence criteria.

Conclusion: Calcium acetate oral solution was well tolerated with a pharmacodynamic and pharmacokinetic profile equivalent to calcium acetate gelcaps.

(ClinicalTrials.gov NCT00742820)

BACKGROUND

Hyperphosphatemia in end-stage renal disease (ESRD) is due to the inability of the damaged kidneys to eliminate phosphate. In hemodialysis patients, hyperphosphatemia is a major cause of morbidity and mortality, primarily due to cardiovascular (CV) complications[1, 2]. Its management through dietary phosphate intake restriction and/or increasing phosphate elimination via dialysis is frequently insufficient to provide adequate control of serum phosphate. Thus, patients are required to take phosphate binders in an attempt to achieve adequate serum phosphorus levels. Despite the widespread prescription of phosphate binders, the reported prevalence of hyperphosphatemia is as high as 52%[3]. Patients on dialysis have a significant pill burden, and phosphate binders account for about one-half of the daily number of pills[4]. High phosphate binder pill burden is a strong determinant of low patient adherence and poor serum phosphorus (P) control.

PhosLo Gelcaps (calcium acetate) is an approved, effective, oral phosphate binder that is routinely used as a treatment option for hyperphosphatemia in patients with ESRD[5]. When taken with meals, calcium acetate combines with dietary phosphate to form insoluble calcium phosphate, which is excreted in the feces. Most ESRD patients require three to four PhosLo Gelcaps with each meal. A novel oral solution formulation of calcium acetate (Phoslyra) has been developed to reduce the daily pill burden as well as to provide an alternative treatment option for patients who are unable or unwilling to use a solid dosage form.

The primary objective of this study was to demonstrate bioequivalence between the novel calcium acetate oral solution (Phoslyra) and PhosLo Gelcaps in healthy volunteers with respect to serum P levels and urinary calcium (Ca) excretion. Secondary objectives were to compare changes in urinary P and serum Ca, as well as serum glucose and insulin levels.

METHODS

The study was designed as a randomized, controlled, 3-arm open-label, cross-over Phase I study to demonstrate the bioequivalence of Phoslyra to PhosLo Gelcaps in healthy subjects. The study protocol and the informed consents were reviewed and approved by an Institutional Review Board prior to the study. The study was conducted in accordance with Good Clinical Practice (GCP), US Code of Federal Regulations (CFR), including the Declaration of Helsinki, and the International Conference on Harmonization (ICH) Guidelines.

Screening took place up to 25 days prior to enrollment. Subjects of both sexes were included if they were aged 18-75 years, had a serum calcium level of 8.6-10.2 mg/dL, a 25-vitamin D level of 20-100 ng/mL, a 1, 25-dihydroxy vitamin D level of 6-62 pg/mL, a fasting glucose level of 65-99 mg/dL (minimum 8 hr fast), an intact parathyroid

Table 1: *Summary of demographic parameters (ITT subjects)*

Demographic Parameters	Sub-parameter	Total[b] N[c]=46
Age (years)		40.6 ±14.7
Gender	Male	18 (39.1%)
	Female	28 (60.9%)
Race	Black/African American	6 (13.0%)
	Caucasian	40 (87.0%)
Ethnicity	Not Hispanic or Latino	46 (100.0%)
Weight (kg)		72.6 ± 11.4
Height (cm)		170.5 ± 8.4
BMI[a] (kg/m^2)		24.9 ± 2.7

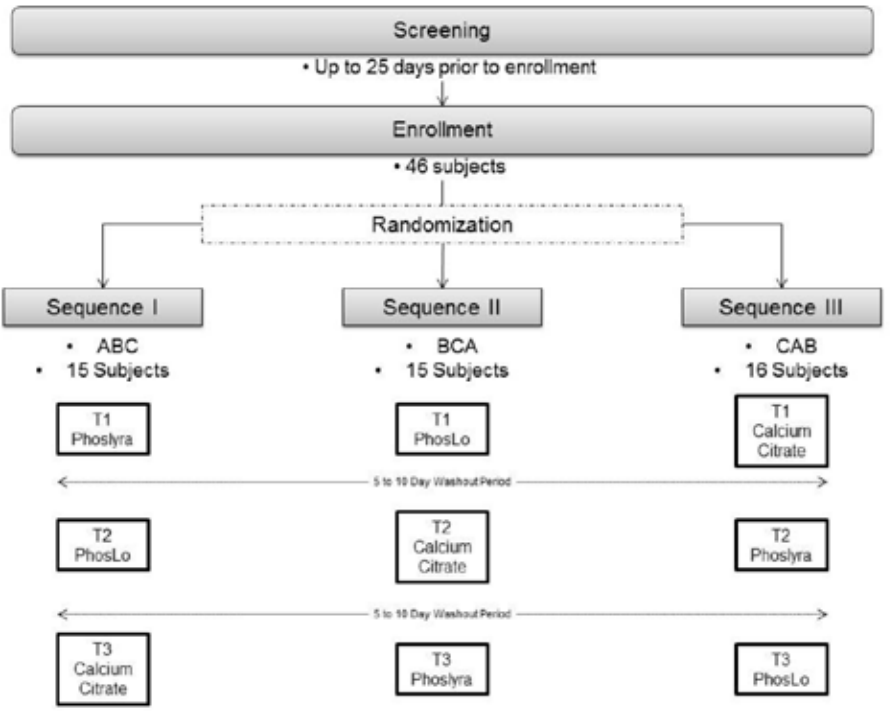
a BMI=body mass index
b Mean±SD for continuous measurements and n(%) for categorical measurements
c N represents the number of total ITT subjects. Subjects included in the PK analysis were similarly distributed by age, gender, race, ethnicity, weight, height, and BMI

Table 2*: Subject Disposition – ITT Subjects*

	Sequence I[a]	Sequence II[b]	Sequence III[c]	Total
Number of subjects randomized	15	15	16	46
Number that did not complete the study at any stage	3 (20%)	3 (20%)	4 (25%)	10 (21.7%)
Reasons for Early Withdrawal				
Total Investigator-initiated discontinuations	1 (6.7%)	2 (13.3%)	0	3 (6.5%)
• Failed to disclose medical history	0	11	0	1
• Syncopal episode	11	0	0	1
• Other – Positive pregnancy test	0	11	0	1
Total Withdrawn Consents	2 (13.3%)	1 (6.7%)	4 (25.0%)	7 (15.2%)
• Phoslyra	1	0	0	1
• PhosLo Gelcaps	1	0	0	1
• Calcium citrate	0	0	2	2
• No Study Medication[1]	0	1	2	3

Percentages were based on number of subjects randomized
[a]Sequence I, from Period 1 to 3: Phoslyra, PhosLo Gelcaps, calcium citrate
[b]Sequence II, from Period 1 to 3: PhosLo Gelcaps, calcium citrate, Phoslyra
[c]Sequence III, from Period 1 to 3: Calcium citrate, Phoslyra, PhosLo Gelcaps
[1]Occured prior to administration of study medication

Figure 1 *– Study Design*



A = Phoslyra; B = PhosLo Gelcaps; C = calcium citrate
T1 = Treatment Period 1; T2 = Treatment Period 2; T3 = Treatment Period 3

hormone level (iPTH) level of 10-65 pg/mL, a serum phosphorus level of 2.5-4.5 mg/dL, and an albumin level of 3.6-5.1 g/dL.

After screening, 46 healthy volunteers were enrolled into the study. Subjects were randomized (1:1:1) to one of three treatment sequences. The treatment sequences were ABC, BCA, and CAB, where A was Phoslyra, B was PhosLo Gelcaps, and C was calcium citrate (Figure 1). The calcium citrate arm provided the positive control for both the serum and urine 24 hr profiles. Each treatment sequence consisted of three treatment periods (one treatment period for each study medication), which were separated by a 5- to 10-day washout period. Further, each treatment period was divided into two stages (Figure 2).

In Stage I (Days -3 to -1), subjects were started on the Controlled Diet. The Controlled Diet consisted of 3 meals per day and was designed to meet the caloric needs for a typical, healthy American adult, with 45-65% of calories from carbohydrates, 10-35% from protein, and 20-25% from fat[6]. The daily totals of dietary phosphorus, calcium, and sodium reflected the current average amounts consumed by an individual on a typical American diet (1,100 to 1550 mg P, 750 to 1,000 mg Ca, and 2,900 to 4,100mg Na)[7]. In Stage II, subjects were started on the study medication and continued on the Controlled Diet.

Study medication dosages with each meal were 30 mL Phoslyra (667 mg calcium acetate per 5 mL), six PhosLo Gelcaps (667 mg calcium acetate/Gelcap), and five-5 calcium citrate caplets (950 mg calcium citrate/caplet), resulting in a daily dose of 90 mL Phoslyra and 18 PhosLo Gelcaps. The calcium acetate doses selected in the study were on the higher end of the dosing spectrum; most ESRD patients require only 3 – 4 PhosLo Gelcaps with each meal. Ap-

***Table 3**: Bioequivalence Assessment of Serum Phosphorus – Adjusted to Baseline (0 – 6hrs)*

Parameter	C_{max} (n=35)		AUC_{0-6} (n=35)	
Treatment	Phoslyra (A)	PhosLo Gelcap (B)	Phoslyra (A)	PhosLo Gelcap (B)
Geometric LS mean, adjusted	1.05	1.10	0.96	0.99
Ratio (A)/(B) (in %)	95.37		97.21	
90% CI	(92.02, 98.88)		(93.47, 100.91)	

C_{max}=peak concentration; AUC^{0-6}= area under the curve from time 0 – 6hrs; LS=least squares; CI=confidence interval 6-hour serum P measurement was missing for one subject

***Table 4**: Bioequivalence Assessment of Urinary Calcium – Adjusted to Baseline (0 – 6hrs)*

Parameter	R_{max} (n=32)		Ae_{0-6} (n=32)	
Treatment	Phoslyra (A)	PhosLo Gelcap (B)	Phoslyra (A)	PhosLo Gelcap (B)
Geometric LS mean, adjusted	1.71	2.03	1.81	2.11
Ratio (A)/(B) (in %)	84.32		85.95	
90% CI	(62.99, 112.89)		(67.34, 109.72)	

R_{max}=maximal rate of urinary excretion; Ae_{0-6}¬=cumulative urinary excretion from 0 – 6hrs; LS=least squares; CI=confidence interval Four subjects (2 in period B and 2 in period A) had no urine collection at the 4 – 6hr time interval

***Table 5:** Bioequivalence Assessment of Urinary Phosphorus – Adjusted to Baseline (0 – 6hrs)*

Parameter	R_{max} (n=28)		Ae_{0-6} (n=28)	
Treatment	Phoslyra (A)	PhosLo Gelcap (B)	Phoslyra (A)	PhosLo Gelcap (B)
Geometric LS mean, adjusted	0.67	0.79	0.58	0.65
Ratio (A)/(B) (in %)	84.55		89.59	
90% CI	(62.74, 113.94)		(64.47, 124.50)	

R_{max}=maximal rate of urinary excretion; Ae_{0-6}¬=cumulative urinary excretion from 0 – 6hrs; LS=least squares; CI=confidence interval A total of 8 subjects when treated with (A) or (B) had either no urine collection at 4 – 6hr time interval, or the concentration levels < LOQ (limit of quantification) at all 3 collection intervals (0–2, 2–4, and 4–6 hour time intervals)

***Table 6**: Bioequivalence Assessment of Serum Calcium – Adjusted to Baseline (0 – 6hrs)*

Parameter	C_{max} (n=36)		AUC_{0-6} (n=36)	
Treatment	Phoslyra (A)	PhosLo Gelcap (B)	Phoslyra (A)	PhosLo Gelcap (B)
Geometric LS mean, adjusted	1.02	1.03	0.95	0.98
Ratio (A)/(B) (in %)	99.04		97.62	
90% CI	(95.30, 102.93)		(95.46, 99.83)	

C_{max}=peak concentration; AUC_{0-6}= area under the curve from time 0 – 6hrs; LS=least squares; CI=confidence interval

proximately equal amounts of elemental Ca, 1,000 mg, were administered in each dose: 1,014 mg in Phoslyra and PhosLo Gelcaps, and 1,000 mg in calcium citrate.

From Day 3 to Day 4 of each period, subjects consumed the Controlled Diet provided by the metabolic kitchen either at home or at the Unit. The Controlled Diet was the same for each treatment period. On Days -3 and -2, subjects consumed their Controlled Diets at home. Prior to the evening meal on Day -2, subjects returned to the Unit and remained there until after breakfast on Day 0. On Day -1, 24-hr serum and urine samples were collected for the baseline assessment. Subjects received their first dose of the study medication along with their morning meal on Day 0. Subjects were then provided with packaged meals of the Controlled Diet to take home for the remainder of Day 0 through the afternoon of Day 2. Study medication was taken three times daily (t.i.d) with each of the provided meals. Prior to the evening meal on Day 2, subjects were readmitted to the Unit. A dose of the study medication was administered to the subjects along with the evening meal on Day 2, and a final dose along with the morning meal on Day 3. A 24-hr pharmacokinetic (PK) sampling and urine collection period followed the final dose of the study medication. On Day 4, subjects were discharged in the morning to begin their 5-10 day washout period, and they returned to their self-selected diet.

Serum glucose was measured to evaluate if the liquid formulation might cause hyperglycemia. Insulin levels were measured to detect any potential effects of Phoslyra on serum insulin.

Statistical Analysis

The full analysis set was based on the intent-to-treat (ITT) principle and included all subjects who met eligibility criteria and were randomized into the study. The PK analysis set consisted of the subset of full analysis set subjects who completed all PK assessments and the three dosing periods. Sample size calculation was based on the 2-period, 2-sequence crossover design, since

Figure 2 *- Treatment Period*

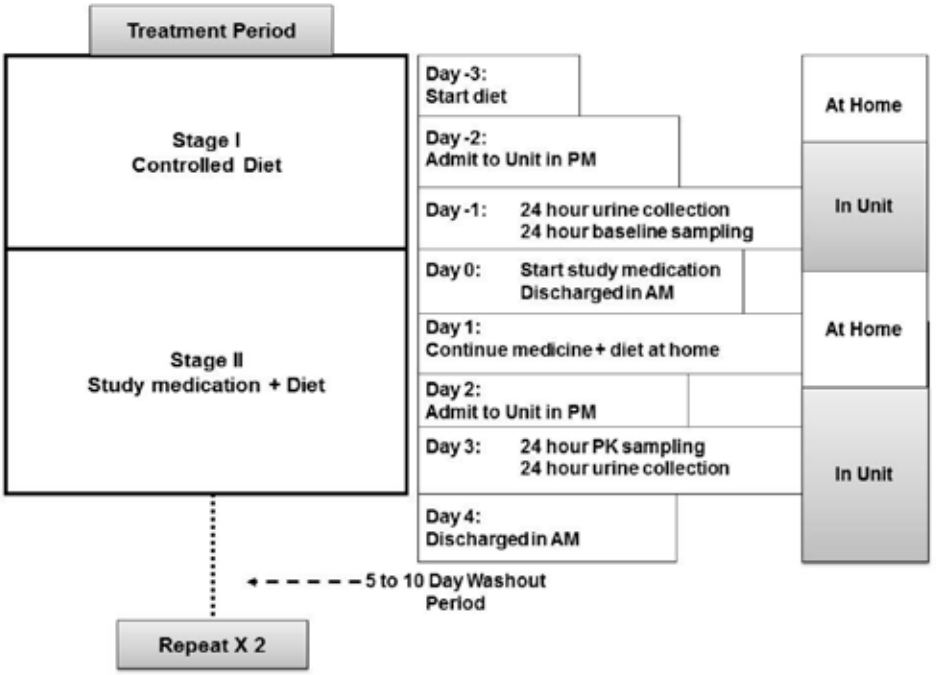


Table 7: *Summary of Study-Related Adverse Events (Stage I) – ITT Subjects*

Stage	MedDRA Preferred Term All Adverse Events (Study-Related)	Treatment Groups		
		Phoslyra	PhosLo Gelcaps	Calcium Citrate
Stage I – Controlled Diet	N	40	40	40
	Headache	5 (5)	2 (2)	3 (3)
	Nausea	0	1 (1)	0
	Nasal Congestion	1 (1)	0	0
	Fatigue	0	1 (1)	0

X(Y) = number of events (number of subjects)

the comparison of primary interest was between Phoslyra and PhosLo Gelcaps. The following design characteristics were used for sample size calculation for bioequivalence using rate of absorption (C_{max}) as the primary measure of bioequivalence under a multiplicative model.

The primary analysis assessed the bioequivalence between calcium acetate oral solution and calcium acetate gelcaps on PK parameters up to 6 hours post dose with baseline adjustment using the ratio of Days 3 to -1. A 90% confidence interval (CI) was derived using a linear mixed effect model. The variance components were used as the covariance matrix for the analysis. Bioequivalence was concluded if the lower and upper bounds of a 90% CI for the ratios C_{max}, R_{max}, Ae_{0-6}, and AUC_{0-6} were within 80–125%.

The secondary comparisons of interest were the bioequivalence of the calcium acetate oral solution to calcium acetate gelcaps with respect to levels of urinary P and serum Ca, and the comparison of serum glucose and insulin level measurements.

RESULTS

There were 46 subjects in the ITT population, and 36 subjects in the PK evaluable population. Ten patients were withdrawn from the study after randomization: 3 from Sequence I, 3 from Sequence II and 4 from Sequence III, leaving 12 subjects in each sequence. Of the withdrawn subjects, 7 (15.2%) withdrew consent and 3 (6.5%) subjects were withdrawn by request of the Investigator. The Investigator-initiated withdrawals occurred prior to administration of any study medication, during Stage I on Day -1. Demographic information and subject disposition are summarized in Tables 1 and 2.

Analysis for the two primary endpoints showed that Phoslyra was bioequivalent to PhosLo Gelcaps based on the 90% CIs of serum phosphorus ratios for C_{max} and AUC_{0-6} (Table 3), and urinary Ca with Phoslyra was not more than that with PhosLo Gelcaps, as the 90% CIs of ratios for R_{max} and Ae_{0-6} were within the upper bound of 125% (Table 4). However, the lower values of the 90% CIs for R_{max} and Ae_{0-6} fell below the lower bound of 80%, indicating that the Phoslyra cohort excreted less Ca in the urine than the PhosLo Gelcaps cohort.

Analysis for the secondary endpoints showed that urinary phosphorus with Phoslyra was not more than that with PhosLo Gelcaps, as the 90% CIs of ratios for R_{max} and Ae_{0-6} were within the upper bound of 125%. However, the lower values of the 90% CIs for R_{max} and Ae_{0-6} fell below the lower bound of 80%, indicating that the Phoslyra cohort excreted less urinary P than the PhosLo Gelcaps (Table 5). Serum Ca with Phoslyra was bioequivalent to that of PhosLo Gelcaps based on the 90% CIs of rations for C_{max} and AUC_{0-6} (Table 6).

The C_{max} and mean glucose concentration during the 6-hour sampling interval were within the strict bioequivalence crite-

ria. However, C_{max} and mean insulin concentration following the Phoslyra treatment, while not significantly different, were 17% and 11% lower, respectively, compared to PhosLo Gelcaps. Insulin levels were within normal pre- and postprandial ranges. The insulin levels demonstrated troughs between meals and postprandial peaks, indicating normal insulinemic responses. No subjects exhibited hyperglycemia, and only 7.6% of 2033 measurements fell in the hypoglycemic range of <65 mg/dL.

There were no deaths or serious adverse events (SAE) in this study. Review of adverse events (AEs), vital signs, and safety laboratory parameters did not raise any safety issues related to the study medication of interest.

In both the calcium acetate oral solution (Phoslyra) and the calcium acetate gelcaps (PhosLo) treatment groups, gastrointestinal (GI) symptoms were the most common (Table 7). The GI-related AEs for subjects who received calcium acetate oral solution included nausea (9 subjects), diarrhea (5 subjects), abdominal pain (2 subjects), and gastroesophageal reflux disease (2 subjects). For the subjects who received calcium acetate gelcaps, the GI-related AEs included nausea (10 subjects) and vomiting (2 subjects). Subjects who received calcium citrate had mild AEs that included 2 subjects with headache and 2 subjects with anorexia. Diarrhea was found to be more common in the Phoslyra group. However, these episodes of diarrhea were mild, transient, and resolved without sequelae.

DISCUSSION

Phosphate retention in patients with ESRD results in hyperphosphatemia, which can lead to secondary hyperparathyroidism, renal osteodystrophy, soft tissue calcification, and mortality. Phosphate binders, which inhibit the absorption of dietary phosphate, are important therapeutic tools in controlling serum P. The pill burden associated with phosphate binder therapy contributes to increased optional fluid intake[8], which may contribute to interdialytic weight gain (IDWG) in dialysis patients, increasing their CV complications[9].

The present study evaluated the bioequivalence between Phoslyra and PhosLo Gelcaps. Two primary endpoints were evaluated using standard bioequivalence techniques: 1) serum P (to assure pharmacodynamic equivalence) and 2) urinary Ca (to assure pharmacokinetic bioequivalence).

In normal health, homeostatic mechanisms maintain serum calcium within a normal range. This value never goes beyond 2% from its set point[10]. Hence, serum calcium is a poor surrogate measure of oral calcium intake[11] and cannot be measured to determine calcium balance or total body calcium content[12]. Urinary Ca was selected as the primary pharmacokinetic bioequivalence parameter because of its limited sensitivity to the strong homeostatic controls in a normal, healthy human. Urinary P and serum Ca were selected as secondary endpoints to demonstrate comparability of the two formulations.

The inclusion of the calcium citrate treatment arm provided a positive control to assure assay sensitivity, as this agent has been demonstrated to yield detectable increases in plasma and urinary Ca levels with supplementation[13]. Observation of these changes in the present study population provided confidence that a finding of "no difference" between Phoslyra and PhosLo Gelcap formulations could not be attributed to methodological flaws in trial design and/or conduct.

The assessments of serum glucose and insulin levels were added to the protocol to ensure the maltitol in the novel formulation did not affect glucose homeostasis.

Based on the serum phosphorus C_{max} (peak concentration) and the AUC_{0-6} (area under the curve from time 0 – 6hrs), the analysis of the primary endpoints demonstrated bioequivalence between Phoslyra and PhosLo Gelcaps.Comparisons of urinary excretion of Ca between the calcium acetate oral solution and PhosLo Gelcaps did not demonstrate traditional bioequiva-

lence. Geometric least square (LS) means for R_{max} and $Ae_{0\ 6}$ in the Phoslyra cohort were approximately 16% and 14% lower, respectively, than in the PhosLo Gelcaps cohort, and the lower limit for the 90% CIs (63% for R_{max} and 67% for Ae_{0-6}) fell below the standard bioequivalence range (80% to 125%). This indicates that the Phoslyra cohort excreted less Ca in the urine than the PhosLo Gelcaps cohort meaning that less Ca was absorbed from the GI tract. This may suggest that more Ca was excreted in the stools as insoluble calcium phosphate.

Of the secondary endpoints, strict bioequivalence was demonstrated for serum Ca between Phoslyra and PhosLo Gelcaps. However, the geometric LS means for R_{max} and Ae_{0-6} for urinary P following Phoslyra were approximately 15% and 10% lower, respectively, than PhosLo Gelcaps, and the lower limit for the 90% CIs (63% for R_{max} and 64% for Ae_{0-6}) fell below the standard bioequivalence range. The finding of lower urinary P is consistent with the lower urinary Ca observation, once again suggesting that more Ca might have been excreted in the stools as Ca x P product. Clinically, this is a desired finding since the purpose of Phoslyra being to decrease dietary P; it highlights the ability of calcium acetate oral solution to effectively bind dietary P in the GI tract.

Analysis of safety endpoints in this study did not raise any drug related safety concerns. Upon review of AEs (Table 7), vital signs, and safety laboratory parameters, Phoslyra was found to be well-tolerated with no safety issues. It is also worth noting that the daily doses of 90 mL Phoslyra and 18 PhosLo Gelcaps used in this study are higher than the total expected daily dose of 60 mL Phoslyra and 12 PhosLo Gelcaps in ESRD patients. The diarrhea episodes resolved without sequelae and did not raise any significant clinical concerns. As with other sugar alcohols, maltitol may produce a laxative effect when consumed at high levels. Maltitol's laxative threshold (suggested daily dose unlikely to cause GI symptoms) is approximately 20–30 g/day, and trial subjects ingested 18 g (90 mL Phoslyra/day). It is expected that typical ESRD patients will consume a smaller volume (45–60 mL Phoslyra/day, containing 9–12 g maltitol). Furthermore, it has been reported that long-term consumption of sugar alcohols can lead to adaptation and improved tolerance[14].

The assessments of serum glucose and insulin levels were added to the protocol as additional safety endpoints to ensure the maltitol in the novel formulation did not affect glucose homeostasis. The analysis of the 6-hour glucose and insulin levels in serum did not indicate any significant influence of maltitol on serum glucose control in the Phoslyra cohort. Subjects with instances of laboratory hypoglycemia had no clinical symptoms and were regarded as a "normal" occurrence in healthy volunteers. Several studies of hypoglycemia in normal, healthy subjects support the frequency of hypoglycemia found in this bioequivalence trial[15, 16, 17, 18], and the number of measurements (155/2033) of hypoglycemia were within the expected ranges for normal healthy subjects as described in the literature. Pre- and postprandial insulin levels were in the normal ranges in both the Phoslyra and PhosLo Gelcaps cohorts and demonstrated troughs between meals and postprandial peaks, indicating normal insulin responses.

CONCLUSION

Calcium acetate, available commercially as PhosLo Gelcaps, is accepted as an efficacious therapeutic agent in reducing the absorption of dietary P. A novel oral solution formulation of calcium acetate, Phoslyra, was developed to reduce the daily pill burden in an attempt to facilitate patient adherence. Phoslyra (calcium acetate oral solution) was found to be safe and similar in its pharmacodynamic and pharmacokinetic profile to PhosLo Gelcaps. Strict bioequivalence between the two treatments was demonstrated for serum P and serum Ca. Less urinary P and urinary Ca excretion was found in the Phoslyra cohort compared to the PhosLo Gelcaps cohort. While the differences may be considered minor, they may

be related to the potentially more efficient binding of dietary P in the GI tract following Phoslyra administration.

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Declaration of competing interests:

All authors are or have been employees of Fresenius Medical Care North America.

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