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APPLICATION NUMBER:

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**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 22-372	Submission Date(s): July 1, 2008
Brand Name	SuPrep Bowel Prep Kit
Generic Name	sodium sulfate, potassium sulfate, magnesium sulfate
Reviewer	PeiFan Bai, Ph.D.
Team Leader	Sue-Chih Lee, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND division	Division of Gastroenterology Products
Sponsor	Braintree Laboratories, Inc
Submission Type; Code	Original
Formulation; Strength(s)	Liquid concentrate of sodium sulfate, USP (17.51 g), potassium sulfate, FCC (3.13 g), magnesium sulfate anhydrous, USP (1.6 g) in 170.41 g water per 6oz bottle
Indication	Gastrointestinal lavage prior to colonoscopy in adults

Table of Contents

Table of Contents	1
1 Executive Summary	2
1.1 Recommendation	2
1.2 Phase IV Commitments	2
1.3 Regulatory Backgrounds.....	2
1.4 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings	2
2 Question Based Review	3
2.1 General Attributes	3
2.2 General Clinical Pharmacology.....	6
2.3 General Biopharmaceutics.....	22
2.4 Analytical Section.....	23
3 Detailed Labeling Recommendations	24
4 Summary of Individual Studies and Clinical Development.....	25

1 Executive Summary

1.1 Recommendation

The application is considered acceptable from the clinical pharmacology perspective provided the labeling comments are adequately addressed by the sponsor.

1.2 Phase IV Commitments

There will be no phase IV Commitments needed to address any clinical pharmacology concerns.

1.3 Regulatory Backgrounds

In a March 26, 2007 end-of-Phase 2 teleconference FDA requested that Braintree conduct studies in people with hepatic impairment and renal insufficiency and examine the effects of the to-be-marketed formulation on "serum/plasma electrolyte profiles (sodium, potassium, magnesium and sulfate)" in these populations.

The FDA reviewed Braintree's proposed protocol and suggested to the sponsor in a July 23, 2007 letter that the Agency recommended a study in patients with moderate renal impairment rather than in patients requiring dialysis. Additionally, The FDA suggested that patients with hepatic impairment need not be studied in comparison to normal volunteers. The sponsor did not adopt the FDA's suggestion and completed its study in hepatic impairment patients anyway. The results are submitted to this NDA.

1.4 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Product: SuPrep Bowel Prep Kit is a colon cleansing preparation consisting of two equal half doses. Each half dose consists of 17.51 g sodium sulfate, 3.13 g potassium sulfate, and 1.6 g magnesium sulfate. SuPrep Bowel Prep Kit may be taken in an overnight or one day oral preparation. Dosing instruction: for each half dose, pour the contents of one 6oz bottle of SuPrep Bowel Prep Kit into the mixing cup provided. One fluid oz equals 29.57 ml. Fill the cup with water to the 16oz fill line and drink the entire 16oz volume (b) (4). Drink two additional 16oz cups of water (b) (4).

Pharmacokinetic studies Following an overnight preparation of the to-be-marketed formulation, the mean (CV%) sulfate pharmacokinetics (PK) parameters are listed below:

Mean (CV%) sulfate PK parameters (corrected for pre-dose sulfate level)

	Mild/moderate hepatic impairment	Healthy subjects	Moderate renal impairment
C _{max} (μmol/L)	560.2 (27.27%)	499.50 (33.03%)	717.0 (37.77%)
AUC(0-tau) (μmol*hr/L)	10751.75 (26.77%)	8,029.88 (42.65%)	12,332.95 (34%)
T _{max} (hr)	14.2 (35.27%)	16.80 (48.47%)	17.5 (16.85%)
T _{1/2} (hr)	5.58 (41.36%)	8.51 (53.76%)	10.16 (91.76%)

AUC(0-tau): AUC over the 24-hr post dose. Hepatic impairment group consisted of 1 moderate impairment and 5 mild impairment patients.

In general, serum sulfate levels increased within one hour after each half-dose and returned to the pre-dose ranges by Day 6. After the 1st half dose, serum sulfate concentrations peaked 4-10 hours following the first dose. Serum sulfate concentrations did not return to the pre-dose levels before the 2nd half dose, and rose even further higher after the 2nd half dose. The concentrations increased until Tmax and began declining thereafter. Serum sulfate did decline to the predose level by day 6 in all three groups.

Mean (CV%) cumulative amounts of urinary sulfate excretion with the 30-hr period following dosing were 6.5g (21.37%), 6.04g (61.93%), and 5.1g (30.67%) in mild or moderate hepatic impairment patients, healthy subjects, moderate renal impairment patients, respectively. Based on the 29.7 g sulfate dose in the SuPrep Bowel Prep Kit, the cumulative % dose excreted in the urine within 30 hrs after first half dose without correction for basal sulfate secretion was approximately 20.3%-21.9% in both healthy and mild or moderate hepatic impairment subjects and was 17% in renal impairment patients.

No treatment-emergent differences between either of the two patient groups and the healthy volunteers with regard to the serum levels of sodium, potassium and magnesium.

2 Question Based Review

2.1 General Attributes

2.1.1 What are the components and composition of SuPrep® Liquid Concentrate?

Material (quality)	Quantity per 6.0 oz bottle	Quantity per dose (two 6oz bottle)	Function
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Sodium Sulfate, USP	17.510 g	35.020 g	Active ingredient
Potassium Sulfate, FCC	3.130 g	6.260 g	Active ingredient
Magnesium Sulfate Anhydrous, USP	1.600 g	3.200 g	Active ingredient
Sodium Benzoate, NF	(b) (4)		
Sucralose			
Malic Acid, FCC			
Citric Acid, USP			
Purified Water, USP			

The proposed marketing package for distribution is a carton containing:

- Two (2) 6 oz light amber (b) (4) bottles containing drug product
- One (1) (b) (4) mixing cup with a 16 oz fill line (b) (4)

2.1.2 What is the proposed indication of SuPrep®

SuPrep Bowel Prep Kit is a gastrointestinal lavage preparation. The proposed indication is cleansing of the colon as a preparation for colonoscopy in adults.

2.1.3 What is the proposed mechanism of action of SuPrep?

SuPrep consists of sulfate anions which are poorly absorbed and used as the dominant osmotic agent for gastrointestinal cleansing. Since there is a limited capacity for intestinal absorption of sulfate, this anion can exert a laxative action when there is sufficient unabsorbed sulfate in the intestine. The osmotic effect of SuPrep thus increases the water content of stool and causes a watery diarrhea.

2.1.4 What are the proposed dosage and route of administration?

The proposed treatment regimen of SuPrep Bowel Prep Kit consists of two half doses. Each half dose consists of 17.51 g sodium sulfate, 3.13 g potassium sulfate, and 1.6 g magnesium sulfate. SuPrep Bowel Prep Kit may be taken in an overnight (b) (4) oral preparation. (b) (4)

Overnight Preparation:

On the day prior to colonoscopy: Pour the contents of one 6oz bottle of SuPrep Bowel Prep Kit into the mixing cup provided. One fluid oz equals 29.57 ml. Fill the cup with water to the 16oz fill line and drink the entire 16oz volume (b) (4). Drink two additional 16oz cups of water (b) (4).

Day of colonoscopy: The morning of colonoscopy (12 hours after evening dose): pour the contents of the second 6oz bottle of SuPrep Bowel Prep Kit into the mixing cup

provided. Fill the cup with water to the 16oz fill line and drink the entire 16oz volume (b) (4). Drink two additional 16oz cups of water (b) (4).

(b) (4)

2.1.5 What are the absorption and elimination characteristics of sulfate ion?

According to the information provided by the sponsor, the main route of sulfate ion elimination after intravenous administration is renal excretion, with 60-80% of the dose eliminated renally. It is expected that renal insufficiency would be related to an increased level of serum sulfates with normal dietary intake. Absorption of sulfate from its magnesium salt appears to be less than other salts; only about 30% was detected in the urine 24 hours after an oral dose of 13.9g. According to Study BLI800-202 with the to-be-marketed formulation in healthy subjects who received two half doses separated by 12 hrs, the cumulative % dose of sulfate secreted in the urine within 30 hrs after the first half dose was approximately 20% with both half doses included in the calculation.

2.1.6 What is the sponsor's rationale of developing sulfate into a product?

According to the sponsor, the amount of phosphate absorbed and the extent of hyperphosphatemia appear to contribute to precipitation of calcium phosphate crystals in the kidney, causing "acute phosphate nephropathy". An improved product would be of low-volume and not produce clinically significant fluid or electrolyte shifts. Sulfate salts are generally more poorly absorbed than phosphates. Sulfate salts would therefore be expected to produce fewer electrolyte and fluid shifts than phosphates.

2.1.7 What is the regulatory background?

In a March 26, 2007 end-of-Phase 2 teleconference FDA requested that Braintree conduct studies in people with hepatic impairment and renal insufficiency and examine the effects of the to-be-marketed formulation on "serum/plasma electrolyte profiles (sodium, potassium, magnesium and sulfate)" in these populations.

The FDA reviewed Braintree's proposed protocol and suggested to the sponsor in a July 23, 2007 letter that the Agency recommended a study in patients with moderate renal impairment rather than in patients requiring dialysis. Additionally, The FDA suggested that patients with hepatic impairment need not be studied in comparison to normal volunteers. The sponsor did not adopt the FDA's suggestion and completed its study in hepatic impairment patients anyway. The results are submitted to this NDA.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the critical clinical pharmacology studies used to support dosing or label claims?

Design of study BLI800-202 (pharmacokinetics and special populations): This was a single center, open label, safety and pharmacokinetics (PK) study of the effects of administering BLI800 to patients with mild-moderate hepatic impairment ((M/MHD-Child-Pugh Stage A or B) or with moderate renal disease in comparison to healthy matched controls. No concomitant laxative treatment was allowed starting five days before admission. The objective of this study was to evaluate and compare the effects on safety measures and clinical chemistry after BLI800 in the proposed patients and healthy controls (N=6 each group). The to-be-marketed formulation was used. The total confinement period was 46 hours.

A total of 18 subjects completed the study. No patients withdrew from the study after receiving medication. BLI800 was administered in two 6-ounce half doses separated by 12 hours. This dosing regimen was investigated in Phase III trials (BLI800-301 and BLI800-302) as well.

6 AM Day 1 Drug Administration

The contents of the 6-ounce bottle of BLI800 (half dose 1) was poured into a mixing cup and then the cup was filled with water to the 16 ounce fill line. Beginning at 6 AM, the patients drank the entire 16-ounce volume over the next 15 minutes, followed by two additional 16-ounce glasses of water over the next 1-3 hours. Additional amounts of water or clear liquids were allowed at any time and in any amounts.

6 PM Day 1 Drug Administration

The second half of the BLI800 dose was administered to the patients at 6 PM as described above.

Meal: A light dinner was served before 8 PM at the Clinical Research Unit (CRU) and the participants did not consume any solid food thereafter until 8 PM on Day 1. Mineral water or other liquids containing sulfate and/or magnesium were not allowed. Patients were permitted to consume only water or clear liquids (non-caffeinated soda, coffee, tea or juices or non-dairy) ad libitum from 8 PM on Day -1 until 8 PM on Day 1 when they had a standard dinner. A standard breakfast (before 8 AM) and lunch (before 12 Noon) were available on Day 2. Patients were excused from the clinic at 12 Noon on Day 2.

Study Demographics

Study Demographics

	Hepatic Disease Patients (N=6)	Renal Disease Patients (N=6)	Healthy Volunteers (N=6)
Age (years)¹ Mean (SD) ²	51.2 (5.74)	53.8 (7.96)	49.0 (6.93)
Gender Female/Male	4/2	3/3	4/2
Race Caucasian Black or African American Other	5 1 0	1 4 1	4 2 0
Ethnicity Non Hispanic or Latino Hispanic or Lation	6 0	5 1	6 0
Height (in) Mean (SD)	66.96 (2.98)	67.18 (4.31)	66.88 (3.77)
Weight (lbs) Mean (SD)	175.47 (26.17)	210.53 (29.03)	197.10 (68.06)
GFR (ml/min/1.73m²) Mean (SD)	88.77 (14.54)	43.87 (2.65)	93.33 (16.93)

(Reference Table 15.1.2 and 15.2.1.1)

(1) Age is calculated using date of birth and Visit 1 date. (2) SD = Standard Deviation

There was only one elderly patient (# 005, 66 years old) so it is not possible to determine the effects of age on the outcomes. Due to the small sample size of the study, it was not possible to determine the effect of gender or race/ethnicity on the safety outcomes.

Though the two half doses were separated by 12 hours, they were administered on the same day, (b) (4).

. Overall, the study design to evaluate the pharmacokinetics of sulfate in healthy subjects, renal impairment patients, and hepatic impairment patients is deemed acceptable.

2.2.2 What are pharmacokinetic characteristics of sulfate ion after oral administration of Suprep® in healthy subjects?

In Study BLI800-202, 6 healthy subjects (2 males, 4 females) participated and completed the study. The to-be-marketed formulation was administered. Blood samples were collected approximately 10 minutes before Dose 1 (first 6-ounce half dose), at 1,2,4, 8, and 10 hours thereafter and then at approximately 10 minutes prior to Dose 2 and at 1, 2,4,8, 12 and 18 hours post Dose 2 (second 6-ounce half dose). Additional samples were collected before 12 Noon on Days 3 and 6. Urine was collected prior to Dose 1 (a single void) and then 0-6, 6-12, 12-24 and 24-30 hours thereafter. Single void samples were also collected before 12 noon on Days 3 and 6. In the FDA's letter of July-23, 2007, the Agency recommended additional two blood samples after the second dose with one at one hour post-dose and another between 12 and 30 hours post does. The sponsor did include those two time points in its blood draws. In this study, safety assessment included 12 lead ECG, vital signs, adverse events, hematology, blood chemistry and urinalysis.

Serum sulfate level

Mean (CV%) pre-dose levels in 6 healthy volunteers were 335.0 µmol/L (34.44%) with individual data being 141 µmol/L, 271 µmol/L, 350 µmol/L, 368 µmol/L, 413 µmol/L, and 467 µmol/L. The range generally described in healthy people subjects are 240-420 µ.mol/L. The sponsor commented that the pre-dose levels in the healthy participants were mostly fall in the normal range and did not provide any comments why one subject's sulfate level was slightly higher than the normal range.

After correcting for the individual patient's pre-dose serum sulfate levels, the arithmetic means (CV%) of sulfate pharmacokinetic parameters were calculated, as shown below.

Mean (CV%) sulfate PK parameters (corrected for pre-dose sulfate level)

Cmax (µmol/L)	499.50 (33.03%)
AUC(0-tau) (µmol*hr/L)	8029.88 (42.65%)
Tmax (hr)	16.80 (48.47%)
T1/2 (hr)	8.51 (53.76%)

AUC(0-tau): AUC over the 24-hr post dose.

By pre-noon on Day 3 and Day 6, mean (SD) serum sulfate concentrations were 365.7 (102.72) µmol/L and 349.2 (90.44) µmol/L in healthy subjects, respectively, showing no statistical differences from their mean (SD) predose concentrations of 335 (115.37) µmol/L. Serum sulfate declined to the predose level by day 6.

Urinary sulfate excretion

The sulfate concentrations at predose, on day 3, and on day 6 are listed below.

Mean (CV%) urine sulfate concentrations (mg/dL)

Predose 1	131.20 (35.81%)
Day 3	145.62 (76.24%)
Day 6	134.65 (55.49%)

The cumulative amount of sulfate excreted in urine over the 30-hr period after the first 6-ounce half dose was calculated by assuming that urinary sulfate is derived only from BL1800 without corrections for basal endogenous sulfate elimination.

Mean (CV%) urine sulfate excretion within 30 hrs after first dose

Cum Ae ₍₀₋₃₀₎ mg	6037.98 (61.93%)
Cum % dose excreted (% of 1 st dose) (0-30hrs) mg	20.35 (61.85%)
Excretion rate (mg/hr)	201.27 (61.93%)

Reviewer's comments: The urine sulfate concentrations were higher on day 3 than predose, and declined to close to predose level on day 6.

Since the subjects received two 6-ounce half doses separated by 12 hrs, the cumulative % dose of sulfate secreted in 30 hrs after the first dose might have included some amount of the second dose. The sponsor did correctly use the amount of 29.7 g sulfate (23.68 sulfate from 35.02 g sodium sulfate, 3.46 g sulfate from 6.26 g potassium sulfate,

and 2.56 g from 3.2 g magnesium sulfate) contained in the to-be-marketed formulation of for its calculation of the cumulative % dose excreted.

The intestinal transit of the second half dose might have been much faster than the first half dose based on the observation that the time to first bowel movement was short (1.54 hrs) in group 2 of Study BLI800-101, not long after the 1st half dose of an experimental formulation, which contained the same amount of sulfate (29.7 g) but different relative amounts of sodium sulfate and magnesium sulfate. Group 2 of Study BLI800-101 received the same overnight administration And the design as this study. It is likely the second half dose was less absorbed than the first half dose due to a shorter transit time induced by 1st half dose. The Cum Ae% secreted in urine within the 30 hrs is not an accurate parameter to reflect low oral absorption, but rather is merely a rough estimate.

2.2.3 What are the impacts of renal or hepatic impairment on the pharmacokinetics of Suprep®?

In Study BLI800-202, the patients with hepatic or renal impairment were also included. In the hepatic impairment group, five patients with hepatic impairment had Class A Child- Pugh scores (5-6 points) while one had moderate impairment (Class B; 8 points). Hepatitis C was the primary disease associated with hepatic impairment in 5/6 patients; alcoholic cirrhosis contributed to the other case. Moderate renal impairment group had their GFRs of 42-48 ml/min.

Pre-dose level of serum sulfate

Mean (CV%) pre-dose levels in 6 healthy volunteers, 6 hepatic impairment, and 6 renal impairment patients were 335.0 µmol/L (34.44%), 407.3 µmol/L (13.41%), 607.0 µmol/L (31.66%), respectively. The pre-dose levels of sulfate were much higher in patients with renal impairment than in normal subjects.

Post-dose level of serum sulfate

After correcting for the individual patient's pre-dose serum sulfate levels, the arithmetic means (CV%) of sulfate pharmacokinetic parameters were calculated, as shown below.

Mean (CV%) sulfate PK parameters (corrected for pre-dose sulfate level)

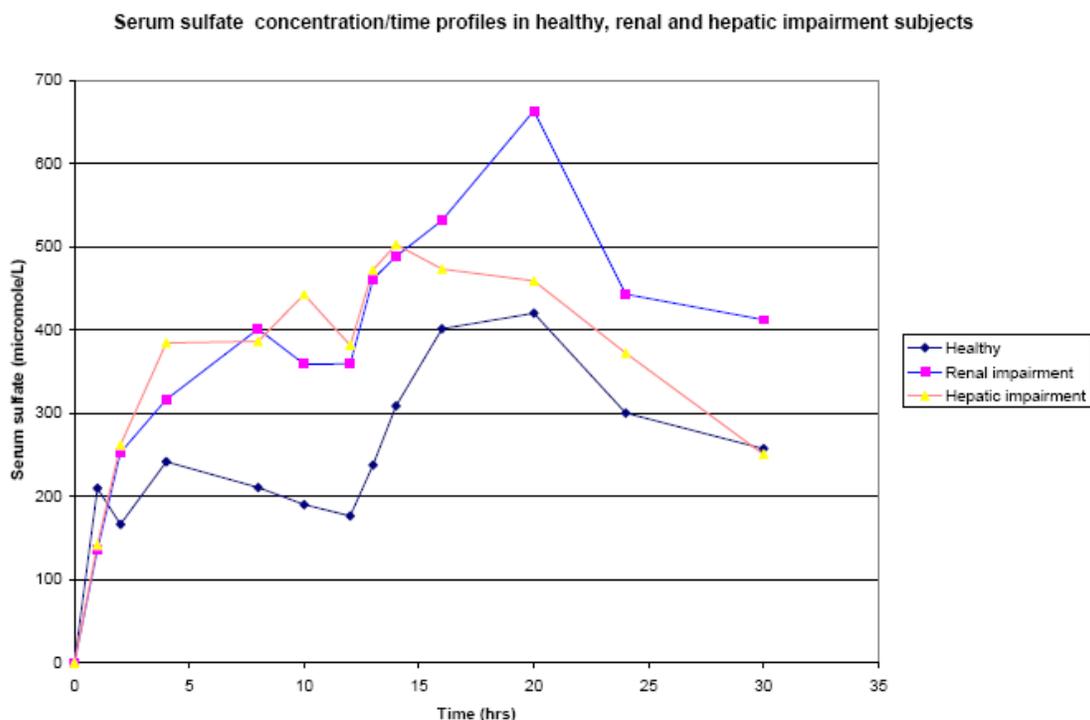
	Mild/moderate hepatic impairment	Healthy subjects	Moderate renal impairment
C _{max} (µmol/L)	560.2 (27.27%)	499.50 (33.03%)	717.0 (37.77%)
AUC(0-tau) (µmol*hr/L)	10751.75 (26.77%)	8,029.88 (42.65%)	12,332.95 (34%)
T _{max} (hr)	14.2 (35.27%)	16.80 (48.47%)	17.5 (16.85%)
T _{1/2} (hr)	5.58 (41.36%)	8.51 (53.76%)	10.16 (91.76%)

Note: N=6 for each group; AUC(0-tau): AUC over the 24-hr post dose.

The renal impairment group had the highest AUC and C_{max} followed by hepatic impairment group and then by healthy subjects. Renal impairment resulted in 53.6% higher mean AUC and 43.5% higher mean C_{max} than healthy subjects. Interesting, healthy subjects had a longer average half-life than the hepatic impairment group; two healthy subjects had a longer half life, 10.4hrs and 16.3 hrs, while the rest shared a similar half life range with the hepatic impairment group. Mean AUC and C_{max} in healthy subjects and hepatic impairment patients were much more similar, though being

33% and 13% higher, respectively, in the latter group. There are no statistical differences in systemic exposure (AUC and Cmax) between healthy and hepatic impairment subjects or between healthy and renal impairment subjects, based on a p value of 0.05. Since sulfate is eliminated mainly via the renal route, it is expected that renal impairment would have a higher impact on the sulfate PK parameters than hepatic impairment. In general, the pharmacokinetic parameters of sulfate are highly variable.

For an easy viewing of serum sulfate comparison among the groups studied after the first dose, mean serum sulfate concentrations (corrected for pre-dose sulfate level) versus time are plotted below.



In general, serum sulfate levels increased within one hour after each half-dose and returned to pre-dose ranges by Day 6. After the 1st half dose, serum sulfate concentrations peaked 4-10 hours the first dose. Serum sulfate concentrations did not return to pre-dose levels before the 2nd half dose, and rose even further higher after the 2nd half dose. The concentrations increased until T_{max} was reached (2 to 6 hours post dose 2) and began declining thereafter.

Serum sulfate did decline to predose level by day 6 in all three groups. Respective mean (CV%) predose and day 6 serum sulfate levels were 335 (115.4) $\mu\text{mol/L}$ and 349.2 (90.44) $\mu\text{mol/L}$ in healthy subjects. By pre-noon on Day 3 and Day 6, mean (SD) serum sulfate concentrations were 391.8 (51.60) $\mu\text{mol/L}$ and 405.5 (50.53) $\mu\text{mol/L}$ in mild-moderate hepatic dysfunction patients, respectively, showing no statistical differences from their mean (SD) predose concentrations of 407.3 (54.63) $\mu\text{mol/L}$. By pre-noon on Day 3 and Day 6, mean (SD) serum sulfate concentrations were 617.8 (138.23) $\mu\text{mol/L}$ and 574.7 (101.15) $\mu\text{mol/L}$ in moderate renal disease patients, respectively, showing no statistical differences from the mean (SD) predose concentrations of 607.0 (192.16) $\mu\text{mol/L}$.

Urinary sulfate excretion

Mean (CV%) urine sulfate concentrations (mg/dL)

	M/MHD	Healthy volunteers	MRD
Predose 1	86.92 (57.63%)	131.2 (35.81%)	607.0 (31.66%)
Day 3	89.83 (75.49%)	145.62 (76.24%)	617.8 (22.37%)
Day 6	70.82 (118.11%)	134.65 (55.49%)	574.7 (17.60%)

M/MHD: mild or moderate hepatic impairment; MRD: moderate renal impairment.

Urinary sulfate concentrations varied among individual patients, as evidenced by the coefficient of variations (CV%).

The cumulative amount of sulfate excreted in urine over the 30-hr period after the first dose was calculated for each group by assuming that urinary sulfate is derived only from BL1800 without corrections for the basal sulfate excretion in individual groups.

Mean (CV%) urine sulfate excretion

	M/MHD	Healthy volunteers	MRD
Cum Ae ₍₀₋₃₀₎ mg	6499.45 (21.37%)	6037.98 (61.93%)	5101.88 (30.67%)
Cum % dose (0-30hrs) mg	21.90 (21.40%)	20.35 (61.85%)	16.18 (30.66%)
Excretion rate (mg/hr)	216.63 (21.37%)	201.27 (61.93%)	170.05 (30.68%)

M/MHD: mild or moderate hepatic impairment; MRD: moderate renal impairment.

Reviewer's comments: Since the subjects received two 6-ounce half doses separated by 12 hrs, the cumulative % dose of sulfate secreted in 30 hrs after the first dose might have included some amount of the second dose. The sponsor did correctly use 29.7 g sulfate for its calculation of the cumulative % dose excreted. The cumulative % doses excreted were higher in both healthy and hepatic impairment groups than in renal impairment group.

Adverse events observed in Study BLI800-202:

Of the events, 19 were judged to be mild and the rest (5) were considered moderate. All events resolved without sequelae. There were 7 cases of headache in 7 patients (29%), abdominal cramps (3 events in 2 patients or 12.5%), nausea (3 events in 3 patients or 12.5%), emesis (1 event or 6%). Ten other adverse events (chest congestion, chills, constipation, fatigue, perianal irritation, sore throat, abnormal urinalysis, 2 patients with elevated serum creatinine and symptomatic hypoglycemia) were all considered mild and resolved on Day 6. ECG (12 leads) assessment was performed at screening, predose on Days 2, 3, and 6. The investigators concluded that no clinically significant ECG abnormality was observed in the study subjects.

Two subjects had a transient elevation in serum creatinine after BLI800. Healthy volunteer 006 had a serum creatinine of 1.0 mg/dL on admission, which stayed in the normal range (0.7 to 1.3 mg/dL) after dosing except at the 30 hour time point (18 hrs post dose 2), when it reached 1.4 mg/dL. By Days 3 and 6, serum creatinine went back to predose levels. Hepatic-impaired subject 009 had serum creatinine within the normal range at all time points, except for Day 6, 1.4 mg/dL. Serum creatinine returned to 0.9

mg/dL on the following day. For both cases, the investigator considered the serum creatinine elevation not to be clinically significant.

Serum creatinine levels were within the normal range in the healthy and hepatic impairment groups throughout the study. Respective mean (SD) serum creatinine levels at predose and on day 6 in renal impairment group were 1.73 (0.34) mg/dL and 1.82 (0.55) mg/dL, showing no significant increase. Mean (SD) serum creatine kinase levels at predose and on day 6 were 127.7 (79.2)u/L and 132.5 (77.1)u/L, 125.3 (92.6)u/L and 192.8 (129.3)u/L, and 157.7 (82.5)u/L and 178.3 (112)u/L, respectively in healthy, hepatic impairment, and renal impairment groups. Mean serum creatine kinase levels were beyond the normal limit of 140u/L for the hepatic impairment group only on day 6 but remained out of range throughout the study period for the renal impairment group. The sponsor reported that troponin-I was negative.

Sponsor's comments: Moderate renal disease and mild/moderate hepatic impairment do not alter the elimination of sulfate to an extent that causes a safety concern.

After dosing with BLI800, serum sulfate levels were elevated in all subjects, especially those with MRD. Levels of serum sulfate may be elevated 7 to 24 times the normal level in an individual with acute renal failure. But, after BLI800, they were approximately only 1/3 of those seen in patients with more severe impairment. The sponsor concluded that, as seen from this and Phase II studies in healthy subjects, BLI800 can be safely administered to patients with moderate renal or hepatic impairment. The degree and extent of hypersulfatemia after BLI800 is insufficient to affect other clinical parameters and is clinically insignificant.

Reviewer's comments: The safety of BLI800 should be derived from larger efficacy and safety studies in humans. The results of this small study should not be used to determine the safety profile of this product.

2.2.4 Are there any differences in serum sodium, potassium, and magnesium between patients and healthy volunteers?

The results of serum analytes from Study BLI800-202 are summarized below.

Mean (SD) serum magnesium (mEq/l)

	MRD	M/MHD	Healthy
Predose 1	1.56 (0.21)	1.75 (0.14)	1.76 (0.10)
12 hrs post dose 2	1.58(0.19)	1.71 (0.16)	1.70 (0.07)
Day 3	1.56 (0.18)	1.67 (0.12)	1.67 (0.11)
Day 6	1.50 (0.1)	1.72 (0.16)	1.64 (0.13)

M/MHD: mild or moderate hepatic impairment; MRD: moderate renal impairment. N=6 for each group.

For magnesium, 2mEq/L equals 1mmol/L. BLI800 did not cause any significant changes from individual predose levels of serum magnesium in any of the groups studied.

Mean (SD) serum potassium (mmol/l)

	MRD	M/MHD	Healthy
Predose 1	4.22 (0.55)	3.98 (0.17)	4.03 (0.16)

12 hrs post dose 2	4.15 (0.60)	4.10 (0.43)	4.00 (0.26)
Day 3	4.17 (0.25)	4.23 (0.38)	3.90 (0.36)
Day 6	4.22 (0.45)	4.18 (0.29)	4.05 (0.26)

M/MHD: mild or moderate hepatic impairment; MRD: moderate renal impairment. N=6 for each group.

One millimole (miliequivalent or meq) of K weights 39 mg and 1mEq/L equals 1 mmol/L for potassium. BLI800 did not cause any significant changes from individual predose levels of serum potassium in any of the groups studied.

Mean (SD) serum sodium (mmol/l)

	MRD	M/MHD	Healthy
Predose 1	138.8 (3.37)	140.8 (1.72)	141.0 (1.41)
12 hrs post dose 2	139.3 (1.86)	141.8 (2.32)	140.3 (1.97)
Day 3	141.2 (2.64)	141.0 (1.41)	139.8 (1.72)
Day 6	140.3 (2.34)	140.8 (1.33)	140.0 (2.76)

M/MHD: mild or moderate hepatic impairment; MRD: moderate renal impairment. N=6 for each group.

BLI800 did not cause any significant changes from individual predose levels of serum sodium in any of the groups studied.

Sponsor: No treatment-emergent differences between either of the two patient groups and the healthy volunteers with regard to any serum analyte, including FDA's specific requests, sodium, potassium and magnesium.

Reviewer: In subjects with moderate renal impairment, serum magnesium slightly increased at 12 hrs post dose 2 but declined to the predose level by Day 3. The sponsor's conclusion is acceptable.

2.2.5 What is pharmacodynamic effect of an experimental formulation of oral sulfate?

Study BLI800-101 was conducted to compare the effects of experimental, sulfate-containing, bowel cleansing preparations (OSS) and commercial Fleet Phosphosoda® (OPS) on fecal parameters, blood electrolyte levels and symptoms. The composition of sponsor's OSS is an experimental preparation and not identical to the to-be-marketed formulation. OPS was used as positive control (Batch number 0535501).

Comparison of the Total Sulfate Salts Content Experimental BLI800-101 and the To-Be-marketed Product

Sulfate	Amount (G)	
	BLI800-101 (OSS)	To-be marketed Product
Na ₂ SO ₄	26.98	35.02
MgSO ₄	11.43	3.2
K ₂ SO ₄	4.14	6.26

Despite the differences in the relative amounts of individual cations, the total amount of sulfate in both BLI800-101 and to-be-marketed formulations are identical, that is 29.65g.

Composition comparison of sponsor's experimental formulation and commercial Fleet Phosphosoda.

Component	Composition in Grams	
	OPS	OSS
(b) (4)		(b) (4)
Na ₂ SO ₄		
MgSO ₄ ·7H ₂ O		
K ₂ SO ₄		
Citric Acid, (b) (4) USP		
(b) (4)		
Sucralose, NF		
Total		

- (b) (4)

OSS solution preparation: The OSS powder (b) (4) was dissolved in 2 liter distilled water (Aqua Pur), and the solution was refrigerated. From this 2 liter solution, 5 glasses of 11 ounces (330 ml) and a sixth glass of 11.8 ounces (350 mL) were prepared. Each 330 ml contained (b) (4) sulfate.

OPS solution preparation (positive control; Batch number 0535501). One kit per subject was packaged as 2 containers of 45 mL each. The pharmacy staff prepared six doses per subject. Per dose 1/3 of each container (15 mL) was diluted with 315 mL of distilled water (Aqua Pur) to produce 11 ounces (330 mL).

Treatment regimen

- Group 1: OPS, six doses of 330 mL in two 45-minute sessions separated by 11 h;
- Group 2: OSS, five doses of 330 mL and one dose of 350 mL in two 45-minute sessions separated by 11 h;
- Group 3: OSS, five doses of 330 mL and one dose of 350 mL in one 90-minute session.

Flowchart of drug administration

Group	Dose	Day 1							Day 2		
		6.45 pm	7.00 pm	7.15 pm	7.30 pm	7.45 pm	8.00 pm	8.15 pm	6.00 am	6.15 am	6.30 am
1	OPS		X	X	X W W W				X	X	X W W W
2	OSS		X	X	X W				X	X	X ⁽¹⁾ W
3	OSS	W	X	X	X	X	X	X ⁽¹⁾ W			

Source: Protocol, Appendix A1

X = 330 ml; X⁽¹⁾ = 350 ml

W = 240 ml water (obligatory, no timeframe specified); additional water was allowed at any time.

Nineteen (19) subjects were actually dosed; one subject (Subject 013) was replaced (with Subject 019) because the former did not receive the complete dose. The total volume of OSS taken by each patient in each group is 2 liters.

Demographic data.

		OPS Group 1 (N=6)	OSS Group 2 (N=6)	OSS Group 3 (N=7)	All subjects (N=19)
Age (years)	n	6	6	7	19
	mean	27.2	25.0	22.0	24.6
	SD	7.99	6.75	1.63	6.01
	minimum	20	19	19	19
	median	24.0	23.0	22.0	22.0
	maximum	39	34	24	39
Height (cm)	n	6	6	7	19
	mean	185.25	184.00	186.13	185.18
	SD	6.463	6.885	8.002	6.851
	minimum	177.5	173.0	174.4	173.0
	median	187.50	184.25	186.50	185.00
	maximum	191.0	194.5	196.0	196.0
Weight (kg)	n	6	6	7	19
	mean	79.55	76.82	75.60	77.23
	SD	13.230	5.840	9.655	9.595
	minimum	64.1	68.7	57.9	57.9
	median	78.30	76.35	79.30	77.20
	maximum	99.1	84.6	85.6	99.1
BMI (kg/m ²)	n	6	6	7	19
	mean	23.10	22.75	21.86	22.53
	SD	2.959	2.141	2.967	2.634
	minimum	19.6	20.4	18.1	18.1
	median	22.92	22.86	21.17	21.89
	maximum	27.2	25.2	27.2	27.2
Race/Ethnic origin: White/not Hispanic or Latino	n (%)	6 (100.0)	6 (100.0)	7 (100.0)	19 (100.0)

N = number of subjects within group; n = number of subjects with data available or number of subjects in specific category. SD= standard deviation.

Eligible subjects were admitted to the CPU (Clinical Pharmacology Unit) at 12 noon on Day 1. Subjects were discharged from the CPU at 6 pm on Day 2 (30 hrs' stay).

Subjects were instructed to eat a regular breakfast before 8 am on Day 1, at home. In the CPU they consumed a light lunch before 2 pm; no red-colored food or beverages were consumed. Thereafter the subjects did not consume any solid food until 12 noon

on Day 2. Water ad libitum was the only permitted liquid until 12 noon on Day 2, apart from one glass of caffeine free tea with 5 g sugar in the evening on Day 1. A specific volume of water was mandatory during dosing sessions. The subjects had a standard lunch around 12 noon on Day 2.

Lunch specifications Day 1

Beverages	Water only
Main Course	two medium sized eggs
Fruit or Vegetable	One half cup of applesauce
Bread	2 slices of white bread or one white roll
Condiments	2 teaspoons of soft margarine
Dessert	4 vanilla wafers

Pharmacodynamic variables investigated were:

- . Bowel movement
 - o Weight, volume, dry weight, percentage of water of the feces pool;
 - o Consistency of each bowel movement using a 100mm Visual Analog Scale (VAS), anchored by "solid and colored" on the left (0 mm) and "clear and Liquid" on the right (100 mm).
 - o Bowel cleansing time: time to first and last bowel movement and time to run clear (on the basis of the consistency VAS results).

All feces were collected from 7 pm on Day 1 until 12 noon on Day 2 (i.e. over a period of 17 hours). The time of each bowel movement was recorded. Subjects reported their experiences with the study treatment on a questionnaire, which was completed at each bowel movement from 7 pm on Day 1 until 6 pm on Day 2. The following question was answered by the subject: "Please record the time of each bowel movement and its consistency, using a 100mm Visual Analog Scale (VAS), anchored by "solid and colored" on the left and "clear and liquid" on the right" Each bowel collection was stored and refrigerated at the CPU until shipment. The feces collections were sent to (b) (4) for analyses.

Mean bowel movement results

(N=6) per Group	OPS Group 1		OSS Group 2		OSS Group 3	
	Mean	(SD)	Mean	(SD)	Mean	(SD)
Frequency of bowel movements	7.2	(2.40)	6.3	(1.37)	6.8	(2.40)
Weight of feces collection (g)	2635	(517)	2442	(468)	2587	(389)
Volume of feces collection (ml)	2598	(505)	2403	(462)	2577	(376)
Dry weight of feces collection (%)	3.94	(0.95)	4.46	(0.69)	3.99	(1.84)
Time to first bowel movement (h)	1.71	(0.62)	1.54	(0.54)	1.11	(0.41)
Time to last bowel movement (h)	16.44	(2.04)	20.47*	(0.84)	16.25	(6.20)
Time to run clear ¹⁾ (h)	6.64	(5.86)	6.26	(4.87)	2.77	(1.79)

- 1) time of 1st score ≥ 89 mm (the lowest maximum score observed in all subjects) of the consistency of stools VAS(visual analog score); * = significantly different from Group 1; p value <0.05

The consistency of stools changed rapidly after administration. Generally within 2 h after dosing the VAS score for consistency of stools was above 50 mm for all subjects. Time to run clear, calculated as the time of 1st VAS score ≥ 89 mm (the lowest maximum score observed in all subjects) ranged from 1.1 to 15.8 h. There were no statistically significant differences observed between groups. The subjects in Group 3 (OSS dosing on Day 1 only) appeared to run clear approximately twice as fast (mean of 2.8 h) as the subjects of Groups 1 and 2 (6.6 and 6.3 h, respectively).

No statistically significant differences were observed between groups for bowel movement frequency, weight, volume or dry weight. Mean values appeared to be similar between groups. However, the mean feces dry weight of OSS Group 2 appeared to be slightly higher as compared to OPS Group 1 and OSS Group 3. The subjects in Group 3 (OSS dosing on Day 1 only) ran clear approximately twice as fast (mean of 2.8 h) as the subjects of Groups 1 and 2 (6.6 and 6.3 h, respectively). The first bowel movement in Group 3 (OSS dosing on Day 1 only) occurred earlier (mean of 1.1 h) than in Groups 1 and 2 (mean of 1.7 and 1.5 h, respectively), but did not result in any statistically significant differences between groups. The last recorded bowel movement in Group 2 (OSS dosing on Day 1 and 2) occurred later (mean of 20.5 h) than in Groups 1 and 3 (mean of 16.4 and 16.3 h, respectively). There was a statistically significant difference between Groups 1 and 2 (p= 0.001).

Drug-related adverse events

System Organ Class Preferred Term	OPS Group 1 (N=6)			OSS Group 2 (N=6)			OSS Group 3 (N=7)			All subjects (N=19)		
	E	n	%	E	n	%	E	n	%	E	n	%
Gastrointestinal disorders	16	6	100	15	6	100	23	7	100	54	19	100
Abdominal discomfort	1	1	16.7	-	-	-	-	-	-	1	1	5.3
Abdominal distension	5	4	66.7	9	6	100	7	7	100	21	17	89.5
Abdominal pain	7	4	66.7	4	4	66.7	6	5	71.4	17	13	68.4
Dysgeusia	1	1	16.7	-	-	-	-	-	-	1	1	5.3
GI motility disorder	-	-	-	-	-	-	2	2	28.6	2	2	10.5
Intestinal hypermotility	-	-	-	-	-	-	1	1	14.3	1	1	5.3
Nausea	2	2	33.3	2	2	33.3	6	5	71.4	10	9	47.4
Vomiting	-	-	-	-	-	-	1	1	14.3	1	1	5.3
General disorders	7	5	83.3	8	5	83.3	8	6	85.7	23	16	84.2
Discomfort	7	5	83.3	6	5	83.3	8	6	85.7	21	16	84.2
Fatigue	-	-	-	2	1	16.7	-	-	-	2	1	5.3
Nervous system disorders	1	1	16.7	-	-	-	2	2	28.6	3	3	15.8
Dizziness	-	-	-	-	-	-	1	1	14.3	1	1	5.3
Dizziness postural	1	1	16.7	-	-	-	-	-	-	1	1	5.3
Headache	-	-	-	-	-	-	1	1	14.3	1	1	5.3
TOTAL	24	6	100	23	6	100	33	7	100	80	19	100

N = number of subjects in specified treatment group, E = number of adverse events, n = number of subjects with adverse events.

The adverse events observed in the OSS groups were not more severe in nature as compared to those observed in OPS group.

Electrolyte levels

Mean change from baseline for serum electrolyte levels were compared at 16 hr and 22 hr post dose (hrs post 1st dose) with the statistical significance shown in the last column.

Mean % changes from baseline for serum electrolyte concentrations

	Mean changes from baseline for serum electrolyte concentrations (%)						p < 0.05	
	OPS Group 1		OSS Group 2		OSS Group 3		16 hr	22 hr
	T = 16 hr	T = 22 hr	T = 16 hr	T = 22 hr	T = 16 hr	T = 22 hr		
Ca (mmol/L)	-2.85	-1.86	0.78	-1.15	1.83	-1.60	* #	-
Ca x P (mg ² *dl ²)	25.0	18.3	-7.93	4.88	-5.72	5.84	* #	-
Cl (mmol/L)	-1.75	-0.44	-1.28	-0.96	-0.97	-0.15	-	-
HCO ₃ (mmol/L)	-8.90	-1.44	-5.53	-3.97	-5.50	-0.86	-	-
K (mmol/L)	-5.12	-6.91	0.82	1.22	4.77	3.95	# \$	#
Mg (mmol/L)	-6.28	1.41	-0.75	3.28	-0.63	5.28	* #	-
Na (mmol/L)	0.84	0.25	0.97	-0.72	-0.35	-0.24	-	-
PO ₄ (mmol/L)	28.7	20.4	-8.76	5.96	-7.38	7.64	* #	-
SO ₄ (mg/dL)	-21.0	-8.60	106	66.6	71.5	59.7	* #	* #

* = Group 2 significantly different from Group 1; p value < 0.05

= Group 3 significantly different from Group 1; p value < 0.05

\$ = Group 3 significantly different from Group 2; p value < 0.05

Calcium: None of the serum Calcium levels observed were out of range, though some small changes did occur after dosing.

Ca X P: There was a negative association between Phosphate and Calcium. Serum Calcium decreased in subjects receiving OPS while serum Phosphate levels increased. Similarly Calcium increased slightly in subjects receiving OSS while serum Phosphate levels decreased. No range was specified for Ca x P, but in the literature, values < 55 mg²/dL² are considered normal. None of the Calcium-Phosphate product values were out of range, although some subjects in Group 1 had high values that reached the upper limit of normal. At 16 h in OPS, mean Ca x P was 52.3 mg²/dL².

Magnesium: Serum magnesium levels had slightly decreased in all subjects at 16 h post-dose and increased again 22 h post-dose, often to even higher levels than observed at baseline, more prominently after OPS than after OSS. The mean change in serum Magnesium levels after OPS (Group 1) was significantly different from that observed after OSS (Groups 2 and 3).

Potassium: None of the serum potassium levels observed were out of range. Mean changes were statistically significantly larger for OPS Group 1 as compared to OSS Groups 3.

Bicarbonate: Serum bicarbonate levels decreased in all treatment groups 16 h post-dose and returned to baseline values 22 h post-dose. None of the serum bicarbonate levels observed were out of range.

Chloride: Serum Chloride levels appeared to decrease very slightly in all treatment groups at 16 h postdose and returned to baseline values 22 h post-dose.

Sodium: Serum Sodium levels had slightly increased in most of the subjects receiving OPS (Group 1) and OSS (Group 2) at 16 h post-dose, while in OSS Group 3 they remained stable. At 22 h post-dose levels had decreased again. None of the serum Sodium levels observed were out of range.

The numbers of subjects in individual groups with out range serum electrolyte levels are listed below. The OPS group has a much larger number of subjects with phosphate level out of normal range either at 16 hr or 22 hr post dose. The OSS groups have only 1 or 2 subjects with phosphate level greater than the normal range.

Number of subjects with out of range serum electrolyte concentrations after initiation of dosing

	OPS Group 1			OSS Group 2			OSS Group 3		
	<Normal	Normal	>Normal	<Normal	Normal	>Normal	<Normal	Normal	>Normal
t = 16 hr									
Mg	1	5	-	-	6	-	-	6	-
PO ₄	-	-	6	-	6	-	-	6	-
t = 22 hr									
Mg	-	6	-	-	6	-	-	6	-
PO ₄	-	1	5	-	5	1	-	4	2

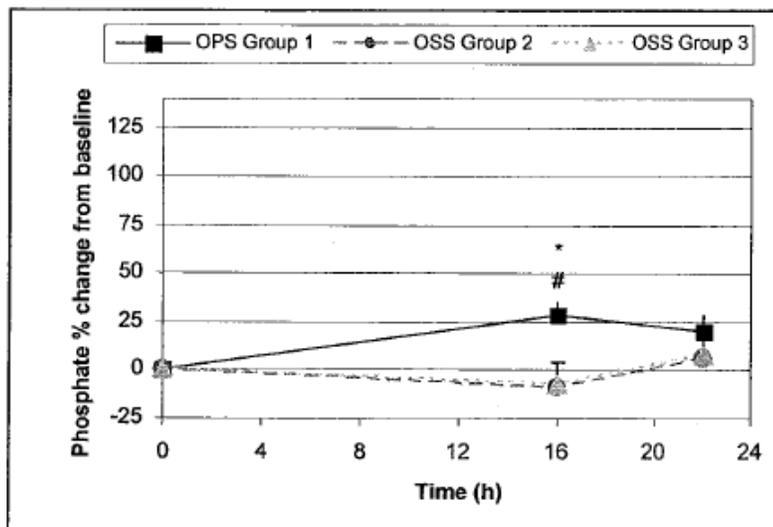
Mean serum phosphate levels increased 28.7 % after receiving OPS (Group 1) at 16 h post-dose. In the OSS groups, phosphate levels decreased, with the exception of Subject 007 and 019, who had high, out of range Phosphate levels on Day 2, 22 h post-dose; their levels up to 1.67 mmol/L were observed. Similarly, urine Phosphate levels increased in 5 of the subjects receiving OPS with mean values up to 52.4 mmol/L, while no clear change could be observed after OSS (Groups 2 and 3).

Baseline urine was collected at 6pm on day while post dose urine voided from 12:00 pm to 7:00 pm on day 1 was collected as “urine pool 1(-7 hr –predose),” and post dose urine voided from 7:00 pm on day 1 to 12 noon on day 2 was collected as “urine pool 2 (predose-17 hr).” Based on the urine pool 2 data, mean urine phosphate levels were significantly higher after OPS (Group 1) as compared to OSS (Groups 2 and 3); 52.4 vs. 18.8 and 15.7 mmol/L, respectively. However the change from baseline after OPS (430 %) was not significantly different from the change observed after OSS (1. and 27.7%, respectively in Groups 2 and 3), probably due to the large between-subject variability.

Serum Magnesium levels had slightly decreased in all subjects at 16 h post-dose and increased again 22 h post-dose, often to even higher levels than observed at baseline, more prominently after OPS than after OSS. Only one subject (OPS Subject 001) showed a postdose serum Magnesium level just below the normal range. Mean serum levels decreased with 6.28 % after OPS (Group 1) at 16 h post-dose, while little change was seen after OSS (Groups 2 and 3).

Urine Magnesium levels measured post-dose were below normal in all subjects receiving OPS (of which 3 subjects already had out of range values pre-dose) and in 2 of the 12 subjects receiving OSS (010 in Group 2 and 019 in Group 3). Lowest levels post-dose were found after OPS (Group 1); levels down to 0.4 mmol/L were observed. Mean urine Magnesium levels decreased after OPS (Group 1) with 48.1% and increased after OSS with 109.9% and 64.1 %, in Groups 2 and 3, respectively. Mean levels and change from baseline after OPS were significantly different from those observed after OSS (both Groups 2 and 3).

Post dose-initiation mean (+ SD) % change from baseline: serum phosphate

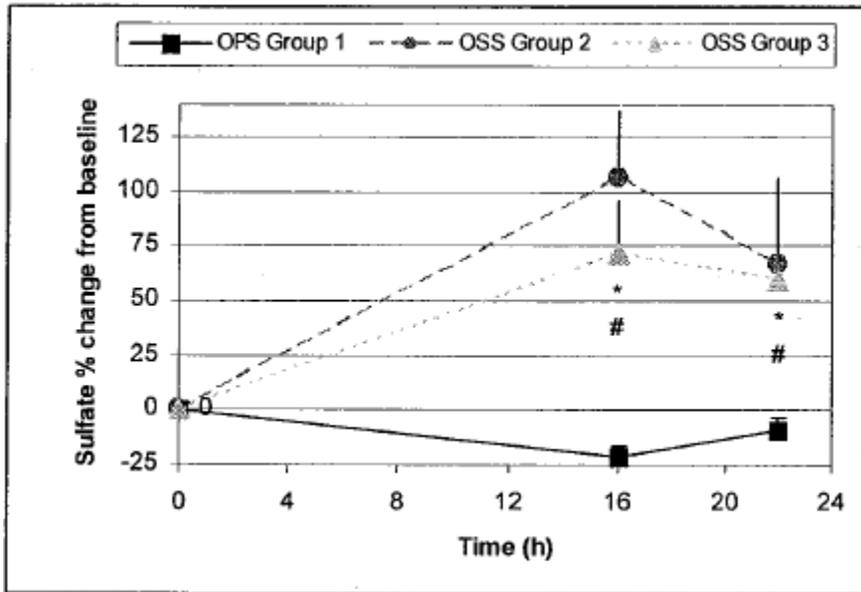


* = Group 2 significantly different from Group 1; p value <0.05
 # = Group 3 significantly different from Group 1; p value < 0.05

Serum sulfate levels significantly increased in all subjects receiving OSS, with maximum values at 16 h post dose. Sulfate levels were higher than baseline at 22 h post-dose, in virtually all subjects receiving OSS. The mean Sulfate increase in OSS Group 2 appeared to be slightly higher than in OSS Group 3 (106.00 vs. 71.46 %, respectively; p = 0.058). None of the subjects in the OPS group had increased serum Sulfate levels.

Urine Sulfate levels significantly increased in all subjects receiving OSS (Groups 1 and 2) and not in subjects receiving OPS (Group 3). Although not significantly different, the mean Sulfate increase in Group 2 appeared to be slightly higher than in Group 3 (472 vs. 306 %, respectively). Fecal Sulfate levels were below the limit of quantification for the OPS group. In OSS Groups 2 and 3, fecal Sulfate output ranged from 314 to 509 mEq. No statistically significant difference was observed between the means of OSS Group 2 and 3 (417 and 441 mEq, respectively).

Post dose-initiation mean (+ SD) % change from baseline: serum Sulfate



* = Group 2 significantly different from Group 1; p value < 0.05
 # = Group 3 significantly different from Group 1; p value < 0.05

Overall electrolyte balance: All electrolyte balances were calculated by amount input via preparation - amount output via feces - amount output in second urine void. Not all electrolyte balances could be calculated due to incomplete data (levels below limit of quantification or not analyzed).

Overall electrolyte balance

	Mean (mEq) ± SD			p < 0.05
	OPS Group 1	OSS Group 2	OSS Group 3	
Cl	-76.8 ± 32.2	-80.8 ± 33.3	-79.3 ± 11.9	-
K	-95.7 ± 32.0	-35.9 ± 22.0	-38.2 ± 15.3	* #
Mg	-35.8 ± 23.7	11.9 ± 24.7	2.97 ± 20.7	* #
Na	6.90 ± 87.2	-7.10 ± 74.5	-37.4 ± 60.7	-
SO₄	-	145 ± 65.4	120 ± 60.5	-

SD = Standard Deviation

* = Group 2 significantly different from Group 1; p value < 0.05

= Group 3 significantly different from Group 1; p value < 0.05

Electrolyte excretion in urine and feces

	Mean % of administered dose in <u>urine</u> ± SD			Mean % of administered dose in <u>feces</u> ± SD		
	OPS Group 1	OSS Group 2	OSS Group 3	OPS Group 1	OSS Group 2	OSS Group 3
Cl	-	246 ± 196	174 ± 86.3	-	247 ± 133	312 ± 131
K	-	58.3 ± 30.7	61.4 ± 18.5	-	117 ± 24.5	119 ± 20.4
Mg	-	3.04 ± 1.51	3.24 ± 1.08	-	90.7 ± 13.0	95.2 ± 10.4
Na	11.2 ± 4.95	15.8 ± 13.3	12.2 ± 5.74	87.2 ± 16.7	86.0 ± 20.0	96.9 ± 19.9
PO₄	14.7 ± 4.78	-	-	-	-	-
SO₄	-	8.71 ± 3.59	8.81 ± 2.92	-	67.7 ± 8.56	71.6 ± 11.2

Approximately 9 % of the Sulfate administered in the OSS Groups 2 and 3 was excreted in urine and approximately 70% in feces (within the 17 hours after dose initiation).

QT effect

QT effect was assessed with 12-lead ECG. Predose ECG was assessed during screening and post dose ECG at 11:00 am on day 2 (i.e. 16 hrs post dose). Statistical comparisons are summarized below.

Results from a paired t-test of QT and QTc

	Mean difference between Predose and Postdose			
	QT (ms)	p-value	QTc (ms)	p-value
OPS Group 1	42.5	0.01	31.2	0.004
OSS Group 2	24.7	0.08	4.33	0.37
OSS Group 3	12.3	0.38	15.0	0.08

These changes were not considered clinically significant as no QTc prolongation in excess of 450 ms was observed in any of the subjects. Mean ECG values were within normal ranges at all time points.

2.3 General Biopharmaceutics

2.3.1 Is the proposed formulation identical to the one used for the pivotal clinical studies?

Yes. The formulations used in the Phase 3 studies (BLI800-301 and BLI800-302) was the same as the to-be-marketed product. Study BLI-202, a pharmacokinetic study in healthy volunteers, and patients with renal and hepatic disease also used the to-be-marketed formulation.

Composition of clinical trial batches
Studies BLI800-202, 301 and 302

(Total dose in patients)

Ingredient	Total dose	Composition	Function
Na ₂ SO ₄	35.02	(b) (4)	Active
MgSO ₄	3.2		Active
K ₂ SO ₄	6.26		Active
Sodium benzoate	(b) (4)		
Flavoring agents	(b) (4)		
Sucralose, NF	(b) (4)		

Where flavoring agents include (b) (4)

2.4 Analytical Section

2.4.1 What analytical methods were used to assess concentrations?

An ion chromatography method was used for the determination of sulfate concentration in human serum and feces. (b) (4)

(b) (4). The samples were analyzed with an IC assay (b) (4)

The set up of ion chromatography:

Analytical Column: (b) (4)

Guard Column: (b) (4)

Column Temperature: 30°C

Mobile Phase: Potassium Hydroxide

(b) (4)

(b) (4)

Gradient:

<u>Time</u> (minutes)	<u>KOH Concentration</u> (mM)
-2.50	38.0
-2.40	0.500
0	0.500
1.00	5.00
2.00	5.00
10.0	38.0

Eluent Generator:

(b) (4)

Suppressor:

(b) (4)

Detector:

(b) (4)

Injection Volume:

25 μ L

Flow Rate:

2.00 mL/minute

The analytical method used is adequate.

2.6.2 Are the analytical assay methods adequately validated?

The calibration standards ranging from 0.500 to 100 ppm sulfate were used. The QC concentrations used were 0, 50, 100 and 200 ppm. The dilution was 20 fold. The lower limit of quantitation of sulfate in serum was 10 ppm(0.208 mEq/L). Analysis of experimental samples in this study resulted in serum sulfate levels ranging from 0.520 to 1.87 mEq/L. The calibration curve has r2 of 0.99976 and a slope of 1.08. The accuracy of the back calculated concentration from the ion chromatography ranged from -3.4% to 6.4% over the concentration range of 0.5ppm to 100 ppm. The analytical methods are adequately validated.

3 Detailed Labeling Recommendations

Section 12

Subsection 12.2 Pharmacodynamics

(b) (4)

Subsection Pharmacokinetics

(b) (4)

Reviewer's suggested version: (b) (4)

(b) (4) Fecal excretion (b) (4) the primary route of sulfate elimination. The disposition of sulfate after SuPrep Bowel Prep Kit was studied in patients (N=6) with mild-moderate hepatic impairment (Child-Pugh grades A and B) and in (b) (4) (N=6) with moderate renal impairment (b) (4) Creatinine clearance of 30 to 49 mL/min). The renal impairment group had the highest AUC and Cmax followed by hepatic impairment group and then by healthy subjects. (b) (4)

(b) (4) Systemic exposure of serum sulfate (AUC and Cmax) was similar between healthy subjects and hepatic impairment patients. Renal impairment resulted in (b) (4) higher mean AUC and (b) (4) higher mean Cmax than healthy subjects. The mean sulfate levels of all three groups returned to their respective baseline levels by day 6 after dose initiation. Urinary excretion of (b) (4), but was approximately 16% lower in moderate renal impairment patients than in healthy volunteers.

4 Summary of Individual Studies and Clinical Development

Study BLI800-202

TITLE: An Open Label Study to Assess the Effect of BLI800 on Safety and Clinical Chemistry Parameters in Patients with Moderate Renal Disease or Hepatic Impairment Compared to Healthy Volunteers

SPONSOR: Braintree Laboratories, Inc.
60 Columbian St. West
P.O. Box 850929
Braintree, MA 02185

PRINCIPAL INVESTIGATOR: Harry Alcorn Jr. Pharm. D.
DaVita Clinical Research
825 South 8th St, Suite 300
Minneapolis, MN 55404

OBJECTIVES: To evaluate and compare the effects on safety measures and clinical chemistry after BLI800 in two groups of patients and one group of normal healthy volunteers (NHV). The patient groups were those with mild or moderate hepatic impairment (M/MHD-Child-Pugh Stage A or B) or moderate renal disease (MRD- FDA Group 3 moderate renal impairment).

The NHV group consisted of healthy volunteers who were age and gender matched to the hepatic and renal patients (i.e., age +/- 7 years, BMI +/- 5, sex, and race).

DESIGN: This was a single center, open label, safety and pharmacokinetic (PK) study of the effects of administering BLI800 to patients with mild-moderate hepatic impairment or moderate renal disease and healthy matched controls. Adverse events and clinical chemistry were studied along with the pharmacokinetics of sulfate.

Study volunteers were given their first half dose (dose 1) in the morning and the second half dose (dose 2) at 12 hours later. The total oral dose of sulfate was 29.7 grams.

SAFETY ASSESSMENTS: 12 lead ECG, vital signs, adverse events, hematology, blood chemistry and urinalysis.

TEST ARTICLE: BLI800 Lot #: RD841.

PK MEASURES AND METHODS: Serum sulfate was measured using a validated ion chromatography method with a Lower Limit of Quantitation (LLOQ) of 10 ppm (104 $\mu\text{mol/L}$). Urinary sulfate was measured by HPLC. The serum sulfate pharmacokinetic parameters AUC(0-t), AUC(0-tau), $T_{1/2}$, Kel, Cmin, Cmax, and Tmax were determined from the serum concentration-time data after dose 1 of BLI800. The cumulative amount of sulfate excreted [Cum.Ae(0-30)], the cumulative percent of dose excreted, and the excretion rate were calculated from the urine data.

SAFETY RESULTS: A total of 18 subjects completed the study. No patients withdrew from the study after receiving medication. There were 6 patients (3 males) with MRD, 6 (2 males) with M/MHD and 6 (2 males) NHVs. There were no on-study deaths. There were no treatment emergent serious adverse events. Adverse events were distributed evenly according to health status and were mainly limited to headache (29%), nausea (12.5%) and abdominal cramps (12.5%). All adverse events were deemed to be mild-moderate in severity.

ECG findings and vital signs were unremarkable.

The Investigator concluded that there were no clinically significant chemistry, hematology, or urinalysis findings. There were no differences in serum sodium, potassium or magnesium between the patient groups and the healthy volunteers. Other differences were small and were generally consistent with the patients' health status.

PK RESULTS:

Serum sulfate levels were highly variable at baseline and at all time points after BLI800 administration, even when the values were adjusted for baseline levels. Sulfate was higher at baseline and after dosing in the renal disease patients. The Cmax and AUC were higher in the renal and hepatic patients. No statistically significant differences were seen between the patient groups and the healthy volunteers with regard to any pharmacokinetic variable. In all patients, sulfate levels returned to pre dose values within 48 hours after dose 1 of BLI800. The following table summarizes the serum pharmacokinetic parameters of sulfate observed after all BLI800 portions ingested.

Health Status Group	Sulfate Pharmacokinetic Parameter*	
	Cmax (µmol/L)	AUC (0-tau) µmol*hr/L
Moderate Renal Impairment (N=6)	717.0 (270.84)	12332.95 (4193.54)
Mild/Moderate Hepatic Impairment (N=6)	560.2 (152.75)	10751.75 (2878.17)
Healthy Volunteers (N=6)	499.5 (165.00)	8029.88 (3424.42)

* Values are means and (SD). (Ref Table 15.2.2.1)

Urinary sulfate excretion was measured for 30 hours starting after dose 1 and did not differ according to health status. The amount of sulfate and the fraction of the dose excreted in urine did not differ across the groups. The mean cumulative amount of the administered dose that was excreted in urine in the first 30 hours starting from dose 1 was 16.3% in MRD patients, 21.1% in M/MHD and 17.7% in the NHVs (Table 15.2.3.2).

CONCLUSIONS:

BLI800 was well-tolerated by patients with MRD and M/MHD. The types and severity of adverse events were similar to those seen in large Phase III trials. No untoward changes were noted in vital signs or clinical chemistry. While patients with MRD had elevated serum sulfate levels at baseline and after BLI800 in comparison to the other health status groups, the elevations were less than those seen in renal failure and were not sufficient to alter biochemical parameters that are associated clinically with hypersulfatemia. After adjusting for baseline sulfate levels, no differences in sulfate PK parameters were seen.

TITLE OF STUDY An Investigation of the Effects of Experimental Bowel Cleansing Preparations on Symptoms, Electrolytes and Fecal Physical and Chemical Properties in Healthy Male Volunteers	
PRINCIPAL INVESTIGATOR Dr. Alina Dobre	
STUDY CENTRE Kendle Clinical Pharmacology Unit, Bolognalaan 40, 3584CJ Utrecht, The Netherlands	
PUBLICATION (REFERENCE) Not applicable	
STUDY PERIOD Screening date of first subject in: April 26, 2006 Date of last subject completed: July 29, 2006	PHASE OF DEVELOPMENT Phase I
OBJECTIVES Compare the effects of an experimental Sulfate-containing bowel cleansing preparation (OSS) and a marketed Phosphate-containing preparation (OPS) on fecal parameters, blood electrolyte levels and subject symptoms.	
METHODOLOGY OPS and OSS were evaluated in a randomized, open label design. Initially 2 groups of 6 healthy normal volunteers were investigated. Subjects were screened within 21 days prior to confinement to the Clinical Pharmacology Unit (CPU). Eligible subjects received either OPS (control) in Group 1 or OSS in Group 2. In both groups the subjects consumed the diluted preparations divided into three doses at 15 minute intervals on Day 1 (evening) and three doses at 15 minute intervals on Day 2 (morning), separated by 11 h (in total 6 doses). Subjects were confined to the CPU for 30 h. The volume of feces they produced was assessed, as well as the effects on urine, stool and plasma electrolytes. Safety was determined by evaluating AEs, a bowel movement symptoms questionnaire (subject diary), standard laboratory tests, vital signs, ECG and physical examination. Based on the results of these 2 groups, one additional group of 6 healthy normal volunteers was dosed with the same doses of OSS but with a different dose scheme (Group 3); the subjects consumed all six doses at 15 minute intervals on Day 1 (evening).	
NUMBER OF SUBJECTS (PLANNED AND ANALYSED) Eighteen (18) subjects were to be dosed. In total 19 subjects were dosed. One subject dropped out after having received 2/3 of the dose and was replaced. Eighteen (18) subjects were dosed completely. All 19 subjects completed the study and were analyzed.	
MAIN CRITERIA FOR INCLUSION/EXCLUSION Subjects were healthy, males between 18 and 40 years of age who voluntarily signed informed consent. Excluded from participation were subjects: <ol style="list-style-type: none"> 1. known or suspected of having any of the following conditions: ileus, gastric retention, bowel perforation, colitis, megacolon and colostomy; 2. with a history of an abnormal 12 lead Electrocardiogram (ECG) or an abnormal ECG at the screening visit; 3. on salt-restricted diets, those with a history or evidence of dehydration, ascites, electrolyte disturbances, renal insufficiency, heart disease or who are taking diuretics or other medications that affect electrolytes; 4. who had a bowel cleansing procedure within the past month or who had taken a laxative within the past 5 days; 5. who had participated in an investigational clinical, surgical, drug, or device study within the past 90 days; 6. who had hepatitis B or C or are human immunodeficiency virus (HIV) positive (test at screening); 7. who had donated blood during the past three months; 8. who were or had been drug users and/or had used alcohol to excess (more than 1 liter of beer per day or the equivalent amount of any other alcoholic beverage); 9. who had any ongoing medical problems that, in the opinion of the Investigator, would have jeopardized the safety of the subject or impact the validity of the study results. 	
TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER An experimental concentrated colonic purgative formulation, made by combining inorganic sulfates in a small volume of water was investigated (Batch number CT2006-1 for Group 2 and CT2006-2 for Group 3). Subjects in Group 2 and 3 received 5 oral solutions of 330 ml and one of 350 ml, together with a prescribed volume of water for a total volume of 2480 ml. Additional water was allowed ad libitum. The composition of the total dose is provided in the table below.	

OSS Composition	Composition in Grams
Na ₂ SO ₄	(b) (4)
MgSO ₄ ·7H ₂ O	
K ₂ SO ₄	
Citric Acid, (b) (4) USP	
(b) (4)	
Sucralose, NF	
Total	

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

A small volume OPS (Fleet Phosphosoda®) was used as positive control (Batch number 0535501). Subjects in Group 1 received 6 oral solutions of 330 ml OPS, together with a prescribed volume of water for a total volume of 3420 ml. Additional water was allowed ad libitum. The composition of the total dose is provided in the table below.

OPS Composition	Composition in Grams
NaH ₂ PO ₄ ·2H ₂ O	(b) (4)
Na ₂ HPO ₄ ·12H ₂ O	
Total	

DURATION OF TREATMENT

The total duration of the study for one subject was approximately 3 weeks, including screening 14-21 days prior to Day 1.

In Group 1 (OPS) and 2 (OSS) subjects consumed three doses at 15 minute intervals on Day 1 (evening) and three doses at 15 minute intervals on Day 2 (morning), separated by 11 h. In Group 3 the subjects consumed all six doses at 15 minute intervals on Day 1 (evening).

CRITERIA FOR EVALUATION – PHARMACODYNAMICS

Pharmacodynamic variables investigated were:

- Bowel movement (weight, volume, dry weight, percentage of water of the feces pool);
- Consistency of each bowel movement using a 100mm Visual Analog Scale (VAS): “solid and colored” - “clear and liquid”;
- Bowel cleansing time: time to first/last bowel movement and time to run clear (on the basis of the consistency VAS results);
- Taste of the preparation using a 100 mm VAS: “acceptable” - “completely unacceptable”.

CRITERIA FOR EVALUATION – SAFETY

Safety was determined at screening and during the study by evaluating the following variables:

- AEs (during the treatment phase only);
- Bowel movement symptoms questionnaire with a scale from 1 to 5 for Urgency, Cramping, Stomach Bloating, Nausea, Vomiting, Overall Discomfort;
- Standard laboratory parameters (hematology, blood chemistry and urinalysis);
- Electrolytes in serum, urine and feces;
- Water balance (total water intake minus total water output);
- Bodyweight;
- Vital signs (sitting and standing blood pressure, pulse rate and temperature);
- 12-lead ECG (after 5 minutes in supine position);
- Physical examination.

STATISTICAL METHODS

Two analysis sets were defined:

Full analysis set (for all safety analyses): all subjects who received any study medication.

Per-protocol (PP) analysis set (for all pharmacodynamic parameters, bowel movement symptoms questionnaire, electrolyte analyses and water balance): all subjects who received the total treatment dose, collected all feces samples, did not receive non-permitted concomitant treatments and did not violate clinically relevant inclusion/exclusion criteria.

Data were listed by subject number, treatment and time point. Observed values were summarized using descriptive statistics by treatment group. Graphical presentations were provided for individual and mean body weight changes, vital signs, QTc and serum electrolytes and for individual hematology and biochemistry parameters, bowel movement symptoms and bowel cleansing (VAS scores).

Differences in group means were tested with independent samples t-tests for all pharmacodynamic parameters, electrolyte analyses and water balance. Differential distribution of the bowel movement symptoms over the treatment groups were tested with a separate Fisher’s exact test for each symptom.

All tables, listings, graphs and statistical analyses were produced with the SAS system, version 8.2.

PHARMACODYNAMIC RESULTS

OSS, in both regimens, was equally potent as OPS with regard to bowel cleansing. The efficacy appeared to have been slightly better for OSS as indicated by slightly higher dry weight and faster bowel cleansing (see Table below).

Mean Bowel Movement Results (N=6) per Group	OPS Group 1		OSS Group 2		OSS Group 3	
	Mean	(SD)	Mean	(SD)	Mean	(SD)
Frequency of bowel movements	7.2	(2.40)	6.3	(1.37)	6.8	(2.40)
Weight of feces collection (g)	2635	(517)	2442	(468)	2587	(389)
Volume of feces collection (ml)	2598	(505)	2403	(462)	2577	(376)
Dry weight of feces collection (%)	3.94	(0.95)	4.46	(0.69)	3.99	(1.84)
Time to first bowel movement (h)	1.71	(0.62)	1.54	(0.54)	1.11	(0.41)
Time to last bowel movement (h)	16.44	(2.04)	20.47*	(0.84)	16.25	(6.20)
Time to run clear ¹⁾ (h)	6.64	(5.86)	6.26	(4.87)	2.77	(1.79)

1) time of 1st score ≥ 89 mm (the lowest maximum score observed in all subjects) of the consistency of stools VAS

* = significantly different from Group 1; p value < 0.05

Generally the taste appeared to be considered most acceptable by the subjects in Group 2 (mean of 30.7 mm) compared to Groups 1 and 3 (means of 53.3 and 55.2 mm respectively). The difference in acceptability between OSS Group 2 and 3 may indicate that OSS is considered less palatable when administered in a shorter time frame. One subject in Group 3 (Subject 013) experienced OSS as unpalatable after the fourth dose and therefore discontinued dosing.

SAFETY RESULTS

- Both OPS and OSS were considered safe and generally well tolerated as assessed by AEs and other safety parameters. Most commonly reported were abdominal discomfort/distension/pain and nausea; expected side effects of the bowel preparations. There appeared to be no clear differences between the groups with regard to the total number of AEs or the total number of subjects reporting them. Generally, the AEs started and resolved earlier when OSS was taken in one 90-minute session (Group 3) but were more intense compared to OPS and OSS taken in two 45-minute sessions separated by 11 h (Group 1 and 2).
- Individual hematology parameters and standard blood chemistry parameters outside of normal ranges were incidentally observed; increase in WBC, hemoglobin, bilirubin, and low glucose levels. These were very likely a result of the study (fasting conditions and diarrhea), but were not considered clinically significant.
- Both administration of OPS and OSS resulted in electrolyte shifts (see the Table below). The shifts in Calcium, Sodium, Potassium, Magnesium and Chloride were generally small and considered not to be of clinical relevance. No shifts were seen for Potassium or Phosphorous with OSS. Statistically significant differences between most of the shifts after OPS and those after OSS were observed, but not between OSS Groups 2 and 3. Particularly large shifts in Phosphate and Ca x P were noted after OPS treatment. Phosphate, Calcium, Ca x P and Magnesium shifts were smaller after OSS. Moreover, Calcium, Phosphate, Ca x P and Potassium shifts after OSS were in the opposite direction compared to those after OPS. Marked increases in Sulfate concentrations were seen in the OSS groups, however, a decrease was observed in the OPS group.
- Serum electrolyte shifts were accompanied by changes in electrolyte output in urine and feces that were explanatory and appeared to be a consequence of the shifts observed in serum. Specifically, administration of OPS resulted in significantly greater negative balance for Potassium and Magnesium. Nearly 3.7 g of Potassium were lost after OPS administration against a loss of 1.4 g following OSS. And 0.9 g of Magnesium was lost after OPS administration against a loss of 0.1-0.3 g following OSS.
- Approximately 70% of the Sulfate administered was recovered in feces. Assuming that Sulfate levels are normally very low (fecal Sulfate levels are below the limit of quantification in the OPS Group), then 70% of the Sulfate administered as OSS is probably not absorbed. The percentage of the administered Phosphate dose excreted in urine was 1.7 times higher than that of the administered Sulfate dose. This suggests that Sulfate was absorbed to a lesser extent than Phosphate. However, these findings need to be interpreted with caution since the excretion of these electrolytes at baseline and the influence of food and water could not be taken into account.
- The mean fluid balance was positive for all groups; total water intake was higher than water loss. Subjects receiving OPS appeared

to be thirstier which may indicate that OSS causes less dehydration than OPS and less disturbances in electrolytes.

- Body weight was slightly decreased in all subjects. Changes in body weight did not significantly differ between treatment groups.
- Incidentally abnormal values were observed with vital signs, 12-lead ECG and physical examination. Despite statistically significant increases in QT and QTc interval in subjects receiving OPS, none of these was considered to be clinically significant, and mean values stayed within reference ranges.

	Mean changes from baseline for serum electrolyte concentrations (%)						p < 0.05	
	OPS Group 1		OSS Group 2		OSS Group 3		16 hr	22 hr
	T = 16 hr	T = 22 hr	T = 16 hr	T = 22 hr	T = 16 hr	T = 22 hr		
Ca (mmol/L)	-2.85	-1.86	0.78	-1.15	1.83	-1.60	* #	-
Ca x P (mg ² *dl ²)	25.0	18.3	-7.93	4.88	-5.72	5.84	* #	-
Cl (mmol/L)	-1.75	-0.44	-1.28	-0.96	-0.97	-0.15	-	-
HCO ₃ (mmol/L)	-8.90	-1.44	-5.53	-3.97	-5.50	-0.86	-	-
K (mmol/L)	-5.12	-6.91	0.82	1.22	4.77	3.95	# \$	#
Mg (mmol/L)	-6.28	1.41	-0.75	3.28	-0.63	5.28	* #	-
Na (mmol/L)	0.84	0.25	0.97	-0.72	-0.35	-0.24	-	-
PO ₄ (mmol/L)	28.7	20.4	-8.76	5.96	-7.38	7.64	* #	-
SO ₄ (mg/dL)	-21.0	-8.60	106	66.6	71.5	59.7	* #	* #

* = Group 2 significantly different from Group 1; p value < 0.05

= Group 3 significantly different from Group 1; p value < 0.05

\$ = Group 3 significantly different from Group 2; p value < 0.05

CONCLUSIONS

OSS was comparable to OPS regarding pharmacodynamic characteristics and safety. However, OSS may be somewhat more favorable than OPS. First, because it has slightly better cleansing characteristics. Second, because the electrolyte shifts after OSS were generally less frequent and smaller than after OPS and the changes after OPS were less often in a favorable direction. Moreover OSS makes the subjects less thirsty and is considered more palatable when administered in two 45 sessions separated by 11 h.

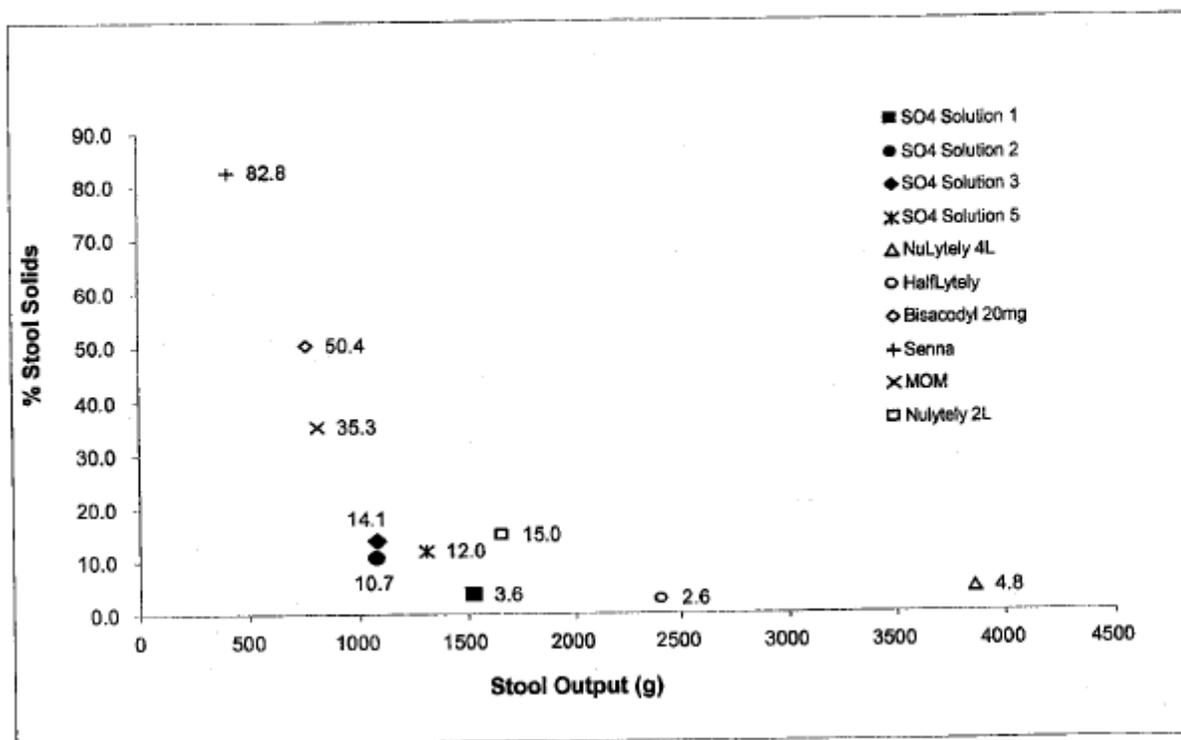
Summary of clinical development

Initial studies identified formulations of sodium-, potassium- and magnesium-sulfate combinations which appeared to have promise, based on the volume of stool produced and patient electrolyte levels. These Phase I studies confirmed that the formulations yielded a volume of feces that was similar to that produced by the hyperosmotic bowel preparation Phospho-Soda and other approved bowel preparations. At the same time they produced minimal changes in fluid and electrolyte balance. Additionally, a measure of the residual stool solids, dubbed the “scatocrit”, further refined these pharmacodynamic measures and could be used to screen formulations for their likely success. A small Phase 2 study confirmed that one of these preparations produced cleansing adequate for colonoscopic examination. Based on the safety and efficacy data reported in these Phase 1 and 2 studies, a to-be-marketed formulation was chosen and two large scale Phase 3 studies were undertaken. These studies are briefly reviewed below.

Fordtran performed a second Phase I study (See Baylor Study 005-082 in Section 5.3.4.1B) to continue the development of a sulfate based bowel cleansing formulation. A technique “scatocrit” measuring the amount of stool solids (percent solids) in a sample of the final diarrheal bowel movement was developed to provide a reliable correlation to cleansing efficacy as determined by actual colonoscopy. Twenty-seven healthy volunteers were enrolled in this open-label, non-randomized study comparing a number of laxatives and bowel cleansing agents including bisacodyl (20 mg), senna, Milk of Magnesia (MOM), NuLYTELY (2 Liters), NuLYTELY (4 Liters), HalfLyte® and Bisacodyl Tablets Bowel Prep Kit (HalfLyte) and four sulfate formulations. Since it is known that 4L NuLYTELY and HalfLyte (DiPalma et al, 2003) provide acceptable bowel cleansing, the efficacy of other combinations or formulations can be predicted based on the % stool solids and stool output of these known products.

The laxatives and bowel cleansing treatments were studied and the final stool analyzed for percent solids. In this study, a plot of stool volume versus percent stool solids was developed (see Figure 2.5.1.4-1).

Figure 2.5.1.4-1: Individual stool output results versus percent stool solids for each laxative.



The figure indicates that stool output of 2400g or greater with percent solids in the final bowel movement of less than 3% is consistent with adequate cleansing.

The study showed that a relationship between total stool output and stool solids (measured from a final BM) could be demonstrated. Laxative products (bisacodyl, senna, MOM) or 2L of NuLYTELY solution are known to be ineffective as bowel cleansing regimens. In this study, they acted as “negative controls” and expectedly failed to produce the targeted stool output and scatocrit measures. Because approved bowel preparation products were included that are known to provide adequate bowel cleansing, stool output and solids measurements can be used to predict adequate cleansing for future test preparations.

The sulfate solutions did not appear to affect serum electrolytes or osmolarity which is consistent with previous observations for sulfate containing solutions (see Phase I Study 001-022 reviewed above). No unexpected or serious adverse events were reported. One of the sulfate solution formulations (#5) was associated with the least net changes in stool electrolytes and was selected for further study with an increased dose.

A third Phase 1 study performed by Fordtran (See Baylor Study 006-181 in Section 5.3.4.1C) compared the safety and efficacy of an optimized sulfate formulation candidate (BLI800 Oral Sulfate Solution) to the marketed products Fleet Phospho-Soda (EZ-Prep) and 4L NuLYTELY in healthy volunteers. Following baseline serum and urine testing, subjects were treated in an in-patient setting during which all stool and urine were collected during and after preparation administration. Primary efficacy was based on total stool output, with percentage of stool solids, or “scatocrit” (described above and in Baylor Study 005-082) serving as a secondary measurement. These endpoints have been utilized in prior studies of both experimental and approved colonoscopy preparations and are surrogate markers of preparation efficacy. Safety was assessed through the collection of adverse event data, blood chemistry, and analysis of urine and stool electrolyte composition.

The Fleet preparation yielded about 2 liters of stool, while the BLI-800 and NuLYTELY preparations both induced about 3 liters of stool. All subjects were adequately hydrated during the preparation, with no net water losses. The scatocrit reported at completion of the BLI-800 preparation averaged 1.6%, similar to NuLYTELY (scatocrit = 1.1%), an approved colonoscopy preparation. The scatocrit following the Fleet preparation was higher, averaging 4.1%.

The Fleet preparation induced significant losses of potassium and hyperphosphatemia (due to phosphate absorption) with concomitant urine calcium reduction. This is consistent with previous literature reports and findings from early phase BLI800 development studies (For example, see CTD Module 5.3.4.1D for Braintree Study BLI800-101). The increase in urinary phosphate excretion and reduction in urinary calcium excretion in the Fleet EZ-Prep subjects was expected based on prior studies, and may be due in part to calcium phosphate precipitation. Analysis of urine from the EZ-Prep study subjects revealed that their urine had an increased tendency to precipitate calcium whereas BLI800 study subject urine had a decreased tendency for calcium precipitation.

There were no on-study deaths and no unexpected adverse events were reported following BLI800 administration.

A fourth Phase 1 study (See BLI800-101, located in Section 5.3.4.1D) compared the effects of an early sulfate formulation (similar to BLI800) to Fleet Phospho-Soda on fecal parameters, blood electrolyte levels and subject symptoms in healthy volunteers. The sulfate formulation that was used in this study is set out in CTD Section 2.5.2.1. Consistent with the Baylor experience, the sulfate formulation compared favorably to Phospho-Soda regarding pharmacodynamic characteristics and safety. The sulfate formulation produced similar stool volumes and less frequent and smaller electrolyte shifts than did Phospho-Soda. Urinary excretion of the administered dose was 40 % less for sulfate than that for phosphate, attesting to lower absorption

Phase II studies.

Two Phase 2 studies were conducted. BLI800-201 (See Module 5 Section 5.3.5.2A for the full report) evaluated a sulfate preparation that was derived from one of the early Fordtran formulations in 9 patients who were undergoing bowel preparation for colonoscopy (this sulfate formulation is described in Section 2.5.2.1). The colonoscopist rated each colonoscopy for cleansing according to a four point scale where a score of 1="poor" and a score of 4="excellent" and also assessed the location and amounts of residual stool and fluid. These scales rate these amounts as 1=absent, 2=small, 3=moderate, 4=excess in each of 5 colon segments (cecum, ascending, transverse and descending colon, and sigmoid/rectum region).

Preparation quality was deemed excellent by the colonoscopist in all cases and all nine patients had no residual stool in all of the segments of the colon.

Table 2.5.1.4-1 shows the mean residual fluid score, standard deviation and the % of patients with each score for each segment.

Table 2.5.1.4-1
Colonoscopy Residual Fluid

	Colon Segment				
	Cecum	Ascending	Transverse	Descending	Sigmoid/Rectum
Mean (SD)	1.11 (0.31)	1.11 (0.31)	1.89 (0.74)	1.11 (0.31)	1.22 (0.42)
Range	1 - 2	1 - 2	1 - 3	1 - 2	
N (%) of patients					
1=absent	8 (89%)	8 (89%)	3 (33%)	8 (89%)	7
2=small	1 (11%)	1 (11%)	4 (44%)	1 (11%)	2
3=moderate	0	0	2 (22%)	0	0
4=excess	0	0	0	0	0

No patient had an excess amount of fluid in any segment. Only the transverse colon in two patients had a “moderate” amount of fluid. Of all the segments 43/45 (96%) were considered to have no or “small” amounts of fluid.

Adverse events of nausea, vomiting, bloating, mouth ulcers and headache were reported. No serious and unexpected adverse events occurred. Laboratory assessments indicated small, non-clinically significant changes.

Braintree study BLI-202 utilized the to-be-marketed formulation that is described in CTD Section 2.5.2.1. This was a pharmacokinetic study in healthy volunteers, and patients with renal and hepatic disease. There were no differences evident in the safety profile for BLI800 among the health status groups. There was no evidence of abnormalities of clinical chemistry. Serum sodium, magnesium and potassium all stayed within the reference ranges. No shifts in anion gap were noted. The amount of sulfate excreted in the urine was similar among the health status groups. Serum pharmacokinetics were not affected by health status.

Braintree Protocol BLI800-202

This study is summarized in Module 2 Section 2.7.2.2.2D (see Module 5 Section 5.3.4.2A for full study report). FDA requested that the pharmacokinetics of sulfate be studied and compared between healthy volunteers and patients. The patient groups were those with mild or moderate hepatic impairment (M/MHD-Child-Pugh Stage A or B) or moderate renal disease (MRD- FDA Group 3 moderate renal impairment).

A total of 18 subjects completed the study; 6 (3 males) with MRD, 6 (2 males) with M/MHD and 6 (2 males) NHVs. There were no withdrawals due to treatment. BLI800 was well-tolerated by patients with MRD and M/MHD. All adverse events were deemed to be mild-moderate in severity. There were no on-study deaths and no treatment emergent serious adverse events. Adverse events were distributed evenly according to health status and were mainly limited to headache (29%), nausea (12.5%) and vomiting (4.2%). No untoward changes were noted in vital signs or clinical chemistry. The Investigator concluded that there were no clinically significant chemistry, hematology, or urinalysis findings. There were no differences in serum sodium, potassium or magnesium between the patient groups and the healthy volunteers. Other differences were small and were generally consistent with the patients’ health status.

Serum sulfate levels were highly variable at baseline and at all time points after BLI800 administration, even when the values were adjusted for baseline levels. Sulfate was higher at baseline and after dosing in the renal disease patients. No statistically significant differences were seen between the patient groups and the healthy volunteers with regard to any pharmacokinetic variable. In all patients, sulfate levels returned to pre dose values within 48 hours after the first dose of BLI800. The amount of sulfate and the fraction of the sulfate dose excreted in urine did not differ across the groups.

While patients with MRD had elevated serum sulfate levels at baseline and after BLI800 in comparison to the other health status groups, the elevations were less than those seen in renal failure and were not sufficient to alter biochemical parameters that are associated clinically with hypersulfatemia. These observations warrant the use of BLI800 in these patient groups.

Phase III studies

The formulation of BLI800 that was used in the Phase 3 studies (BLI800-301 and BLI800-302) was the same as the to-be-marketed product and is described fully in CTD Section 2.5.2.1. The primary efficacy variable for both studies was the investigator rating of colon cleansing as assessed during colonoscopy for routine indications. The cleansing assessment was based on a four point scale ranging from "poor" to "excellent" used in previous studies which were the basis for approval of NuLYTELY (NDA 19-797) and HalfLyte (NDA 21-551).

Braintree Protocol BLI800-301 was a single-blind, multicenter study that evaluated same-day administration of BLI800 compared to MoviPrep. In this study, the two 6oz portions of BLI800 were administered one to two hours apart. The Intent-to-Treat (ITT) population included 387 outpatients scheduled for colonoscopy for a routinely accepted indication. The study demonstrated that BLI800 was not inferior to MoviPrep ($p < 0.001$), and also equivalent to MoviPrep ($p = 0.614$) with respect to physician ratings of colon preparation in completing patients.

Treatment emergent adverse events were equivalent between the two treatment groups although in questionnaires BLI800 patients scored a slightly higher incidence of vomiting compared to Moviprep patients. This difference was less than previously observed for 4 liter lavage preparations (NuLYTELY, GoLYTELY). Most patients reporting these symptoms had completed both doses of their preparation in about 1 hour. Therefore, labeling should encourage a longer wait period (2 hours) between the doses. No other significant differences related to adverse events were noted. There were no on-study deaths and no treatment emergent serious adverse events.

Braintree Protocol BLI800-302 was a single-blind, multicenter study that evaluated two-day administration of BLI800 compared to Moviprep. In this study, patients took their one half their preparation dose the evening prior to colonoscopy, and the second half the morning of their procedure. The Intent-to-Treat (ITT) population included 364 outpatients scheduled for colonoscopy for routinely accepted indications. The study demonstrated that BLI-800 was not inferior ($p < 0.001$), and also equivalent to Moviprep ($p = 0.391$) with respect to physician ratings of colon preparation in completing patients.

The incidence and intensity of patient reported preparation symptoms were similar between the two groups. No statistically significant differences were reported for abdominal cramping, nausea, bloating and vomiting in the total population or in any demographic subgroup. BLI800 patients had significantly lower ratings of overall discomfort than Moviprep patients. There were no treatment emergent serious adverse events in the BLI800 group.

In a combined analysis of studies BLI800-301 and 302, as shown in Table 2.5.4-4, the overall preparation cleansing score (assessed by the colonoscopist) was better for BLI800 than for Moviprep.

These studies demonstrated that BLI800 administered as a same day or two-day preparation is at least equivalent, and may be superior in its overall cleansing ability, to Moviprep in cleansing the colon prior to colonoscopy. Qualitatively better cleansing results were obtained with either preparation with an overnight preparation regimen.

4.3.1. Cover sheet and OCP Filing/Review Form

Cover Sheet and OCP Filing/Review Form

Office of Clinical Pharmacology New Drug Application Filing and Review Form				
General Information About the Submission				
	Information			Information
NDA Number	NDA 22-372	Brand Name	Suprep	
OCP Division (I, II, III)	III	Generic Name	Sodium sulfate, potassium sulfate and magnesium sulfate	
Medical Division	Gastroenterology	Drug Class		
OCP Reviewers	PeiFan Bai	Indication(s)	Bowel cleansing prior to colonoscopy	
OCP Team Leader	Sue-Chi Lee	Dosage Form	Oral solution	
Date of Submission	July 1, 2008	Proposed Dosing Regimen	44.48 g of sulfate salts in 12 ounces of water prior to colonoscopy	
Estimated Due Date of OCP Review	Aug 25, 2008	Route of Administration	oral	
Medical Division Due Date	Sep 25, 2008	Sponsor	Braintree Lab, Inc	
PDUFA Due Date	Oct. 25, 2008	Priority Classification	standard	
Clin. Pharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies				
HPK Summary				
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	X	6		
Healthy Volunteers-				
single dose:				
multiple dose:				

Patients-				
single dose:	X	5		
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:	X	1		
renal impairment:	X	1		
hepatic impairment:	X	1		
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X			
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		5		
Filability and QBR comments				

	"X" if yes	Comments
Application filable ?	x	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm	x	Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	What are the design features of the submitted studies used to support the labeling claims and fulfillment of PWR?	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Jane Bai
3/26/2009 02:17:47 PM
BIOPHARMACEUTICS

Sue Chih Lee
4/10/2009 07:59:03 PM
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