

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
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Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

MEMORANDUM

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Sponsor: Braintree Laboratories, Inc.

Drug: SuPrep Bowel Prep Kit (sodium sulfate, potassium sulfate
and magnesium sulfate)

NDA: 22-372

Subject: Quantitative Safety Review of SuPrep Phase 3 Studies

Summary and Conclusions

This memorandum provides an assessment of safety for BLI800, SuPrep Bowel Prep Kit (sodium sulfate, potassium sulfate and magnesium sulfate) based on data from two Phase 3 trial (301 and 302) submitted by the sponsor to assess the efficacy and safety of the drug. The drug is indicated to prepare subjects for colonoscopy by cleansing the bowels of fecal material. The Division of Gastroenterology Products requested an evaluation of outlier chemical values based on data from the two trials. There are several issues present that could have an impact on safety evaluation.

The statistical assessment in this memorandum is exploratory in nature, and it is not meant to support in any meaningful way the decision-making process. Note that the trials under consideration were not designed to ascertain safety, and so statistical inference on safety issues is not possible.

- There appears to be evidence suggesting the presence of a relationship between the use of SuPrep over the active control (MoviPrep) and the number of subjects for whom **Calcium and Uric Acid** levels fall outside of the defined normal range during the Phase 3 trials. A subject was defined as “Flagged” if their value for a chemical of interest fell outside the normal range after treatment, when their baseline value was within the normal range (or abnormal in the opposite direction); 12.13% of SuPrep patients were Flagged for Calcium during the course of the studies, as compared to 7.20% of MoviPrep patients. For Uric Acid, 21.56% of Suprep patients and 14.67% of MoviPrep patients were Flagged for Uric Acid. No evidence exists that there is an interaction with any demographic category.
- Furthermore, for both SuPrep and MoviPrep, the evidence suggests that the two-day regimen is related to more subjects having abnormal **Calcium** values during the course of the trial, as opposed to the one-day regimen. In the one-day regimen study (301), 6.77% of all subjects (7.73% of SuPrep and 5.70% of MoviPrep subjects) became Flagged for Calcium, as compared to 12.71% of all subjects (16.57% of SuPrep and 8.74% of MoviPrep subjects) in the two-day regimen study (302). No interaction could be found with treatment, nor any confounding with demographic variables.
- There appears to be evidence suggesting that SuPrep may be related to lower rates of being Flagged for **Chloride** than MoviPrep. The percentages of patients that become Flagged for Chloride throughout the study were 6.47% for SuPrep and 14.93% for MoviPrep. No demographic or study interactions could be find with this result.
- Across treatments and regimens, there appeared to be a relationship between gender and becoming Flagged for **Creatinine**. While 3.21% of females met the criteria of being Flagged for Creatinine, 9.97% of males in the two studies did. There were no

visible confounding effects with treatment, regimen, or other demographic characteristics. The clinical reviewer may determine whether this possible finding, which does not pertain uniquely to SuPrep, is of interest or concern.

- There appeared to be a possible significant relationship between a treatment of SuPrep and the reporting of **Vomiting** Adverse Events (AEs); across studies, 25 (10.93%) of SuPrep patients and 14 (3.72%) of MoviPrep patients reported Vomiting AEs.
- Within the subjects taking SuPrep, evidence suggests that the one-day regimen (study 301) was more strongly related with **Abdominal Distension** AEs than the two-day regimen (study 302). Of SuPrep patients, 57.22% of those on the one-day regimen and 42.54% of those on the two-day regimen reported Abdominal Distension.
- Across subjects that were assigned either treatment, those that were Flagged for **Serum Osmolality** appeared to experience more **Abdominal Pain** AEs during the study, and ones that were Flagged for **Sodium** appeared to experience more **Vomiting** AEs. Out of the 123 subjects who were Flagged for Serum Osmolality, 64 (52.03%) reported an Abdominal Pain AE, as compared to 216 (34.39%) of the 628 subjects who were not Flagged for Serum Osmolality. Of the 37 subjects Flagged for Sodium, 7 (18.92%) reported experiencing Vomiting, while only 48 (6.72%) of the 714 subjects that were not Flagged for Sodium reported this AE. These effects were across treatments and regimens, and no confounders not otherwise listed in this summary could be found.
- Female subjects across treatments and regimens appeared to be at higher risk for Abdominal Distension, Abdominal Pain, Discomfort, Nausea, and Vomiting AEs. Table 1 summarizes the number and percent of the 409 females and 342 males assigned treatments that experienced each of these events.

Table 1: Adverse Events of Concern by Sex

N (% of Sex)	Female (N=409)	Male (N=342)
Abdominal Distension	244 (59.66)	149 (43.57)
Abdominal Pain	182 (44.50)	108 (31.58)
Discomfort	281 (68.70)	186 (54.39)
Nausea	188 (45.97)	107 (31.29)
Vomiting	45 (11.00)	10 (2.92)

This apparent increase in event occurrence risk did not differ significantly by treatment.

- The number of subjects for whom tests were redrawn does not appear to be related to the treatment arm to which they were assigned; however, the lack of proper documentation regarding the reasons for some of these retests may be a concern.

Overall, there appear to be few safety issues of note for the SuPrep Bowel Prep Kit. However, the apparent increased incidence of Vomiting Adverse Events and increases of Calcium and Uric Acid may require additional evaluation by the clinical reviewers. The main body of this memorandum will provide further information on the above results. The appendix to this memorandum contains graphical representations of the distribution of chemical values for each study and treatment.

Objective

Two clinical trials were submitted by the sponsor with the objective of supporting the efficacy and safety of SuPrep Bowel Prep Kit when compared against MoviPrep (the active control). The two trials's primary objective was to support efficacy for the One-Day and Two-Day treatment regimes. A secondary objective was to evaluate the safety of the drug. Note that safety evaluation is exploratory in nature and no statistical inference can be made from it.

Background

On July 1, 2008, Braintree Laboratories, Inc. submitted NDA 22-372 to apply for the approval of BLI800 (SuPrep Bowel Prep Kit) as a bowel cleansing pre-treatment for subjects who will be undergoing colonoscopy. Two Phase 3 clinical trial datasets, BLI800-301 and BLI800-302, were submitted, along with Phase 1 and Phase 2 datasets that will not be considered in this memorandum. These trials pertained to, respectively, the one-day and two-day regimens of the SuPrep treatment; each trial used a comparable regimen of the approved MoviPrep treatment as an active control.

On September 1, 2009, the Division of Gastroenterology Products (DGP) submitted a formal Consult request to the Quantitative Safety and Pharmacoepidemiology Group (QSPG, now Division VII), requesting the following:

- Demographics data for subjects in each study for whom the following bodily chemicals were in the normal range at baseline, but abnormal in the indicated direction during the course of the study: Bicarbonate (low), BUN (high), Calcium (high/low), Chloride (high/low), creatinine (high), Magnesium (high), Phosphorus (high/low), Potassium (high/low), Serum Osmolality (high/low), Sodium (high/low), Uric Acid (high).
- Attempt to establish whether there are any demographic correlates with the above abnormalities.

- Analyze whether there are any correlations between the above abnormalities and adverse events.

This memorandum is in response to this consult request and will address these points.

Datasets

The submitted two Phase 3 clinical datasets (BLI800-301 and BLI800-302); each consisted of approximately 400 subjects that were randomly assigned to either treatment with SuPrep or MoviPrep bowel preparation treatments. Each trial included subjects that were majority White (88.14% of Study 301, 86.93% of Study 302), with Black or African-American subjects representing most of the remaining subjects in each study (11.38% of Study 301 subjects, 9.33% of Study 302 subjects). Note that for analysis purposes, the Race category “Native Hawaiian / Other Pacific Islander” was combined with the category “Other,” as only one subject was in the former category. The majority of subjects identified as not Hispanic or Latino (93.99% of Study 301, 94.99% of Study 302). Sex was fairly evenly distributed (54.57% of Study 301 and 54.09% of Study 302 subjects were Female). The assessment for this memorandum was performed with the final versions of the datasets obtained from the sponsor. Table 2 shows the number of subjects in each demographic category across the studies and treatments.

Table 2: Subject demographics

Number of subjects in category		Study 301		Study 302	
		SuPrep (N=194)	MoviPrep (N=193)	SuPrep (N=181)	MoviPrep (N=183)
Sex	Female	110	103	98	98
	Male	84	90	83	85
Race	Asian	1	0	8	2
	Black or African-American	21	23	16	16
	White	169	169	154	160
	Other	1	0	3	1
Ethnicity	Hispanic or Latino	14	11	6	13
	Not Hispanic or Latino	180	182	175	170

Study Design

During the initial screening visit (Visit 1), subjects were assessed for whether they met the inclusion/exclusion criteria; for the sake of brevity, these criteria will not be repeated here.

If these criteria were met, the subject was randomized 1:1 to SuPrep or MoviPrep. Subjects were randomized by being assigned the lowest drug kit number available. Both studies were selectively single-blind: the patients were aware of their treatment, but the colonoscopist and some other unspecified study personnel were kept blinded and were not allowed to take part in randomization, drug dispensation, drug return, and accountability. Subjects were instructed to not discuss the specifics of their treatment with staff members. Any unblinding of the colonoscopist or other blinded personnel was supposed to be recorded as a violation of protocol.

Both treatments were orally ingested, to be accompanied by large amounts of water, in two separate doses. Depending upon the regimen, these two doses were approximately two hours apart (Study 301) or 10-12 hours apart (Study 302).

The screening visit (Visit 1) was defined by protocol to be within 15 days prior of the colonoscopy (Visit 2); this was the only screening for inclusion/exclusion criteria that occurred. On Visit 2, the follow-up visit (Visit 3) was scheduled to be approximately 30 days post-colonoscopy. Batteries of tests to determine the levels of various bodily chemicals were performed at each visit.

Chemical abnormalities

In discussions with the DGP, it was determined that the main focus of the clinical team's interest was subjects for whom bodily chemical levels were in the normal range at baseline (Visit 1), but were subsequently outside of the normal range, either on the day of the colonoscopy (Visit 2), or at the follow-up meeting that happened approximately 30 days after the colonoscopy (Visit 3). The analysis, therefore, focused upon those subjects that met this criteria; for brevity, such subjects will hereafter be referred to as "Flagged" patients with respect to the chemical for which such an abnormality occurred. Additionally, patients for whom the screening visit was abnormal, but the Visit 2 or Visit 3 measurements were abnormal in the opposite direction (e.g. abnormally low value at screening, abnormally high value at colonoscopy) were also termed Flagged.

A secondary interest of the DGP, brought up in discussions, was the subjects who had tests redrawn during the course of the study. Particularly of interest were redraws that took place too far from the colonoscopy (Visit 2) or the follow-up visit (Visit 3). Thus, before the results for each chemical are given, it is important to briefly discuss how redrawn measurements were handled in the analysis. There were 35 subjects for whom at least one of the laboratory tests was redrawn. The statistical assessment addressed redraws by a set of rules that attempted to model as closely as possible the desires expressed by the DGP in discussions. If the original draw was not marked as missing, then the original draw value was retained as the "true" measurement for the given Visit, and the redraw was marked as a redraw for that

visit. If the original measurement for that visit was missing, then the redraw may have been accepted in place of the original measurement if one of the following criteria was met:

- For Visit 1, if the redraw was taken at least 24 hours before the day of colonoscopy.
- For Visit 2, if the redraw was taken less than 24 hours after the original attempt of the Visit 2 measurement.
- For Visit 3, if the redraw was taken within one week of the original attempt of the Visit 3 measurement.

If none of these criteria were met, the original value for the visit was marked as missing and the redraw specifically marked as a redraw for that visit. If the criteria were met, then the redraw was treated as the original measurement for the visit, for ease of analysis. A complete listing of patients for whom any measurements were redrawn was made and is available so that cross-referencing can be performed to determine which subjects had their redrawn measurements treated as original values. Note that a subject would be termed as “Flagged” if any of their Visit 2 or Visit 3 measurements, including redraws or original measurements that were later redrawn, were abnormal. Additionally, if no screening visit value was available, then it was considered to be “normal” for the purposes of determining whether a subject was Flagged. These methods may cause a slightly higher rate of “false positives” for Flagged status, but they maintain a conservative approach to the treatment of safety. These criteria are subject to concurrence with the opinion of the medical reviewer. Table 3 shows the number of redraws by study (regimen), treatment, and visit.

Table 3: Frequency of redrawn subjects by study, treatment, and visit

Study	Treatment	N (% of Study/Treatment) redrawn		
		Visit 1	Visit 2	Visit 3
301	SuPrep (N=194)	5 (2.58)	3 (1.55)	3 (1.55)
	MoviPrep (N=193)	5 (2.59)	3 (1.55)	0 (0)
302	SuPrep (N=181)	5 (2.76)	3 (1.66)	0 (0)
	MoviPrep (N=183)	4 (2.19)	1 (.55)	2 (1.09)

Since this assessment of the data is exploratory and the trials were not conducted with safety as a primary objective, only descriptive measures are provided.

In addition to the subsections below, a series of graphical representations of the range of values obtained for each chemical are attached in Appendix A.

Bicarbonate

Out of the 751 subjects in Studies 301 and 302, 112 (14.91%) were marked as Flagged for Bicarbonate. Table 4 summarizes how Flagged for Bicarbonate subjects were distributed

for demographic factors; each cell contains the number of subjects Flagged for Bicarbonate, and the percent of all subjects matching that combination of factors those Flagged subjects represent.

Table 4: Frequency of subjects Flagged for Bicarbonate

N (% of cell) Flagged for Bicarbonate		Study 301		Study 302	
		SuPrep (N=194)	MoviPrep (N=193)	SuPrep (N=181)	MoviPrep (N=183)
Total Flagged		23 (11.86)	35 (18.13)	27 (14.92)	27 (14.75)
Sex	Female	15 (13.64)	21 (20.39)	14 (14.29)	19 (19.39)
	Male	8 (9.52)	14 (15.56)	13 (15.66)	8 (9.4)
Race	Asian	0 (0)	—	3 (37.5)	0 (0)
	Black or African-American	4 (19.05)	7 (30.43)	4 (25.00)	1 (6.25)
	White	19 (11.24)	28 (16.57)	19 (12.34)	25 (15.63)
	Other	0 (0)	—	1 (33.33)	0 (0)
Ethnicity	Hispanic or Latino	0 (0)	3 (27.27)	0 (0)	1 (7.69)
	Not Hispanic or Latino	23 (12.78)	32 (17.58)	27 (15.43)	26 (15.29)

Table 5 shows the three subjects with Bicarbonate levels that appeared to be outside the range of the majority of data. The normal range for Bicarbonate measurements is 22–29, as defined by the sponsor.

Table 5: Subjects with extreme Bicarbonate values

Patient	Study	Treatment	Age	Sex	Race	Ethnicity	Visit 1	Visit 2	Visit 3
01047	301	MoviPrep	51	F	White	Not H/L	27	15	23
07047	301	SuPrep	55	F	White	Not H/L	22	11	21
09011	301	MoviPrep	70	F	White	Not H/L	23	15	23

BUN

Across studies, 75 (9.99%) of subjects were Flagged for BUN. As with Bicarbonates, Table 6 gives the prevalence of Flagged for BUN status among demographic categories; no strong evident relationships seem to exist between these categories and being Flagged for BUN.

Two subjects had BUN values that were far outside the range of the rest of the data; normal BUN values are in the range of 6–19.

Table 6: Frequency of subjects Flagged for BUN

N (% of cell) Flagged for BUN		Study 301		Study 302	
		SuPrep (N=194)	MoviPrep (N=193)	SuPrep (N=181)	MoviPrep (N=183)
Total Flagged		24 (12.37)	14 (7.25)	16 (8.84)	21 (11.48)
Sex	Female	12 (10.90)	6 (5.83)	8 (8.16)	11 (11.22)
	Male	12 (14.29)	8 (8.89)	8 (9.64)	10 (11.76)
Race	Asian	0 (0)	—	1 (12.50)	0 (0)
	Black or African-American	2 (9.52)	1 (4.35)	1 (6.25)	1 (6.25)
	White	22 (13.02)	13 (7.69)	14 (9.09)	20 (12.50)
	Other	0 (0)	—	0 (0)	0 (0)
Ethnicity	Hispanic or Latino	1 (7.14)	0 (0)	1 (16.67)	2 (15.38)
	Not Hispanic or Latino	23 (12.78)	14 (7.69)	15 (8.57)	19 (11.18)

Table 7: Subjects with extreme BUN values

Patient	Study	Treatment	Age	Sex	Race	Ethnicity	Visit 1	Visit 2	Visit 3
03042	301	MoviPrep	65	F	White	Not H/L	18	20	29
13022	302	SuPrep	45	M	Black or African-American	Not H/L	15	18	30

Calcium

Seventy-two (9.59%) of the subjects studied were marked as being Flagged for Calcium. Table 8 shows the breakdown of subjects Flagged for Calcium by demographic category, study, and treatment.

Table 8: Frequency of subjects Flagged for Calcium

N (% of cell) Flagged for Calcium		Study 301		Study 302	
		SuPrep (N=194)	MoviPrep (N=193)	SuPrep (N=181)	MoviPrep (N=183)
Total Flagged		15 (7.73)	11 (5.70)	30 (16.57)	16 (8.74)
Sex	Female	9 (8.18)	5 (4.85)	15 (15.31)	10 (10.20)
	Male	6 (7.14)	6 (6.67)	15 (18.07)	6 (7.06)
Race	Asian	0 (0)	—	1 (12.50)	0 (0)
	Black or African-American	3 (14.29)	0 (0)	2 (12.50)	2 (12.50)
	White	12 (7.10)	11 (6.51)	26 (16.88)	14 (8.75)
	Other	0 (0)	—	1 (33.33)	0 (0)
Ethnicity	Hispanic or Latino	0 (0)	1 (9.09)	1 (16.67)	1 (7.69)
	Not Hispanic or Latino	15 (8.33)	10 (5.49)	29 (16.57)	15 (8.82)

Note from Table 8 that 45 (12%) of subjects assigned to SuPrep were Flagged for Calcium, as opposed to 26 (7.18%) of MoviPrep patients. This apparent difference between the two treatments seems to be particularly strong for Study 302 (the two-day regimens). Interpretation of this finding and whether it should be monitored further are deferred to the clinical judgment.

Similarly, the evidence suggests a relationship between study/regimen and being Flagged for Calcium; 26 (6.72%) of the subjects in Study 301 (one-day regimen) and 46 (12.64%) of the subjects in Study 302 (two-day regimen) were Flagged for Calcium. This relationship seems to be present even when the apparent treatment effect is considered. While the medical review demonstrated that the One-Day treatment regimen had several safety concerns that were more severe than in the Two-Day regimen, it appears that with respect to having normal Calcium levels, the One-Day regimen may be preferable.

Three subjects had Calcium values that were outside the measurements for the rest of the data and are summarized in Table 9. The normal range for Calcium is 8.4–10.2.

Table 9: Subjects with extreme Calcium values

Patient	Study	Treatment	Age	Sex	Race	Ethnicity	Visit 1	Visit 2	Visit 3
02001	301	SuPrep	52	F	White	Not H/L	9.5	7.8	9.5
07047	301	SuPrep	55	F	White	Not H/L	9.1	7.9	8.8
20005	302	SuPrep	58	F	White	Not H/L	9.3	5.5	9.3

Chloride

Approximately one out of every ten (80, 10.65%) of subjects were Flagged for Chloride. Table 10 summarizes the counts of this status across demographics, studies, and treatments.

There appears to be a quite strong relationship between being Flagged for Chloride and treatment. Unlike the apparent relationships with chemicals such as Calcium, however, SuPrep was associated with a lower rate of Flagged for Chloride. While 24 (6.4%) of SuPrep subjects were Flagged for Chloride, 56 (14.89%) of MoviPrep subjects were so Flagged. This may be indicative of a safety issue where SuPrep is superior to its active control, though inference is not possible to test this. There doesn't appear to be any other demographics that are related to differences in Flagged for Chloride rates.

Two subjects, summarized in Table 11, had Chloride values that appeared to be far outside the spread of the majority of the data. The normal range for Chloride values is 96–108.

Table 10: Frequency of subjects Flagged for Chloride

N (% of cell) Flagged for Chloride		Study 301		Study 302	
		SuPrep (N=194)	MoviPrep (N=193)	SuPrep (N=181)	MoviPrep (N=183)
Total Flagged		12 (6.19)	29 (15.03)	12 (6.63)	27 (14.75)
Sex	Female	7 (6.36)	17 (16.50)	6 (6.12)	20 (20.41)
	Male	5 (5.95)	12 (13.33)	6 (7.23)	7 (8.24)
Race	Asian	0 (0)	—	1 (12.50)	0 (0)
	Black or African-American	0 (0)	4 (17.39)	0 (0)	2 (12.50)
	White	12 (7.10)	25 (14.79)	11 (7.14)	25 (15.63)
	Other	0 (0)	—	0 (0)	0 (0)
Ethnicity	Hispanic or Latino	1 (7.14)	2 (18.18)	0 (0)	0 (0)
	Not Hispanic or Latino	11 (6.11)	27 (14.84)	12 (6.86)	27 (15.88)

Table 11: Subjects with extreme Chloride values

Patient	Study	Treatment	Age	Sex	Race	Ethnicity	Visit 1	Visit 2	Visit 3
15045	302	SuPrep	53	F	White	Not H/L	100	100	89
20005	302	SuPrep	58	F	White	Not H/L	103	124	105

Creatinine

Forty-seven (6.26%) of study subjects were classified as Flagged for Creatinine. The demographics breakdown of this status is contained in Table 12.

Table 12: Frequency of subjects Flagged for Creatinine

N (% of cell) Flagged for Creatinine		Study 301		Study 302	
		SuPrep (N=194)	MoviPrep (N=193)	SuPrep (N=181)	MoviPrep (N=183)
Total Flagged		16 (8.25)	13 (6.74)	9 (4.97)	9 (4.92)
Sex	Female	5 (4.55)	3 (2.91)	3 (3.06)	2 (2.04)
	Male	11 (13.10)	10 (11.11)	6 (7.23)	7 (8.24)
Race	Asian	0 (0)	—	0 (0)	0 (0)
	Black or African-American	2 (9.52)	2 (8.70)	3 (18.75)	1 (6.25)
	White	13 (7.69)	11 (6.51)	6 (3.90)	8 (5.00)
	Other	0 (0)	—	0 (0)	0 (0)
Ethnicity	Hispanic or Latino	1 (7.14)	1 (9.09)	0 (0)	0 (0)
	Not Hispanic or Latino	15 (8.33)	12 (6.59)	9 (5.14)	9 (5.29)

Creatinine was the only chemical that appeared to have a relationship with Gender among those considered. Out of the subjects studied, 13 (3.18%) of the females were Flagged for

Creatinine, as compared to 34 (9.94%) males. No other factors could be found that seemed to contribute to this apparent difference.

One subject had a Creatinine value that appeared to be far outside the range of the majority of the data. The normal range for a male’s Creatinine is 0.5–1.2.

Table 13: Subject with extreme Creatinine values

Patient	Study	Treatment	Age	Sex	Race	Ethnicity	Visit 1	Visit 2	Visit 3
05018	301	MoviPrep	49	M	White	Not H/L	1.1	1.9	1.2

Magnesium

Only one subject in either of the studies was termed Flagged for Magnesium. Obviously, it is impossible to draw any reasonable conclusions from this single occurrence. The pertinent information for this subject is given below.

Table 14: Subject Flagged for Magnesium

Patient	Study	Treatment	Age	Sex	Race	Ethnicity	Visit 1	Visit 2	Visit 3
11019	302	SuPrep	50	M	White	Not H/L	2	2.2	1.8

Phosphorus

Phosphorus was a chemical for which 74 (9.85%) of the subjects were Flagged. Table 15 contains the breakdown across demographics. No strong relationships are apparent in the data.

There were three subjects for whom a Phosphorus value was far outside the range of the rest of the data; their demographics are summarized in Table 16. The normal range for Phosphorus is 2.6–4.5.

Potassium

Of the study subjects, 73 (9.72%) were Flagged for Potassium. Table 17 has the demographics and the breakdown of Flagged proportions among categories. As with Phosphorus, no demographic appears to have a strong relationship with being Flagged for Potassium.

The four subjects for whom a Potassium value seemed far outside the range of the rest of the data are summarized in Table 18. The normal range for Potassium is 3.5–5.1.

Table 15: Frequency of subjects Flagged for Phosphorus

N (% of cell) Flagged for Phosphorus		Study 301		Study 302	
		SuPrep (N=194)	MoviPrep (N=193)	SuPrep (N=181)	MoviPrep (N=183)
Total Flagged		21 (10.82)	15 (7.77)	17 (9.39)	21 (11.48)
Sex	Female	5 (4.55)	3 (2.91)	3 (3.06)	2 (2.04)
	Male	11 (13.10)	10 (11.11)	6 (7.23)	7 (8.24)
Race	Asian	0 (0)	—	0 (0)	0 (0)
	Black or African-American	2 (9.52)	2 (8.70)	3 (18.75)	1 (6.25)
	White	13 (7.69)	11 (6.51)	6 (3.90)	8 (5.00)
	Other	0 (0)	—	0 (0)	0 (0)
Ethnicity	Hispanic or Latino	1 (7.14)	1 (9.09)	0 (0)	0 (0)
	Not Hispanic or Latino	15 (8.33)	12 (6.59)	9 (5.14)	9 (5.29)

Table 16: Subjects with extreme Phosphorus values

Patient	Study	Treatment	Age	Sex	Race	Ethnicity	Visit 1	Visit 2	Visit 3
07037	301	SuPrep	59	F	White	Not H/L	3.4	4	5.2
12030	302	MoviPrep	30	F	White	Not H/L	3.2	3	5.9
18025	302	MoviPrep	53	F	White	Not H/L	4.3	3.9	5.5

Table 17: Frequency of subjects Flagged for Potassium

N (% of cell) Flagged for Potassium		Study 301		Study 302	
		SuPrep (N=194)	MoviPrep (N=193)	SuPrep (N=181)	MoviPrep (N=183)
Total Flagged		16 (8.25)	17 (8.81)	17 (9.39)	23 (12.57)
Sex	Female	9 (8.18)	8 (7.77)	10 (10.20)	11 (11.22)
	Male	7 (8.33)	9 (10.00)	7 (8.43)	12 (14.12)
Race	Asian	0 (0)	—	0 (0)	1 (50.00)
	Black or African-American	2 (9.52)	1 (4.35)	0 (0)	2 (12.50)
	White	14 (8.28)	16 (9.47)	16 (10.39)	20 (12.50)
	Other	0 (0)	—	1 (33.33)	0 (0)
Ethnicity	Hispanic or Latino	0 (0)	4 (36.36)	0 (0)	2 (15.38)
	Not Hispanic or Latino	16 (8.89)	13 (7.14)	17 (9.71)	21 (12.35)

Serum Osmolality

Across studies, 123 (16.38%) of subjects were Flagged for Serum Osmolality. The table below contains the distribution of Flagged status among the demographics.

Those who were Flagged for Serum Osmolality had a mean age 55.28 (sd: 11.54), and those who were not Flagged had a mean age 56.62 (sd: 11.42).

Table 18: Subjects with extreme Potassium values

Patient	Study	Treatment	Age	Sex	Race	Ethnicity	Visit 1	Visit 2	Visit 3
02019	301	Suprep	62	F	White	Not H/L	4	5.8	4.9
04023	301	SuPrep	55	M	White	Not H/L	4.5	6	4.2
15036	302	SuPrep	76	M	Philipeno	Not H/L	4.3	6.1	4.4
15063	302	MoviPrep	72	M	White	Not H/L	4.4	6.7	.

Table 19: Frequency of subjects Flagged for Serum Osmolality

N (% of cell) Flagged for Serum Osmolality		Study 301		Study 302	
		SuPrep (N=194)	MoviPrep (N=193)	SuPrep (N=181)	MoviPrep (N=183)
Total Flagged		25 (12.89)	34 (17.62)	37 (20.44)	27 (14.75)
Sex	Female	14 (12.73)	25 (24.27)	23 (23.47)	11 (11.22)
	Male	11 (13.10)	9 (10.00)	14 (16.87)	16 (18.82)
Race	Asian	0 (0)	—	2 (25.00)	1 (50.00)
	Black or African-American	2 (9.52)	5 (21.74)	3 (18.75)	4 (25.00)
	White	21 (12.43)	28 (16.57)	31 (20.13)	22 (13.75)
	Other	1 (100.00)	—	1 (33.33)	0 (0)
Ethnicity	Hispanic or Latino	2 (14.29)	5 (45.45)	0 (0)	1 (7.69)
	Not Hispanic or Latino	23 (12.78)	29 (15.93)	37 (21.14)	26 (15.29)

There was one patient that had a Serum Osmolality value that appeared far from the range of the rest of the data. Their demographics are provided in Table 20. The normal range for Serum Osmolality is 285–295.

Table 20: Subject with extreme Serum Osmolality values

Patient	Study	Treatment	Age	Sex	Race	Ethnicity	Visit 1	Visit 2	Visit 3
11002	302	MoviPrep	68	M	White	Not H/L	295	308	.

Sodium

Sodium was one of the chemicals with the least number of Flagged subjects, with only 37 (4.93%) having this status across treatments and studies. The distribution across demographics is in Table 21; there were no apparent relationships between categories and being Flagged for Sodium that could be found.

One subject had a Sodium value that appeared to be outside the range of the rest of the data. The normal range for Sodium is 136–145.

Table 21: Frequency of subjects Flagged for Sodium

N (% of cell) Flagged for Sodium		Study 301		Study 302	
		SuPrep (N=194)	MoviPrep (N=193)	SuPrep (N=181)	MoviPrep (N=183)
Total Flagged		6 (3.09)	10 (5.18)	11 (6.08)	10 (5.46)
Sex	Female	5 (4.55)	4 (3.88)	6 (6.12)	5 (5.10)
	Male	1 (1.19)	6 (6.67)	5 (6.02)	5 (5.88)
Race	Asian	0 (0)	—	0 (0)	0 (0)
	Black or African-American	1 (4.76)	1 (4.35)	1 (6.25)	2 (12.50)
	White	5 (2.96)	9 (5.33)	10 (6.49)	8 (5.00)
	Other	0 (0)	—	0 (0)	0 (0)
Ethnicity	Hispanic or Latino	0 (0)	1 (9.09)	0 (0)	1 (7.69)
	Not Hispanic or Latino	6 (3.33)	9 (4.95)	11 (6.29)	9 (5.29)

Table 22: Subject with extreme Sodium values

Patient	Study	Treatment	Age	Sex	Race	Ethnicity	Visit 1	Visit 2	Visit 3
11024	302	MoviPrep	53	M	White	Not H/L	140	138	150

Uric Acid

Being Flagged for Uric Acid was fairly common across studies, with 135 (17.98%) subjects being marked as this status. The demographics of these subjects are summarized in Table 23.

Table 23: Frequency of subjects Flagged for Uric Acid

N (% of cell) Flagged for Uric Acid		Study 301		Study 302	
		SuPrep (N=194)	MoviPrep (N=193)	SuPrep (N=181)	MoviPrep (N=183)
Total Flagged		47 (24.23)	29 (15.03)	33 (18.23)	26 (14.21)
Sex	Female	21 (19.09)	15 (14.56)	17 (17.35)	12 (12.24)
	Male	26 (30.95)	14 (15.56)	16 (19.28)	14 (14.29)
Race	Asian	1 (100.00)	—	3 (37.50)	0 (0)
	Black or African-American	4 (19.05)	3 (13.04)	7 (43.75)	3 (18.75)
	White	42 (24.85)	26 (15.38)	23 (14.94)	23 (14.38)
	Other	0 (0)	—	0 (0)	0 (0)
Ethnicity	Hispanic or Latino	1 (7.14)	2 (18.18)	3 (50.00)	3 (23.08)
	Not Hispanic or Latino	46 (25.56)	27 (14.84)	30 (17.14)	23 (13.53)

As with Calcium, there is an apparent relationship between being Flagged for Uric Acid and treatment; 80 (21.33%) of SuPrep subjects were so Flagged, while 55 (14.63%) of MoviPrep

patients were. Whether this is of medical concern and necessitates further scrutiny and monitoring should be considered by the medical division.

There were four subjects, summarized in Table 24, with Uric Acid values that appear to be outside the range of the majority of the data. The normal range for Uric Acid is 2.4–5.7 for females and 3.4–7 for males.

Table 24: Subject with extreme Uric Acid values

Patient	Study	Treatment	Age	Sex	Race	Ethnicity	Visit 1	Visit 2	Visit 3
01037	301	MoviPrep	65	F	White	Not H/L	5.4	8.1	6.2
07006	301	SuPrep	56	F	White	Not H/L	5.5	9	5.7
13033	302	Suprep	54	F	White	Not H/L	5.4	7.4	7.2
19014	302	SuPrep	41	M	White	Not H/L	6.6	6.9	9.6

Adverse Events

Interaction with Treatment

There was a strong apparent difference between whether a subject was on the SuPrep or MoviPrep treatment arm across studies and whether she or he experienced a Vomiting Adverse Event. 41 (10.93%) of SuPrep patients were recorded as experiencing vomiting, as compared to 14 (3.72%) of MoviPrep patients. This is consistent with the findings of the medical officer.

This reviewer was unable to replicate the medical officer’s result that nausea and vomiting were significantly more frequent in the One-Day regimen SuPrep group (Study 301) than in the Two-Day regimen SuPrep group (Study 302). However, it appeared that the AE Abdominal Distension occurred in a higher proportion in the One-Day SuPrep group than the Two-Day SuPrep group, since 111 (57.22%) of the One-Day SuPrep and 77 (42.54%) of the Two-Day SuPrep subjects reported this event.

No other Adverse Events appeared to have an evident difference between the two groups or between study protocols. Table 25 gives the occurrence of AEs across studies and treatments for all AEs that were reported by at least one subject.

Interaction with Flagged Status

The Adverse Event reports were analyzed to look for possible relationships with being Flagged for the bodily chemicals of influence. This subsection lists those significant-seeming

Table 25: Adverse Event occurrence

Adverse Event Number of subjects experiencing (% of Study/Treatment arm)	Study 301		Study 302	
	SuPrep (N=194)	MoviPrep (N=193)	SuPrep (N=181)	MoviPrep (N=183)
Abdominal Distension	111 (57.22)	107 (55.44)	77 (42.54)	98 (50.78)
Abdominal Pain	71 (36.60)	68 (35.23)	69 (38.12)	81 (44.26)
Abomdinal Pain (Upper)	0 (0)	1 (.52)	0 (0)	0 (0)
Alanine Aminotransferase Increased	0 (0)	0 (0)	1 (.55)	0 (0)
Anal Discomfort	1 (.52)	2 (1.03)	0 (0)	0 (0)
Anxiety	0 (0)	0 (0)	0 (0)	1 (.55)
Aspartate Amintransferase Increased	1 (.52)	0 (0)	0 (0)	0 (0)
Artiocentricular Block Complete	1 (.52)	0 (0)	0 (0)	0 (0)
Blood Creatinine Phosphokinase Increased	1 (.52)	0 (0)	0 (0)	0 (0)
Blood Lactate Dehydrogenase Increased	1 (.52)	0 (0)	0 (0)	0 (0)
Blood Urine Present	0 (0)	0 (0)	1 (.55)	0 (0)
Bradycardia	0 (0)	0 (0)	0 (0)	1 (.55)
Chills	1 (.52)	2 (1.03)	1 (.55)	0 (0)
Colitis Ischaemic	0 (0)	0 (0)	0 (0)	1 (.55)
Diarrhoea	1 (.52)	0 (0)	0 (0)	0 (0)
Discomfort	123 (63.40)	116 (60.10)	102 (56.35)	126 (68.85)
Dizziness	0 (0)	1 (.52)	0 (0)	0 (0)
Dry Mouth	1 (.52)	0 (0)	0 (0)	0 (0)
Dysuria	1 (.52)	0 (0)	0 (0)	0 (0)
Feeling Hot	0 (0)	0 (0)	0 (0)	1 (.55)
Headache	4 (2.06)	3 (1.55)	2 (1.10)	1 (.55)
Influenza	0 (0)	0 (0)	0 (0)	1 (.55)
Kidney Enlargement	0 (0)	0 (0)	1 (.55)	0 (0)
Large Intestine Perforation	0 (0)	0 (0)	0 (0)	1 (.55)
Mouth Ulceration	1 (.52)	0 (0)	0 (0)	0 (0)
Nasopharyngitis	0 (0)	0 (0)	2 (1.10)	0 (0)
Nausea	89 (45.88)	75 (38.86)	69 (38.12)	62 (33.88)
Non-Cardiac Chest Pain	0 (0)	0 (0)	0 (0)	1 (.55)
Pruritus	1 (.52)	0 (0)	0 (0)	0 (0)
Respiratory Distress	0 (0)	0 (0)	0 (0)	1 (.55)
Sinus Tachycardia	0 (0)	0 (0)	0 (0)	1 (.55)
Urinary Tract Infection	0 (0)	0 (0)	1 (.55)	0 (0)
Vomiting	25 (12.89)	7 (3.63)	16 (8.84)	7 (3.83)

relationships that could be found, though due the amount of tests performed, the statistical significance of these correlations may be less than reported.

Out of the 123 subjects who were Flagged for Serum Osmolality, 64 (52.03%) experienced Abdominal Pain (including 1 patient with Upper Abdominal Pain) during the course of the study. In contrast, 216 out of the 599 (36.06%) of those subjects not Flagged for Serum Osmolality reported Abdominal Pain. The estimated odds ratio that a Flagged for Serum Osmolality subject would experience Abdominal Pain during the study as compared to a non-Flagged subject were 1.92 (95% CI: 1.30, 2.84). This relationship did not appear to be modulated by treatment or any other demographics.

Similarly, the data suggest that being Flagged for Sodium is positively related to experiencing Vomiting. Out of the 37 subjects that were Flagged for Sodium, 7 (18.92%) suffered Vomiting, as compared to 48 out of the 709 (6.68%) that were not Flagged for Sodium. The odds that a Flagged for Sodium subject would experience Vomiting were 3.21 times that of a non-Flagged for Sodium subject (95% CI: 1.34, 7.70). Note that caution is required on interpretation of this result in light of the low number of Vomiting events. While this reviewer does believe that this relationship may be worthy of further scrutiny, care must be taken with a finding that is contributed to by such a low number of events.

Interaction with Gender

There were five Adverse Events for which a possible relationship with Gender appeared in the data: Abdominal Distension, Abdominal Pain, Discomfort, Nausea, and Vomiting.

244 out of the 409 (59.66%) of the females in the study suffered Abdominal Distension during the course of the study across treatments, as compared to 149 out of the 342 males (43.57%). Females had an estimated odds of experiencing Abdominal Distension 1.92 times those of males (95% CI: 1.43, 2.56). This relationship did not appear to be modified by the treatment arm of the subject.

Similarly, females had higher prevalence than males of Abdominal Pain (44.25% versus 31.58%), Discomfort (68.70% versus 54.39%), Nausea (45.97% versus 31.29%), and Vomiting (11.00% versus 2.92%). Respectively, their odds of reporting these Adverse Events were 1.72 (95% CI: 1.27, 2.32), 1.84 (95% CI: 1.37, 2.48), 1.87 (95% CI: 1.38, 2.52), and 4.10 (95% CI: 2.04, 8.27) times higher than the males in the study. Since the data also suggest (see above) that SuPrep is related to a higher incidence of Vomiting events, it is suggested that the labeling for SuPrep indicate that Vomiting events are a possible side effect, and that females may be at higher risk for Vomiting, as well as Abdominal Distension, Abdominal Pain, Discomfort and Nausea. Language for medical professionals should also be added to recommend that patients who develop vomiting be monitored for sodium irregularities (see above).

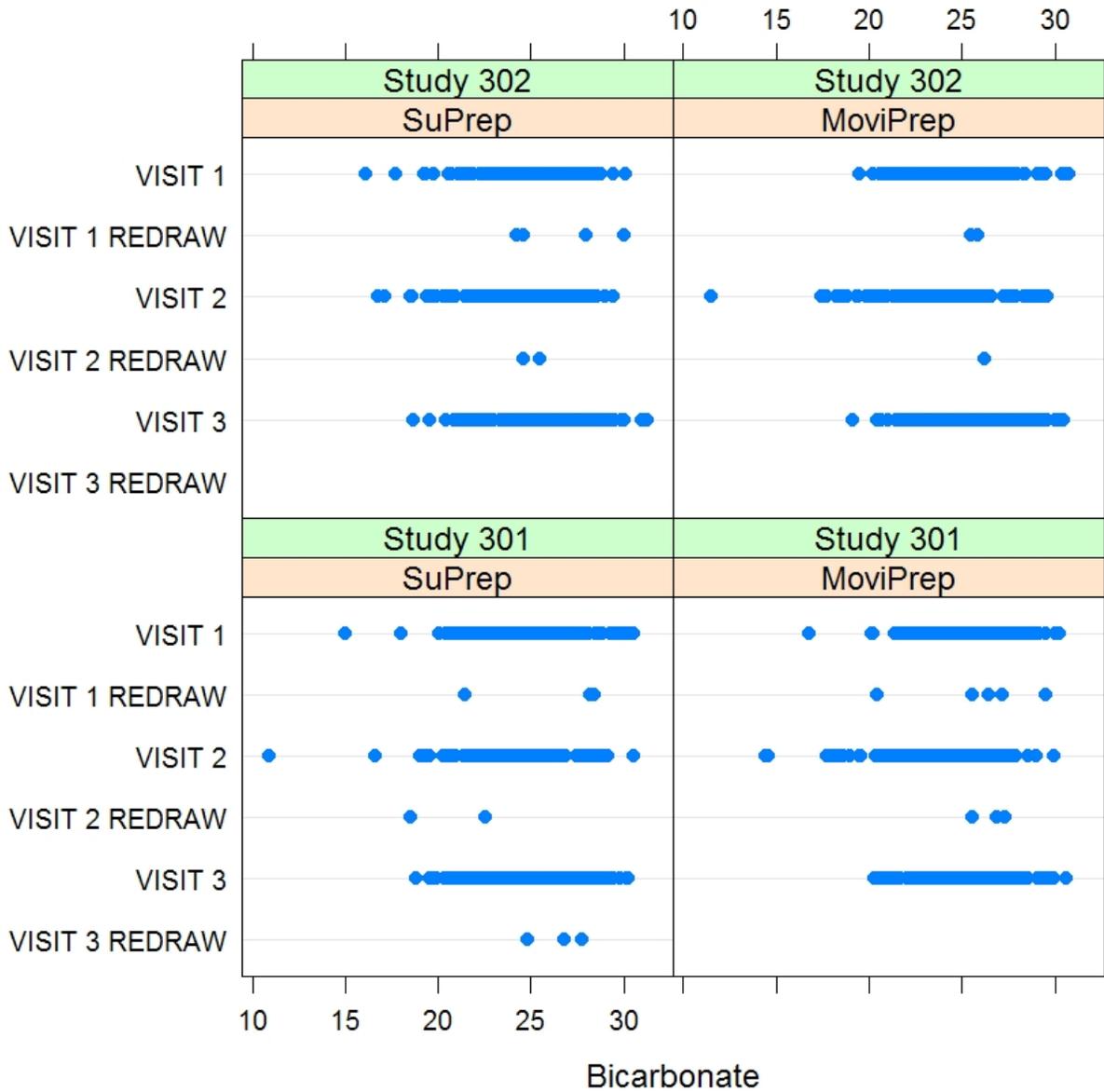
Conclusion

This memorandum highlights some of the areas where the descriptive statistics appear to suggest a possible relationship. As noted, any statistical finding is deemed exploratory and hypothesis-generating. The medical reviewers should discuss whether post-marketing clinical trials to observe and determine the strength of the possible effects of SuPrep upon Calcium and Uric Acid might be considered, as well an investigation into the possible evidence of abnormal Creatinine responses to the kit in men. The medical reviewers may also consider whether to call for further scrutiny into the possible higher risk of SuPrep causing vomiting events over the active control, and the apparent higher risk of Abdominal Distension with the one-day dose.

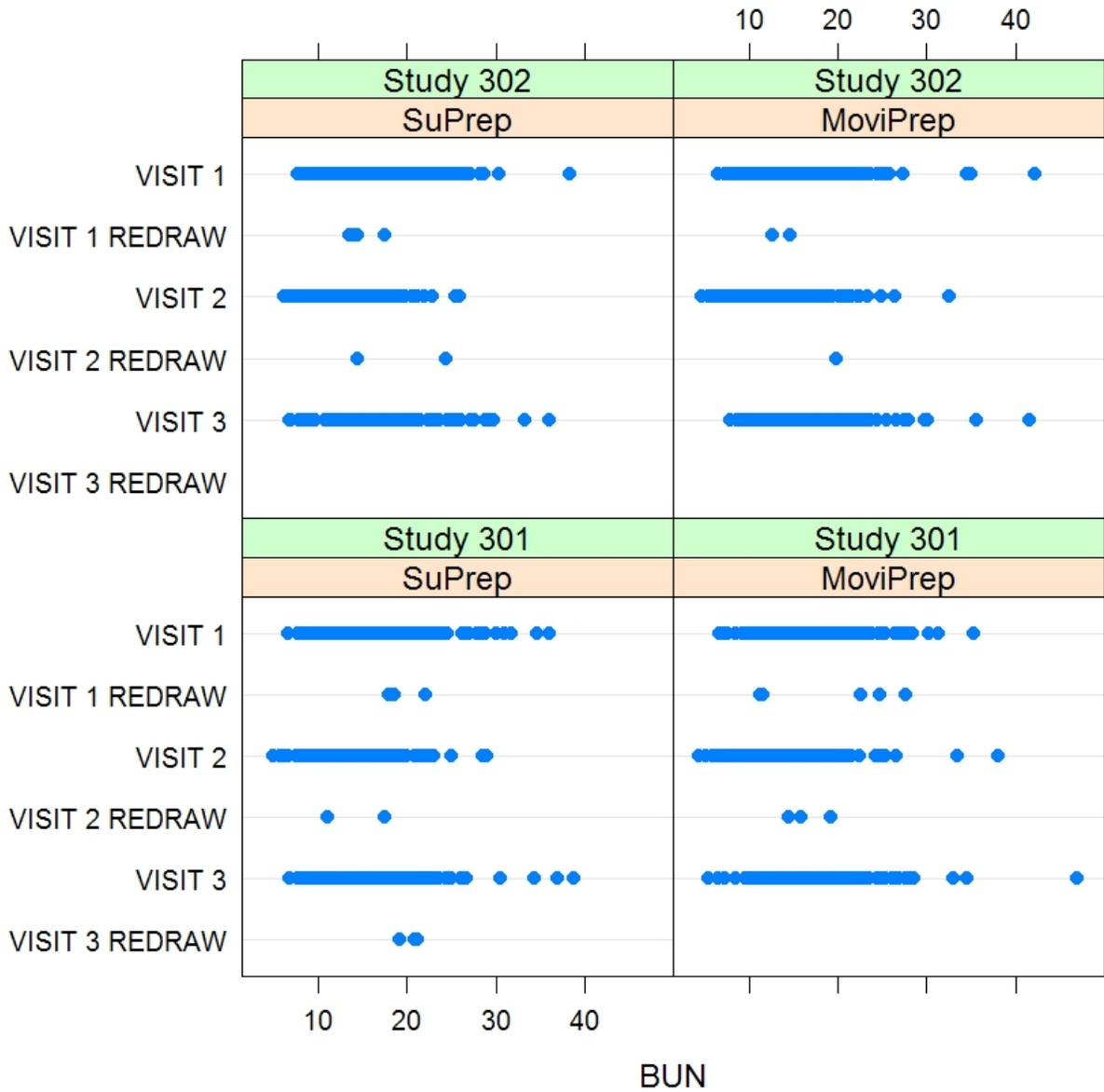
The largest safety concern with regards to the SuPrep data is not a matter of statistical quantification, but rather one of data integrity. As noted by Dr. Gatti, the NDA process for BLI800 faced several difficulties due to sponsor inability to share the entirety of the clinical data. Further, as analysis for this memorandum was performed, this reviewer noted that for several subjects, redraws of their blood work were taken without any reason noted in the comments section of the dataset. Of particular concern is the fact that this seemed to occur when several of the subject's chemical measurements were outside of the normal range. This did not appear to be restricted or heavily weighted toward either treatment arm—it occurred for both SuPrep and Moviprep subjects—and may possibly be related to a protocol for double-checking abnormal measurements. However, the lack of written records for the justification for a large portion of the redraws is cause for further concern regarding the integrity of the data provided by the sponsor. With this in mind, this reviewer even more strongly supports the elicitation of a post-marketing commitment to carry out more methodical clinical trials with more strict adherence to protocol to ensure the safety of BLI800.

Appendix: Graphical Representations of Chemical Levels

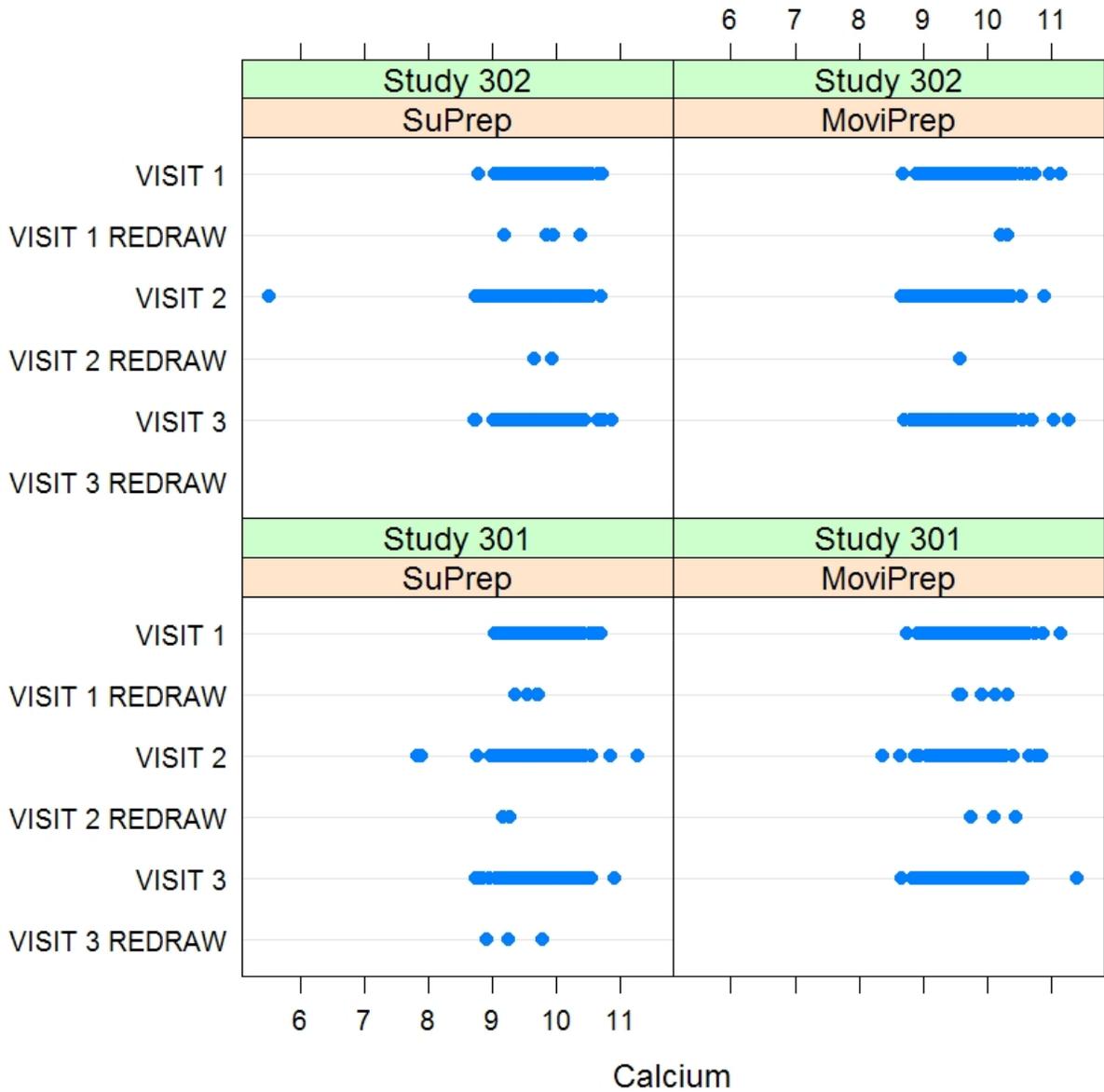
Bicarbonate Values Across Visits



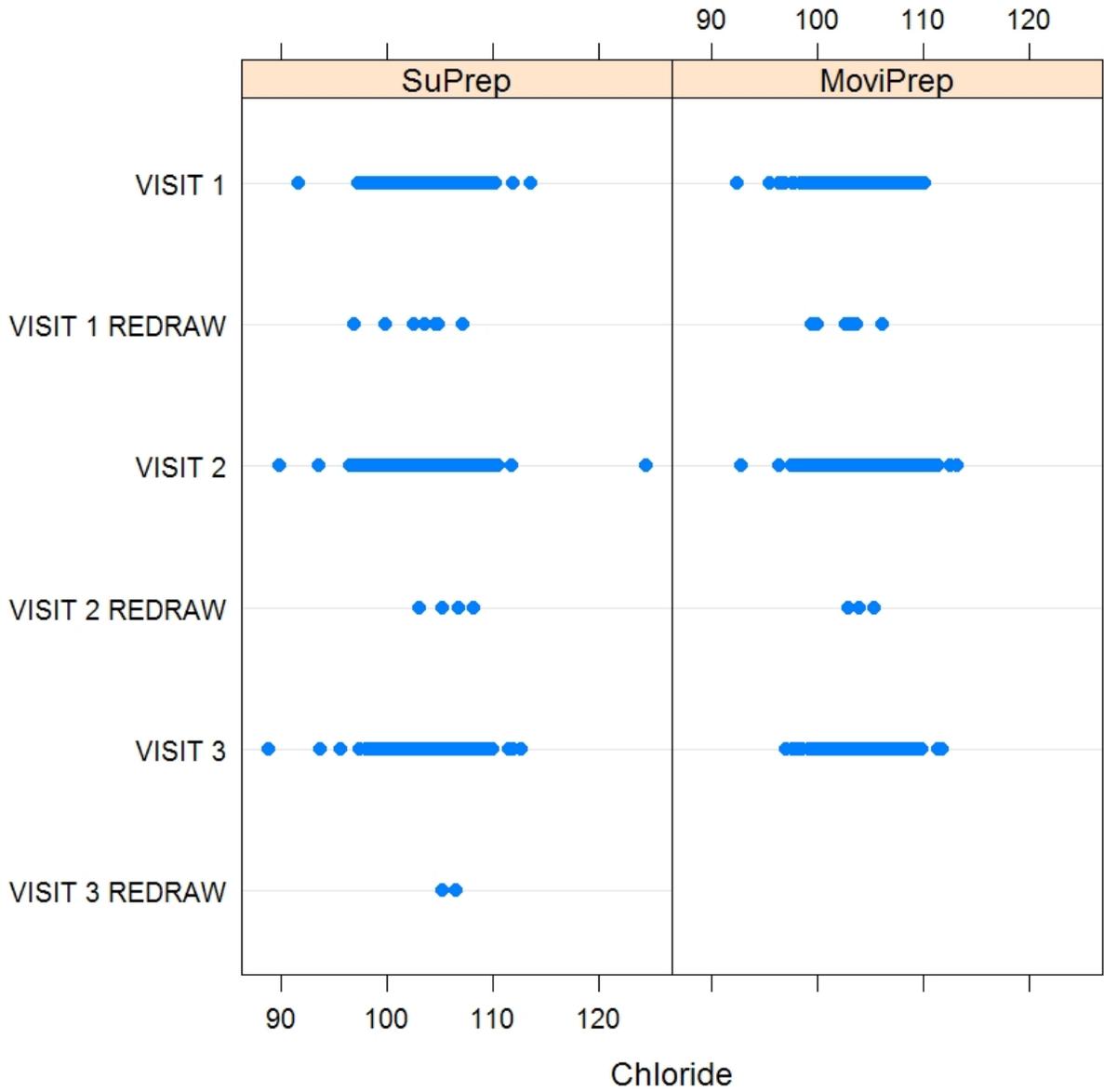
BUN Values Across Visits



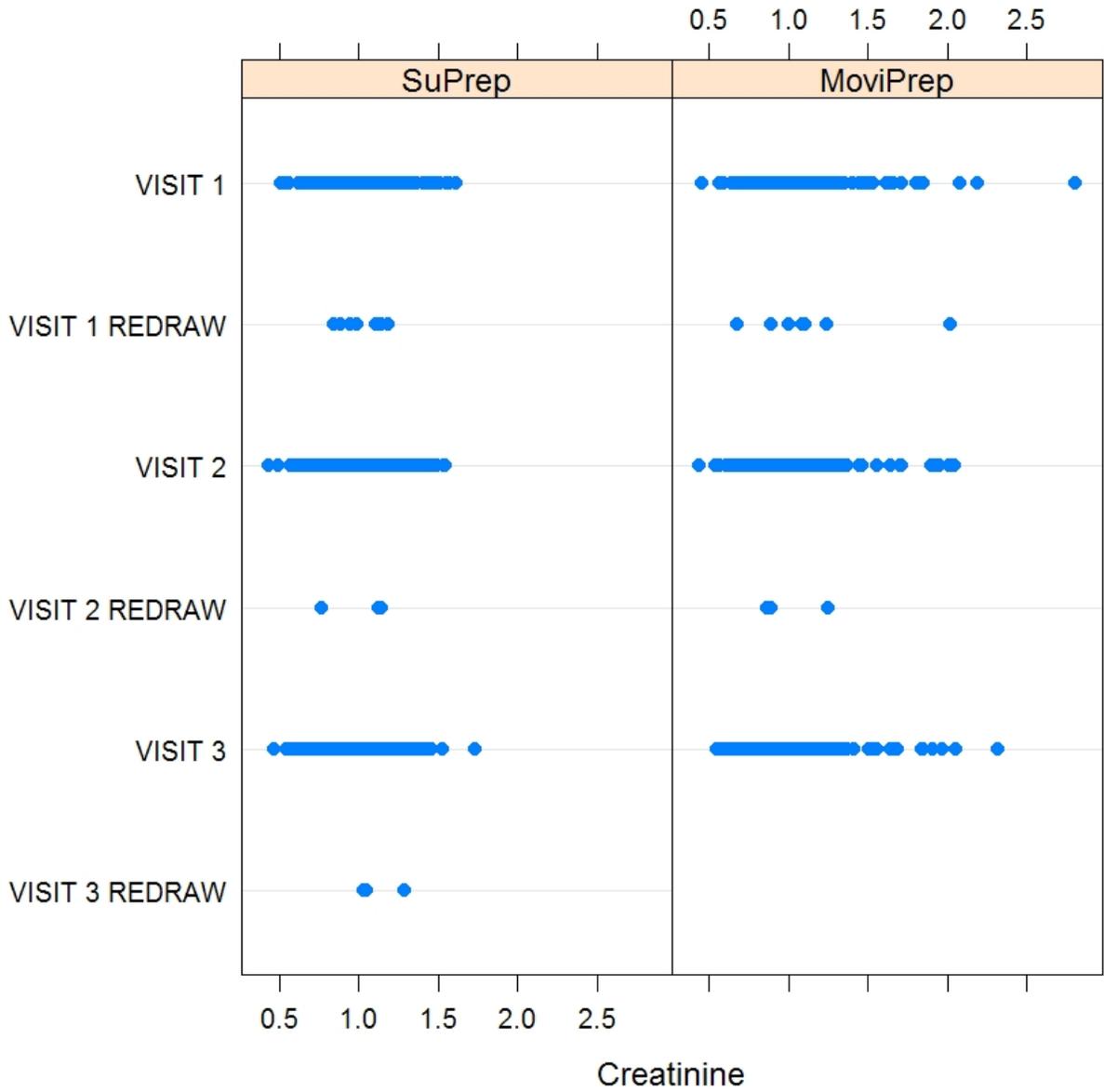
Calcium Values Across Visits



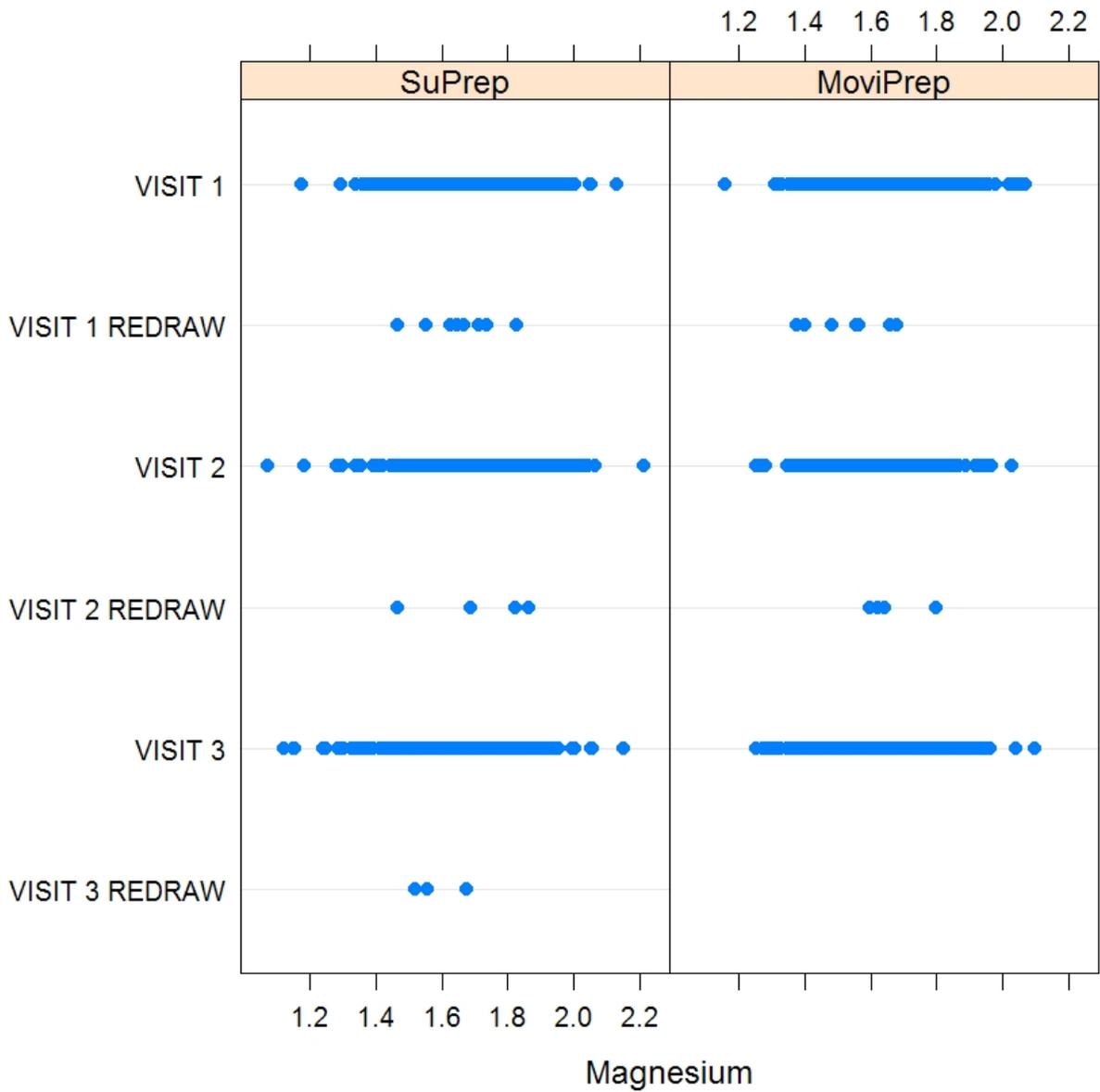
Chloride Values Across Visits



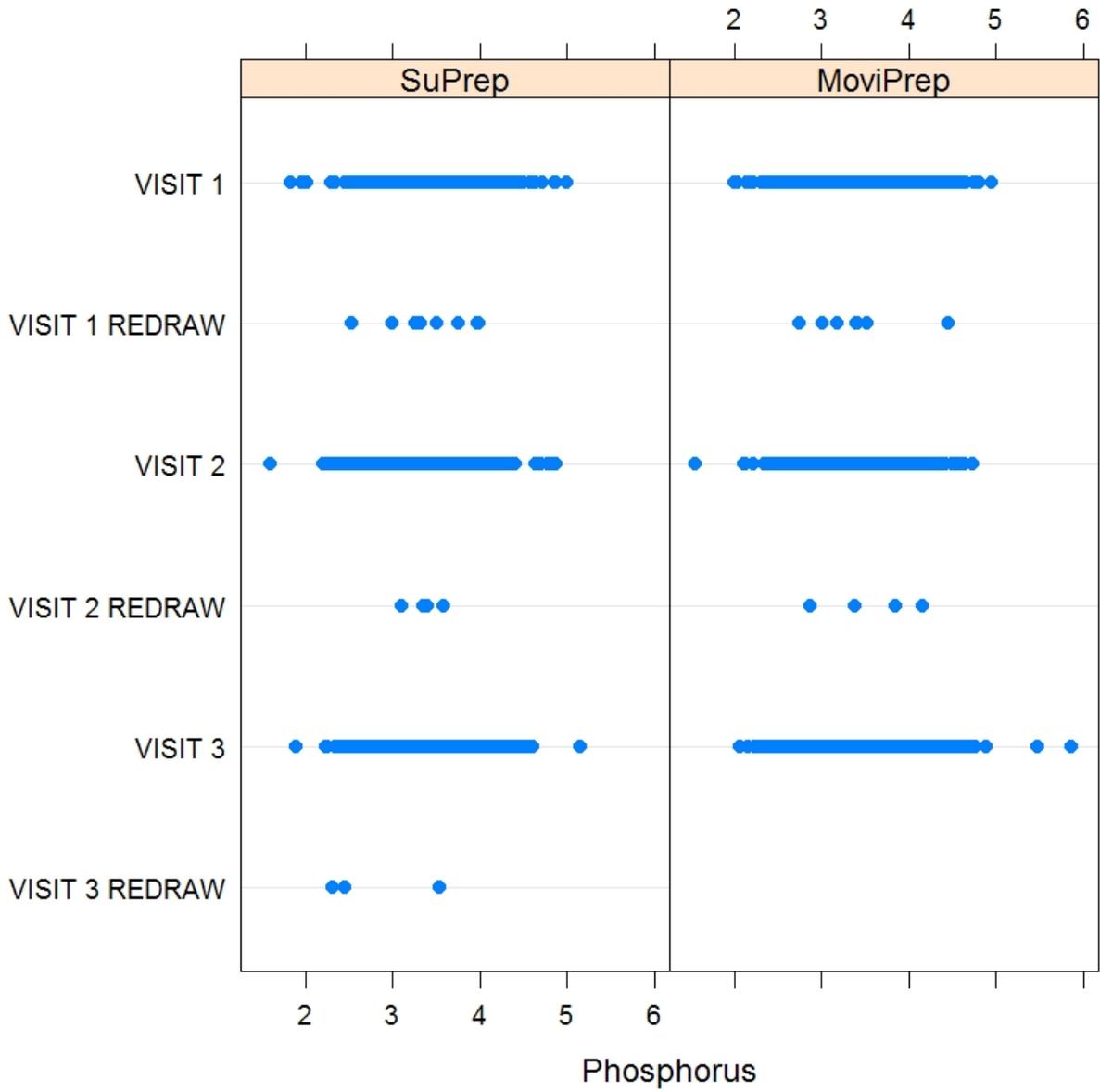
Creatinine Values Across Visits



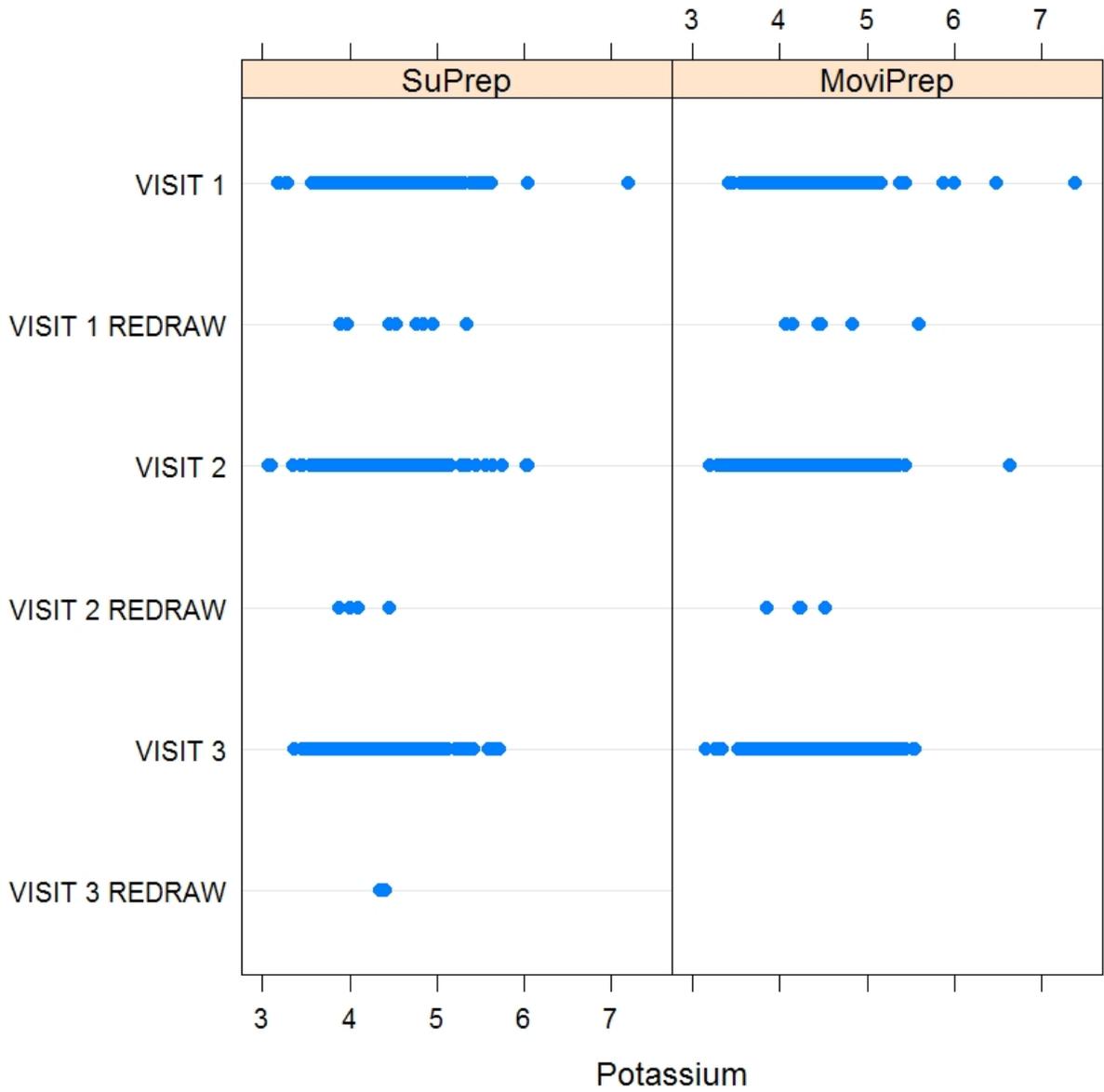
Magnesium Values Across Visits



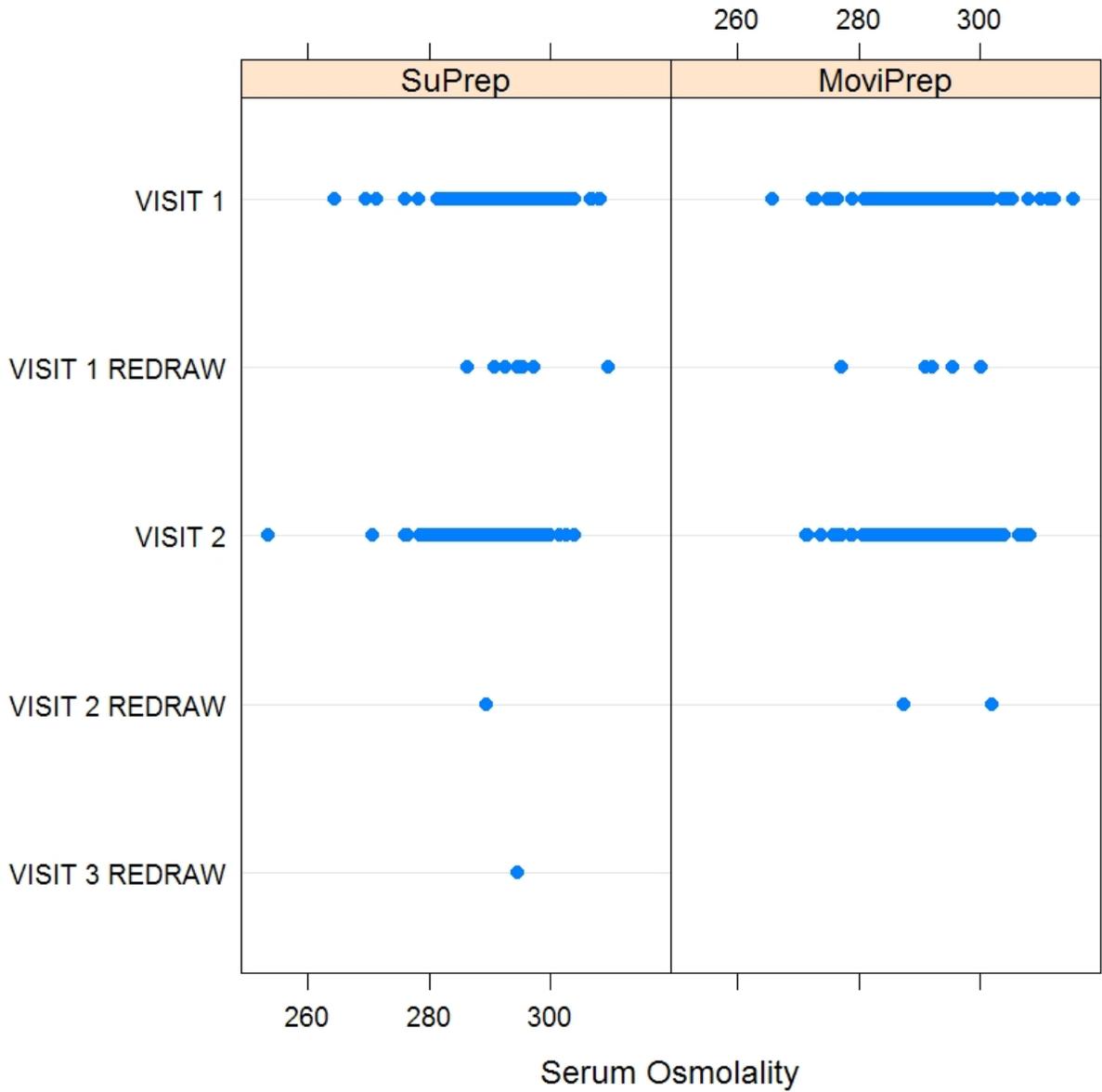
Phosphorus Values Across Visits



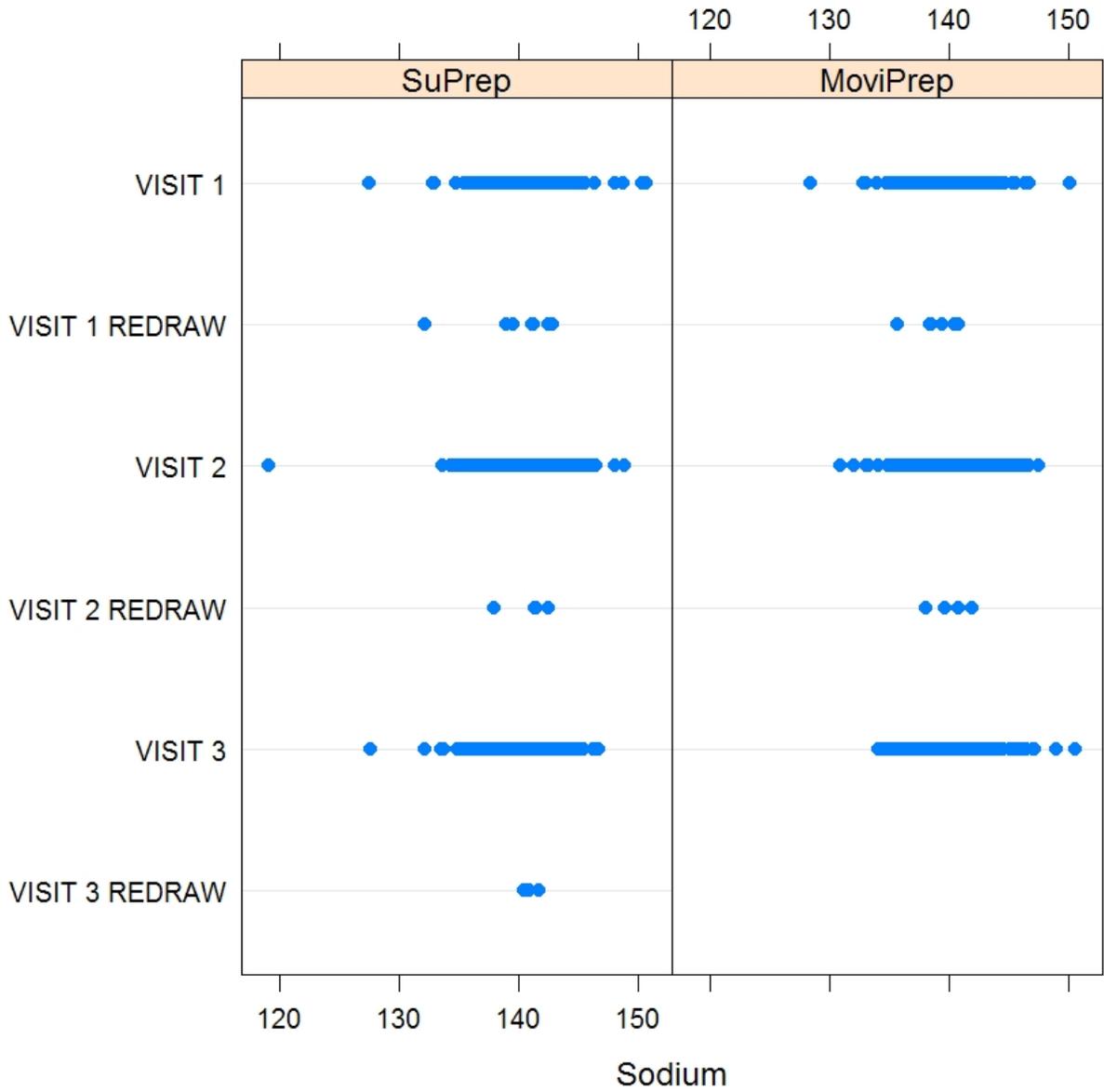
Potassium Values Across Visits



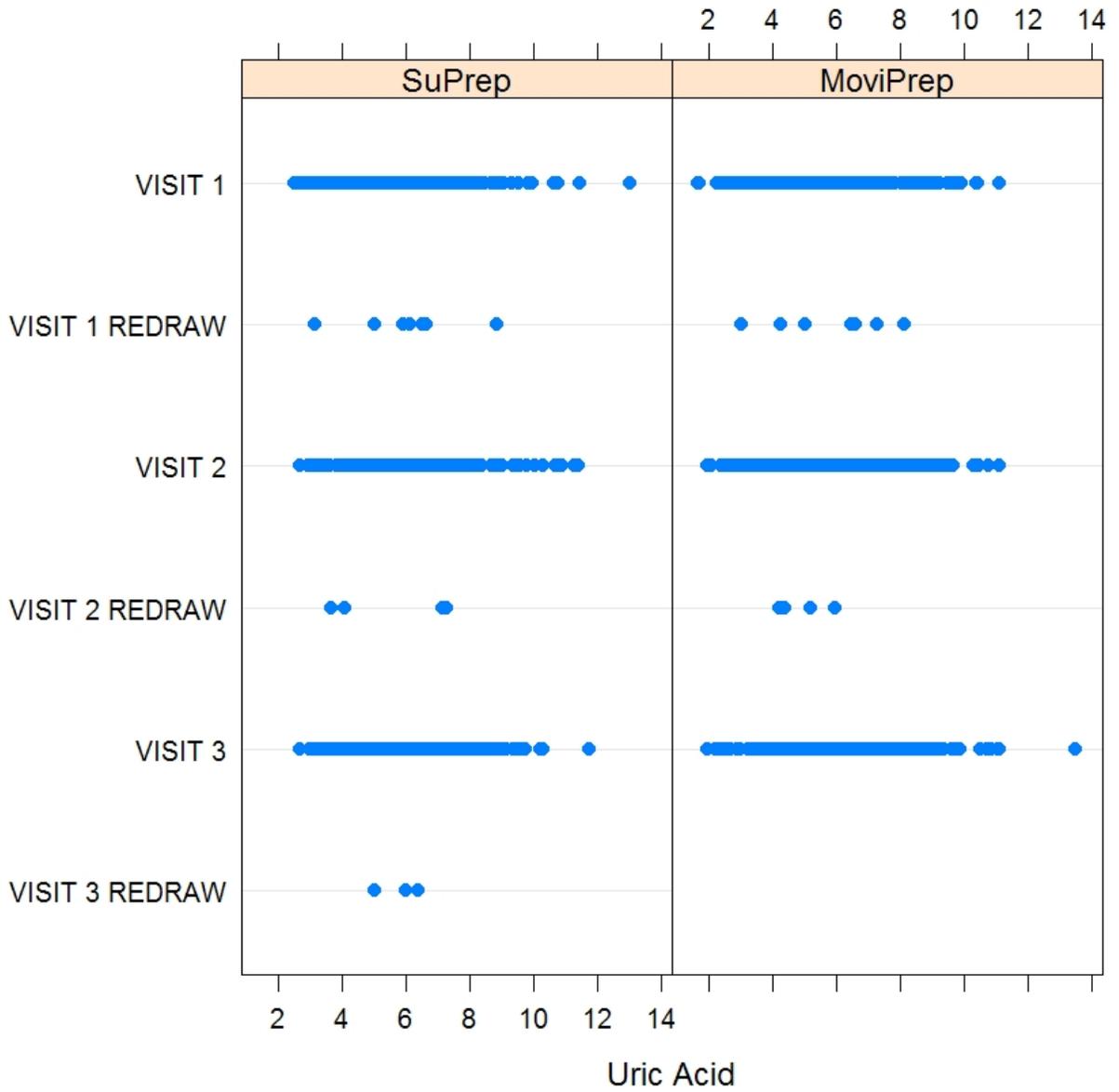
Serum Osmolality Values Across Visits



Sodium Values Across Visits



Uric Acid Values Across Visits



Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22372	ORIG-1	BRAINTREE LABORATORIES INC	SUPREP BOWEL PREP KIT

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 22-372

Drug Name: SuPrep (sodium sulfate, potassium sulfate and magnesium sulfate)
oral solution

Indication(s): Gastrointestinal lavage prior to colonoscopy

Applicant: Braintree Laboratories, Inc.

Date(s): Received July 2, 2008 {DUFA: August 2, 2009}

Review Priority: Standard

Biometrics Division: Division of Biometrics III

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Keywords: clinical studies, NDA review, non-inferiority, ITT

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The sponsor conducted two adequate and well-controlled studies to assess the efficacy of SuPrep colonic purgation: BLI800-301, one-day preparation; and BLI800-302, a split dose, 2 day preparation. In both studies, the SuPrep and MoviPrep formulations performed similarly.

In Study BLI800-301 the percent of successful preparations for SuPrep and MoviPrep were 82% and 80%, respectively, and the lower limit of the 95% confidence interval of the difference in rates was -5.7%. For Study BLI800-302, the percent of successful preparations for SuPrep and MoviPrep was 97% and 96%, respectively, with a lower limit of the 95% confidence interval of the difference of -2.2%.

Although the sponsor did not adequately justify their choice of a 15% non-inferiority margin, the resulting lower confidence limits of -5.7% and -2.2% are sufficiently above the -15% threshold to support non-inferiority with respect to colonic purgation.

For Study BLI-800-301, the adverse event rate for any AE for SuPrep was statistically significantly higher than that for Moviprep, for patients aged greater than 65 year old and for patients in the high risk status subgroup.

1.2 Brief Overview of Clinical Studies

1.2.1 Study BLI800-301

This study is a randomized, parallel, multi-center, single-blind, non-inferiority study, comparing BLI800 vs. MoviPrep as bowel preparations. MoviPrep is FDA approved for bowel cleansing prior to colonoscopy in adult 18 years of age and older. Both preparations were completed on the day prior to colonoscopy.

The objective of this study was to compare the safety and efficacy of BLI800 Oral Sulfate Solution vs. MoviPrep as bowel preparation before colonoscopic examination in adult subjects.

Subject participation in this study lasted up to 60 days. At screening visit (Visit 1) was performed within 15 days of the colonoscopy. Subjects meeting all inclusion/exclusion criteria were randomized during the screening visit to receive either BLI800 or MoviPrep. Subjects returned to the clinic the day after completing the preparation for colonoscopy (Visit 2). A follow-up visit was performed 30 days after the colonoscopy to assess the occurrence of serious adverse events and to collect blood samples for analysis.

In this single-blinded study, to ensure an unbiased evaluation of the study preparations, the colonoscopist was not allowed to perform any drug related activities. Subjects were instructed not to discuss their study preparation with any staff member.

The colonoscopy was performed by a physician and bowel cleansing was evaluated on a 4-point scale (poor, fair, good, and excellent).

The primary efficacy was assessed on the basis of a binary outcome of overall preparation success (grading score=3 or 4) or failure (grading score=1 or 2) by the blinded colonoscopist.

1.2.2 Study BLI800-302

The design of this study is similar to that of Protocol BL1-800-301 with exception in number of days of preparation. In Protocol BL1-800-301, the preparation was administered as one-day preparation. But, in this study, the preparation will be administered as a split dose, 2-day preparation.

The efficacy of MoviPrep administered as a one-day preparation has been previously reported as 73%. But, based on results reported in the MoviPrep labeling, the success rate for MoviPrep administered as a split dose, 2-day preparation was expected to be approximately 89%.

1.3 Statistical Issues and Findings

For quality of colonic purgation, in both studies ((BLI800-301, one-day preparation) and (BLI800-302, a split dose, 2 day preparation), the 95% confidence lower limits of the differences between BLI800 and MoviPrep of the proportion of subjects with successful preparation were -5.7% and -2.2%, respectively.

For both studies, the sponsor proposed the 15% of non-inferiority margin without any justification. The sponsor needs provide more detailed justification on the selection of non-inferiority margin of 15%.

For Study BL800-301, the margin of 15% implies that as much as a 20.5% relative decrease of assumed expected event rate of 73% might occur in patients prepared with BLI800. It may not have been acceptable. If a maximum of a 10% relative decrease as acceptable, then the more appropriate margin would have been 7%.

Based on an ITT analysis which included all randomized subjects, BL800 patients experienced similar preparation success to MoviPrep. The confidence interval of the treatment difference in success rates falls between the predetermined equivalence margin of $\pm 15\%$. Furthermore, the absolute value of the lower limit of the confidence interval was 6.2% which is less than 7%, the non-inferiority margin recommended by this reviewer.

Furthermore, in order to determine whether BLI800 would be superior to placebo if placebo arm were included in this study, the reviewer computed 95% confidence interval on the success rate of BLI800 for true ITT population. This resulted in a lower limit of

71.6%. If the medical division determines that the upper limit of 95% confidence interval of the historical success rate for placebo would be less than 71.6%, then BLI800 could be considered effective from that perspective.

For Study BI800-302, the expected event for control was larger (89%) and thus the non-inferiority margin should have been much less than sponsor's 15%. A margin of 15% implies that as much as a 16.8% relative decrease of assumed expected event rate of 89% might occur in patients prepared with BLI800. This may not have been acceptable. If a maximum of a 5% relative decrease as acceptable, then the more appropriate margin would have been 4%.

Based on ITT analysis which included all randomized subjects, BL800 patients experienced similar preparation success rates to MoviPrep. The confidence interval of the treatment difference falls between the predetermined equivalence margin of $\pm 15\%$. Furthermore, the absolute value of the lower limit of the confidence interval (4.9%) is slightly greater than 4%, the non-inferiority margin recommended by this reviewer.

This reviewer performed a statistical analysis of preparation cleansing score using CMH (Cochran-Mantel-Haenszel) method for ordinal data with modified ridit scores. Result from this analysis showed that BLI800 was slightly better than MoviPrep in preparation cleansing score ($p=0.0340$).

Furthermore, in order to determine whether BLI800 would be superior to placebo if placebo arm were included in this study, the reviewer computed 95% confidence interval on the success rate of BLI800 for true ITT population. This resulted in a lower limit of 87.3%. If the medical division determines that the upper limit of 95% confidence interval on the historical success rate for placebo would be less than 87.3%, then BLI800 could be considered effective from that perspective.

2. INTRODUCTION

2.1 Overview

SuPrep is intended to replace the sodium phosphate preparation (such as Fleet Phospho-soda), which have been linked to renal failure and nephrocalcinosis.

In the current NDA, the sponsor seeks approval of SuPrep (sodium sulfate, potassium sulfate and magnesium sulfate for oral solution), a low-volume liquid for oral administration intended for bowel cleansing prior colonoscopy.

2.2 Data Sources

In support of this claim, the sponsor had submitted two pivotal trials:

Protocol BLI800-301: A Safety and Efficacy Evaluation of BLI800 Oral Sulfate Solution vs MoviPrep as Bowel Cleansing Preparations in Adult Patients

Protocol BLI800-302: A Safety and Efficacy Evaluation of BLI800 Oral Sulfate Solution vs MoviPrep as Bowel Cleansing Preparations in Adult Patients

The sponsor submitted the paper submission containing of Vols. 1.1, 2.1, 3.1-3.2, 4.1-4.2, 5.1-5.2, 6.1-6.2, 7.1, 8.1, 9.1-9.4, 10.1-10.4 dated July 2, 2008. All data were submitted in electronic format to the EDR. The sponsor has also submitted a response for FDA Information Request dated November 20, 2008.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study BLI800-301

3.1.1.1 Study Design

This study was a randomized, parallel, multi-center, single-blind, non-inferiority study, comparing BLI800 vs. MoviPrep as bowel preparations. Both preparations were completed on the day prior to colonoscopy.

The objective of this study was to compare the safety and efficacy of BLI800 Oral Sulfate Solution vs. MoviPrep as bowel preparation before colonoscopic examination in adult subjects.

Subject participation in this study lasted up to 60 days. At screening visit (Visit 1) was performed within 15 days of the colonoscopy. Subjects meeting all inclusion/exclusion criteria were be randomized during the screening visit to receive either BLI800 or MoviPrep. Subjects returned to the clinic the day after completing the preparation for colonoscopy (Visit 2). A follow-up visit was performed 30 days after the colonoscopy to assess the occurrence of serious adverse events and to collect blood samples for analysis.

BLI800 consisted of two 6 ounce doses, each containing the following ingredients in liquid form:

Component	Grams
Na ₂ SO ₄	17.51
MgSO ₄	1.6
K ₂ SO ₄	3.13
Sodium Benzoate	(b) (4)
Flavoring agents	(b) (4)
	(b) (4)

MoviPrep is FDA approved for bowel cleansing prior to colonoscopy in adults 18 years of age and older.

In this single-blinded study, to ensure an unbiased evaluation of the study preparations, the colonoscopist was not allowed to perform any drug related activities. Subjects were instructed not to discuss their study preparation with any staff member.

During Visit 1, subjects were provided with instructions on how to use the study preparation. Subjects self-administered the assigned study preparation on the day before their scheduled colonoscopy according to the instructions.

Subjects that had clinically significant electrolyte abnormalities, in the opinion of the principle investigator, based on Visit 1 laboratory results were discontinued from the study. These subjects were classified as screen failures.

On Visit 2, subjects returned to the study center for colonoscopy on the day following completion of their preparation. Subjects were to bring back the Treatment Questionnaire. Prior to the colonoscopy, subjects were to complete the Symptom Scale on five-point scale (1 to 5) to report their overall experience with the preparation.

Subjects were instructed not to discuss their preparation with any staff member.

The colonoscopy was performed by a physician and evaluated on a 4-point scale (poor, fair, good, and excellent).

At Visit 2, study personnel scheduled a follow-up visit to be conducted 30 days after the date of colonoscopy.

3.1.1.2 Sponsor's Analysis

A total of 416 patients were screened. Of which 408 were randomized and dispensed study medication (204 in BLI800 and 204 in MoviRep). A total of 387 patients (194 in BLI800 and 193 in MoviPrep) were included in the sponsor's Intent-to-Treat analysis. The sponsor's ITT analysis excluded 10 BLI800 patients and 11 MoviPrep patients. The reasons for discontinuation in the sponsor's ITT group are given below.

**Reasons for Patient Discontinuation
Intent-to-Treat Population**

	BLI800 (n)	MoviPrep (n)
Total ITT Patients	194 (100%)	193 (100%)
Completing Patients	190 (97.9%)	192 (99.5%)
Patients Discontinued	4 (2.1%)	1 (0.5%)
Reasons for discontinuation:		
Adverse event	3 (75%)	1 (100%)
Other ¹	1 (25%)	0 (0%)

¹Patient 07029 discontinued due to insurance coverage issues.
(reference table 14.1.1 in Section 14)

3.1.1.2.1 Planned Analysis

Any subject who completely or partially took study drug but did not have a colonoscopy due to non-preparation related reasons was not be included in the primary and secondary efficacy analysis. All subjects were included in the safety analysis.

The sponsor did not state Intent to Treat (ITT) analysis in the protocol and stated it but failed pre-specified it in the SAP.

The sponsor pre-specified Nonevaluable Patients in the protocol and the SAP as

Any subject who completely or partially took study drug but did not have a colonoscopy due to non-preparation related reasons was not to be included in the primary and secondary efficacy analysis.

Primary efficacy was to be assessed on the basis of a binary outcome of overall preparation success (grading score=3 or 4) or failure (grading score=1 or 2) by the blinded colonoscopist. Any subject who did not have a colonoscopy based on the Investigator’s assessment of the cleansing, for whom cleansing was not adequate for evaluation or due to preparation related adverse events was considered as a “failure.”

Success rate was to be analyzed using CMH Chi-square adjusting for the effect of investigator site. If required by the analysis, smaller sites will be pooled to maintain an adequate number of subjects per site for the analysis. The formal hypothesis test result (p-value) for treatment difference was presented together with a two-sided 95% confidence interval for the difference.

The primary endpoint of treatment success was to be tested sequentially (hierarchical structure) with the first test being non-inferiority test based upon the treatment difference.

The primary endpoint of treatment success was to be tested using a non-inferiority test with a non-inferiority margin of 15%.

A rejection of the null hypothesis was to trigger superiority testing based upon the treatment difference.

The two hypothesis tests were hierarchically structured so that the second test (superiority) was only be considered if the first test (non-inferiority) was rejected. The superiority test was powered to detect an absolute difference of 12%. There was no alpha adjustment for the second test as a result of the hierarchical testing.

Secondary endpoints included adequacy of cleaning (cleaning adequate for evaluation) and need for preparation.

Secondary endpoints were to be analyzed using CMH Chi-square adjusting for any site effects for counts (percentage) responses and two-way ANOVA with terms for treatment, site and their interaction for mean response. No adjustment was made for multiplicity testing of secondary endpoints. Results were to be presented for the treatment effects (p-values) and two-sided 95% confidence interval for the treatment differences.

The primary analysis and selected secondary analyses were to be descriptively summarized by gender, race, and age group.

Four hundred (400) subjects were to be randomly assigned to one of the two preparations in a ratio of 1:1 (200 subjects per group). A dropout rate of approximately 5% per treatment group is expected. The efficacy of MoviPrep administered as a one-day preparation had been previous reported as 73%. Assuming a similar success rate for BLI800, based on a one-sided 0.025 level chi-square test for non-inferiority, 185 subjects per group will have 90% power to detect a non-inferiority margin difference of 15% of the expected control response.

If the null hypothesis was rejected after the first non-inferiority test, secondary superiority testing was to be performed. A sample size of 185 per group wouldl have 80% power to detect a treatment difference of 12% with alpha=0.025 using a one-sided chi-square test.

3.1.1.2.2 Treatment Group Comparability

The summary of results of comparability of treatment groups for demographic and baseline characteristics for all randomized patients are given in Appendix Table 1.

As seen from Appendix Table 1, no statistically significant differences between the two treatment groups were observed for demographic and baseline characteristics with exception for higher risk (p=0.0375).

3.1.1.2.3 Sponsor’s Analysis of Primary Efficacy Parameter

The examination physician rated each colonoscopy for cleansing according to four point scale where a score of 1=“poor” and a score of 4=“excellent.” Cleansing score for bowel preparations by treatment group are given below.

Preparation Cleansing Score

Score	BLI800 n (%)	MoviPrep n (%)
4 Excellent	86 (44.6%)	72 (37.3%)
3 Good	73 (37.8%)	83 (43.0%)
2 Fair	22 (11.4%)	31 (16.1%)
1 Poor	9 (4.7%)	6 (3.1%)
Mean Score	3.24	3.15

(reference table 14.2.1.1 in Section 14)

The table includes all 382 patients (190 BLI800 and 192 MoviPrep) that had a colonoscopy. As seen from table above, the distribution of scores for each cleansing category was similar.

Primary efficacy was assessed on the basis of a binary outcome of overall preparation success (grading score=3 or 4) or failure (grading score=1 or 2) by the blinded colonoscopist. Result from primary efficacy responder analysis is given below.

Number and Percent of Successful Preparations Protocol BLI800-301 Sponsor’s ITT Analysis

Treatment	Rate	Diff (BLI800 – MoviPrep)	95% C.I.
BLI800	159/194 (82.0%)	1.6%	(-5.7%, 9.8%)
MoviPrep	155/193 (80.3%)		

Copied from sponsor Table 301-5

As seen from the table above, BL800 patients experienced similar preparation success to MoviPrep. The confidence interval falls between the predetermined equivalence margin of $\pm 15\%$.

3.1.1.2.4 Sponsor’s Analysis of Secondary Efficacy Parameters

A secondary endpoint was adequacy of cleaning (cleaning adequate for evaluation). A preparation was considered adequate if the physician response to the question “Was cleansing adequate for evaluation?” on the physician’s colonoscopy examination form was ‘Yes.’ Result from secondary efficacy responder analysis is given below.

**Number and Percent of Adequate Preparations
Protocol BLI800-301
Sponsor’s ITT Analysis**

Treatment	Rate	Diff (BLI800 – Moviprep)	95% C.I.
BLI800	178/190 (93.7%)	-1.1%	(-5.8%, 3.6%)
Moviprep	182/192 (94.8%)		

Copied from sponsor Table 301-7

As seen from the table above, most preparations for either treatment were considered to be adequate.

3.1.1.3 Reviewer’ Comments and Evaluation

3.1.1.3.1 Comments on Control Arm

The control arm for this study was Moviprep. Moviprep was approved in 2005. One of studies (NRL994-01/2001 supporting approval was designed as randomized, active-controlled, single-blind, multi-center, pivotal phase 3 study to compare Moviprep versus standard regimen golytely (PEG+E). The success rate of effective gut cleansing was 88.9% in the Moviprep group compared with 94.8% in the golytely (PEG+E) group. This resulted in a difference of -5.9% in favor of golytely with a lower bound of 95% confidence interval of -12.0%.

In this study, standard regimen golytely (PEG+E) was not used as control arm. Instead Moviprep was used as control arm. Consequently, there may be concern for “biocreep”.

3.1.1.3.2 Non-inferiority Margin

The sponsor proposed the 15% of non-inferiority marginal without any justification. The sponsor should have provided more detailed justification on the selection of non-inferiority margin of 15%.

Choosing a margin of 15% implies that as much as a 20.5% relative decrease of assumed expect event rate of 73% might occur in patients prepared with BLI800. It may not be clinically acceptable. If up a 10% relative decrease is deemed, then a margin of 7% would have been more appropriate.

3.1.1.3.3 Reviewer’s Comments on Sponsor’s Analysis of Primary Efficacy Endpoint

3.1.1.3.3.1 Primary Efficacy Endpoint

The sponsor’s ITT analysis for primary efficacy endpoint did not include all randomized patients. It is not a true “ITT” analysis. There were 21 patients (10 in BLI800 and 11 in Moviprep) were excluded from the sponsor’s ITT analyses. If these 21 patients were

considered to be” failed,” result from primary efficacy responder analysis for true ITT population is given below.

**Number and Percent of Successful Preparations
Protocol BLI800-301
True ITT Analysis**

Treatment	Rate	Diff (BLI800 – Moviprep)	95% C.I.
BLI800	159/204 (77.9%)	1.9%	(-6.2%, 10.1%)
Moviprep	155/204 (76.0%)		

Compiled by this reviewer.

As seen from the table above, for a true ITT analysis which includes all randomized subjects, BL800 patients experienced similar preparation success to Moviprep. The confidence interval falls between the predetermined equivalence margin of $\pm 15\%$. Furthermore, the absolute value of the lower limit of the confidence interval is less than 7%, the more desired non-inferiority margin recommended by this reviewer.

Furthermore, in order to determine whether BLI800 would be superior to placebo if placebo arm were included in this study, the reviewer computed a 95% confidence interval on the success rate of BLI800 for true ITT population. This resulting lower limit of the two-sided 95% confidence intervals on the success rate for BLI800 is 71.6%. If the medical division determines that the lower limit of the two-sided 95% confidence intervals on the success rate for BLI800 is higher than the upper limit of 95% confidence interval on the historical success rate for placebo if it exists, then BLI800 could be considered effective from this perspective.

3.1.1.3.3.2 Subgroup Analyses

Results from subgroup analyses of primary efficacy endpoint by gender, age, and site are given below for the true ITT analysis. In this analysis, patients with missing data were considered as “failures.” Patients that reported a medical history of cardiac, renal or vascular problems (hypertension), or diabetes were defined by the sponsor as “high risk.”

**Number and Percent of Successful Preparations
Protocol BLI800-301
True ITT Analysis**

Subgroup	BLI800	MoviPrep	Diff	95% CI
Gender				
Male	73/90 (81.1%)	71/94 (75.5%)	5.6%	(-6.3%, 17.4%)
Female	86/114 (75.4%)	84/110 (76.4%)	-0.9%	(-12.1%, 10.3%)
Age (yrs)				
< 65	116/150 (77.3%)	120/150 (80.0%)	-2.7%	(-11.9%, 6.6%)
≥ 65	43/54 (79.6%)	35/54 (64.8%)	14.8%	(-1.9%, 31.5%)
High risk				
No	92/116 (79.3%)	74/95 (77.9%)	1.4%	(-9.7%, 12.6%)
Yes	67/88 (76.1%)	81/109 (74.3%)	1.8%	(-10.3%, 13.9%)
Site				
1	16/23 (69.6%)	17/24 (70.8%)	1.3%	(-27.4%, 24.9%)
2	16/20 (80.0%)	18/20 (90.0%)	-10.0%	(-31.9%, 11.9%)
3	28/38 (73.7%)	23/37 (62.2%)	11.5%	(-9.5%, 32.5%)
4	17/20 (85.0%)	15/20 (75.0%)	10.0%	(-14.6%, 34.6%)
5	15/18 (83.3%)	14/18 (77.8%)	5.6%	(-20.2%, 31.4%)
6	1/2 (50.0%)	1/2 (50.0%)	0.0%	(-98.0%, 98.0%)
7	14/24 (58.3%)	17/24 (70.8%)	-12.5%	(-39.3%, 14.3%)
8	1/3 (33.3%)	2/3 (66.7%)	-33.3%	(-100.0%, 42.1%)
9	26/27 (96.3%)	22/26 (84.6%)	11.7%	(-3.9%, 27.3%)
10	24/27 (88.9%)	24/28 (85.7%)	3.2%	(-14.4%, 20.7%)
11	1/2 (50.0%)	2/2 (100.0%)	-50.0%	(-100.0%, 19.3%)

Compiled by this reviewer.

As seen from the table above, treatment difference was consistent among subgroups of gender, age, and high risk.

3.1.1.3.4 Reviewer’s Comments on Sponsor’s Analysis of Secondary Efficacy Variables

The sponsor’s ITT analysis for secondary efficacy endpoint did not include all randomized patients. It is not a true “ITT” analysis. There were 26 patients (14 in BLI800 and 12 in MoviPrep) were excluded from the sponsor’s ITT analyses. If these 26 patients were considered to be “failed,” result from secondary efficacy responder analysis for true ITT population is given below.

**Number and Percent of Adequate Preparations
Protocol BLI800-301
True ITT Analysis**

Treatment	Rate	Diff (BLI800 – MoviPrep)	95% C.I.
BLI800	178/204 (87.3%)	-2.0%	(-8.2%, 4.3%)
MoviPrep	182/204 (89.2%)		

Compiled by this reviewer.

As seen from the table above, a true ITT analysis which includes all randomized subjects shows that BL800 patients experienced similar adequate preparations success to MoviPrep. The confidence interval falls between the predetermined equivalence margin of $\pm 15\%$. Furthermore, the absolute value of the lower limit of the confidence interval is slightly larger than 7%, the non-inferiority margin as recommended by this reviewer.

3.1.1.3.5 Reviewer's Analysis of Preparation Cleansing Score

The examination physician rated each colonoscopy for cleansing according to four point scale where a score of 1="poor" and a score of 4="excellent." This reviewer performed a statistical analysis of preparation cleansing score using CMH (Cochran-Mantel-Haenszel) method for ordinal data with modified ridit scores. Result from this analysis showed that there was no treatment difference between BLI800 and MoviPrep in preparation cleansing score ($p=0.2615$).

3.1.2 BL1-800-302

3.1.2.1 Study Design

The design of this study is similar to that of Protocol BL1-800-301 with exception in the number of days of preparation. In Protocol BLI-800-301, preparation was to be administered as one-day preparation. But, in Protocol BLI-800-302, preparation was to be administered as a split dose, 2-day preparation.

The efficacy of MoviPrep administered as a one-day preparation has been previous reported as 73%. But, based on results reported in the MoviPrep labeling, the success rate for MoviPrep administered as a split dose, 2-day preparation was expected to be approximately 89%.

3.1.2.2 Sponsor's Analysis

A total of 379 patients were screened, randomized and dispensed study medication (190 in BLI800 and 189 in MoviRep). A total of 364 patients (181 in BLI800 and 183 in MoviPrep) were included in the sponsor's Intent-to-Treat analysis. 363 of the 364 patients that received their study preparation fully completed the study. Patient 12017 did not take her assigned preparation but had to reschedule her colonoscopy due to a family emergency. The sponsor's ITT analysis excluded 16 patients (10 in BLI800 and 6 in MoviPrep)..

3.1.2.2.1 Planned Analysis

The planned analysis for this study is similar to that for Protocol BL1-800-301.

3.1.2.2.2 Treatment Group Comparability

The summary of results of comparability of treatment groups for demographic and baseline characteristics for all randomized patients is given in Appendix Table 2.

As seen from Appendix Table 2, no statistically significant differences between the two treatment groups were observed for demographic and baseline characteristics.

3.1.2.2.3 Sponsor's Analysis of Primary Efficacy Variable

The examination physician rated each colonoscopy for cleansing according to four point scale where a score of 1="poor" and a score of 4="excellent." Cleansing score for bowel preparations by treatment group are given below.

Preparation Cleansing Score

Score	BLI800 n (%)	MoviPrep n (%)
4 Excellent	114 (63.3%)	96 (52.5%)
3 Good	61 (33.9%)	79 (43.2%)
2 Fair	3 (1.7%)	6 (3.3%)
1 Poor	2 (1.1%)	2 (1.1%)
Mean Score	3.59	3.47

(reference table 14.2.1.1 in Section 14)

The table includes all 363 patients (180 BLI800 and 183 MoviPrep) that had a colonoscopy. As seen from table above, the distribution of scores for each cleansing category was similar.

Primary efficacy was assessed on the basis of a binary outcome of overall preparation success (grading score=3 or 4) or failure (grading score=1 or 2) by the blinded colonoscopist. Result from the primary efficacy responder analysis is given below.

Number and Percent of Successful Preparations Protocol BLI800-302 Sponsor's ITT Analysis

Treatment	Rate	Diff (BLI800 – MoviPrep)	95% C.I.
BLI800	175/180 (97.2%)	1.6%	(-2.2%, 5.4%)
MoviPrep	175/183 (95.6%)		

Copied from sponsor Table 302-5

As seen from the table above, BL800 patients experienced similar preparation success to MoviPrep. The confidence interval falls between the predetermined equivalence margin of $\pm 15\%$.

3.1.2.2.4 Sponsor’s Analysis of Secondary Efficacy Variable

A secondary endpoint was adequacy of cleaning (cleaning adequate for evaluation). A preparation was considered adequate if the physician response to the question “Was cleansing adequate for evaluation?” on the physician’s colonoscopy examination form was ‘Yes.’ Results from the secondary efficacy responder analysis are given below.

Number and Percent of Adequate Preparations Protocol BLI800-302 Sponsor’s ITT Analysis

Treatment	Rate	Diff (BLI800 – MoviPrep)	95% C.I.
BLI800	178/180 (98.9%)	-0.0%	(-2.2%, 2.1%)
MoviPrep	181/183 (98.9%)		

Copied sponsor from Table 302-7

As seen from the table above, BL800 patients experienced similar adequate preparations to MoviPrep. The confidence interval also falls between the predetermined equivalence margin of $\pm 15\%$.

3.1.2.3 Reviewer’ Comments and Evaluation

3.1.2.3.1 Non-inferiority Margin

The sponsor proposed the 15% of non-inferiority marginal without any justification. The sponsor should have provided more detailed justification on the selection of non-inferiority margin of 15%.

When an assumed expected event for a control is large (e.g. 90% or more), the non-inferiority margin should be tight. The margin should be much less than sponsor’s 15%.

Choosing of a margin of 15% implies that as much as a 16.8% relative decrease of assumed expect event rate of 89% might occur in patients prepared with BLI800. This may not be clinically acceptable. If up a 5% relative decrease is acceptable, then the non-inferiority margin should have been only around 4%.

3.1.2.3.2 Reviewer’s Comments on Sponsor’s Analysis of Primary Efficacy Endpoint

3.1.2.3.2.1 Primary Efficacy Endpoint

The sponsor’s ITT analysis is a modified ITT analysis which excluded Patient 12017 who did take her assigned preparation but had to reschedule her colonoscopy due to a family emergency. If this patient was considered as “failure”, the treatment difference would be

1.1% instead of 1.6%. The lower limit of 2-sided 95% confidence interval of treatment difference would be -2.9% instead of -2.2%.

Furthermore, the sponsor’s ITT analysis for primary efficacy endpoint did not include all randomized patients. It is not a true “ITT” analysis. There were 16 patients (10 in BLI800 and 6 in MoviPrep) were excluded from the sponsor’s ITT analyses. If these 16 patients were considered to be “failed,” result from primary efficacy responder analysis for true ITT population is given below.

**Number and Percent of Successful Preparations
Protocol BLI800-302
True ITT Analysis**

Treatment	Rate	Diff (BLI800 – MoviPrep)	95% C.I.
BLI800	175/190 (92.1%)	-0.5%	(-5.8%, 4.9%)
MoviPrep	175/189 (92.6%)		

Compiled by this reviewer.

As seen from the table above, for true ITT analysis which included all randomized subjects, BL800 patients experienced similar preparation success to MoviPrep. The confidence interval falls between the predetermined equivalence margin of $\pm 15\%$. Furthermore, the absolute value of the lower limit of the confidence interval is slightly greater than 4%, the non-inferiority margin recommended by this reviewer.

Furthermore, in order to determine whether BLI800 would be superior to placebo if placebo arm were included in this study, the reviewer computed a 95% confidence interval on the success rate of BLI800 for true ITT population. This resulted lower limit of the two-sided 95% confidence intervals on the success rate for BLI800 of 87.3%. If the medical division determines that this lower limit is higher than the upper limit of 95% confidence interval on the historical success rate for placebo, if exists, then BLI800 could also be considered effective from that perspective.

3.1.2.3.2.2 Subgroup Analyses

Results from subgroup analyses of primary efficacy endpoint by gender, age, and site are given below for true ITT analysis. In this analysis, patients with missing data were considered to “failure”. Patients that reported a medical history of cardiac, renal or vascular problems (hypertension), or diabetes were defined as “high risk.”

**Number and Percent of Successful Preparations
Protocol BLI800-302
True ITT Analysis**

Subgroup	BLI800	MoviPrep	Diff	95% CI
Gender				
Male	81/87 (93.1%)	82/87 (94.3%)	-1.1%	(-8.4%, 6.1%)
Female	94/103 (91.3%)	93/102 (91.2%)	0.1%	(-7.7%, 7.8%)
Age (yrs)				
< 65	134/144 (93.1%)	141/150 (94.0%)	-0.9%	(-6.6%, 4.7%)
≥ 65	41/46 (89.1%)	34/39 (87.2%)	1.9%	(-11.9%, 15.8%)
High risk				
No	93/102 (91.2%)	96/103 (93.2%)	-2.0%	(-9.4%, 5.3%)
Yes	82/88 (93.2%)	79/86 (91.9%)	1.3%	(-6.5%, 9.1%)
Site				
11	18/23 (90.0%)	18/20 (90.0%)	0.0%	(-18.6%, 18.6%)
12	13/15 (86.7%)	15/15 (100.0%)	-13.3%	(-30.5%, 3.9%)
13	22/23 (95.7%)	23/23 (100.0%)	-4.3%	(-12.7%, 4.0%)
14	14/15 (93.3%)	15/15 (100.0%)	-6.7%	(-19.3%, 6.0%)
15	38/40 (95.0%)	35/40 (87.5%)	7.5%	(-4.8%, 19.8%)
16	12/14 (85.7%)	12/13 (92.3%)	-6.6%	(-30.0%, 16.8%)
17	7/7 (100.0%)	5/6 (83.3%)	16.7%	(-13.2%, 46.5%)
18	14/15 (93.3%)	12/15 (80.0%)	13.3%	(-10.5%, 37.2%)
19	19/21/ (90.5%)	20/22 (90.9%)	-0.4%	(-17.8%, 16.9%)
20	18/20 (90.0%)	20/20 (100.0%)	-10.0%	(-23.2%, 3.2%)

Compiled by this reviewer.

As seen from the table above, treatment difference was consistent among subgroups of gender, age, and high risk.

3.1.2.3.3 Reviewer’s Comments on Sponsor’s Analysis of Secondary Efficacy Variables

The sponsor’s ITT analysis for secondary efficacy endpoint did not include all randomized patients. It is not a true “ITT” analysis. There were 16 patients (10 in BLI800 and 6 in MoviPrep) were excluded from the sponsor’s ITT analyses. If these 16 patients were considered to be “failed,” result from secondary efficacy responder analysis for true ITT population is given below.

**Number and Percent of Adequate Preparations
Protocol BLI800-302
True ITT Analysis**

Treatment	Rate	Diff (BLI800 – MoviPrep)	95% C.I.
BLI800	178/190 (93.7%)	-2.1%	(-6.6%, 2.4%)
MoviPrep	181/189 (95.8%)		

Compiled by this reviewer.

As seen from the table above, for a true ITT analysis which included all randomized subjects, BLI800 patients experienced similar adequate preparations success to MoviPrep. The confidence interval falls between the predetermined equivalence margin of $\pm 15\%$. Furthermore, the absolute value of the lower limit of the confidence interval is slightly larger than 4%, the non-inferiority margin recommended by this reviewer.

3.1.2.3.4 Reviewer's Analysis of Preparation Cleansing Score

The examination physician rated each colonoscopy for cleansing according to four point scale where a score of 1="poor" and a score of 4="excellent." This reviewer performed a statistical analysis of preparation cleansing score using CMH (Cochran-Mantel-Haenszel) method for ordinal data with modified ridit scores. Result from this analysis showed that BLI800 was slightly better than MoviPrep in preparation cleansing score ($p=0.0340$).

3.2 Evaluation of Safety

3.2.1 Study BLI800-301

No statistically significant differences between the preparations with respect to adverse events were detected. The expected categories of nausea, vomiting, abdominal pain and distension were the most common.

Patients rated their symptoms of cramping, stomach bloating, nausea, vomiting, and overall discomfort using a five point scale of 1="None", 2="Mild", 3="Bothersome", 4="Distressing", and 5="Severely distressing".

A comparison of the two groups revealed a very small but statistically significant difference in the mean patient symptom ratings for vomiting symptoms (1.23 vs. 1.07; $p=0.009$).

For vomiting symptoms, fewer patients reported mild to severe symptoms with MoviPrep as compared to BLI800 (13% vs. 4%; $p=0.017$).

A greater percentage of elderly patients (> 65 years old) in the BLI800 group seemed to experience an adverse event compared to the MoviPrep group (28.3% vs. 5.6%; $p=0.01$).

Mean patient symptom rating in the elderly population was generally slightly higher in the BLI800 as compared to the MoviPrep group; only the vomiting symptom reached statistical significance.

Female BLI800 patients reported slightly more vomiting symptoms than MoviPrep patients (1.39 vs. 1.09; $p=0.004$). Symptoms of nausea were slightly higher in BLI800 females as well, although the difference was not statistically significant (1.97 vs. 1.66; $p=0.068$).

Slightly more high-risk patients in the BLI800 group experienced adverse events compared to the MoviPrep group (16% vs. 5%; p=0.023). Gastrointestinal symptoms were slightly higher in BLI800 (12% vs. 5%; p=0.107), although the difference was not statistically significant.

3.2.2 Study BLI800-302

No statistically significant differences between the preparations with respect to adverse events were detected. The expected categories of nausea, vomiting, abdominal pain and distension were the most common.

Patients rated their symptoms of cramping, stomach bloating, nausea, vomiting, and overall discomfort using a five point scale of 1="None", 2="Mild", 3="Bothersome", 4="Distressing", and 5="Severely distressing".

A comparison of the two groups revealed slight differences in the mean patient symptom ratings for stomach bloating and vomiting symptoms. Both differences failed to reach statistical significance.

Patient symptom ratings by severity revealed a statistically significant difference in overall discomfort favoring BLI800 (43% vs. 31%; p=0.007).

Mean patient symptom ratings in the elderly population was slightly higher in the BLI800 as compared to the MoviPrep group for vomiting symptom , it failed to reach statistical significance (1.16 vs. 1.00; p=0.069).

With respect to patient reported symptoms, no statistically significant differences were detected between groups on the basis of gender, with the exception of overall discomfort. BLI800 males experienced less overall discomfort than males in the MoviPrep group (1.55 vs. 1.80; p=0.010).

3.2.3 Subgroup Analysis of Any AE by Age and High Risk Status

Per medical officer's request, this reviewer tabulated patients with "Did patient have any AEs" by age (≤ 65 and > 65) and those at high risk status for Studies BLI-800-301 and BLI-800-302. Summary of the results is given below.

Proportion of Patients with Observed Any AE by Age

Study	Age	BLI800 (%)	MoviPrep (%)	Diff (BLI-Movi)	95% C. I.
BLI-800-301	≤ 65	17/155 (11.0%)	21/161 (13.0)	-2/0%	(-9.2%, 5.1%)
	> 65	13/46 (28.3%)	2/36 (5.6%)	22.7%	(7.7%, 37.7%)
	Total	30/201 (14.9%)	23/197 (11.7%)	3.2%	(-3.4%, 9.9%)
BLI-800-302	≤ 65	16/152 (10.5%)	11/153 (7.2%)	3.3%	(-3.0%, 9.7%)
	> 65	1/35 (2.9%)	3/32 (9.4%)	-6.5%	(-18.0%, 5.0%)
	Total	17/187 (9.1%)	14/185 (7.6%)	1.5%	(-4.1%, 7.1%)

Compiled by this reviewer.

Proportion of Patients with Observed Any AE by High Risk Status

Study	High Risk	BLI800 (%)	MoviPrep (%)	Diff (BLI-Movi)	95% C. I.
BLI-800-301	No	15/114 (13.2%)	17/95 (17.9)	-4.7%	(-14.6%, 5.2%)
	Yes	15/87 (17.2%)	6/102 (5.9%)	11.3%	(2.2%, 20.5%)
	Total	30/201 (14.9%)	23/197 (11.7%)	3.2%	(-3.4%, 9.9%)
BLI-800-302	No	15/101 (14.9%)	5/98 (5.1%)	9.8%	(1.6%, 17.9%)
	Yes	2/86 (2.3%)	9/87 (10.3%)	-8.0%	(-15.2%, -0.9%)
	Total	17/187 (9.1%)	14/185 (7.6%)	1.5%	(-4.1%, 7.1%)

Complied by this reviewer.

As seen from the Table above, for study BLI-800-301, the adverse event rate for any AE for BLI800 was statistically significantly higher than that for Moviprep for patients aged greater than 65 year old since the 95% confidence interval of treatment difference does not contain zero. But for study BLI-800-302, the adverse event rate for any AE for BLI800 was slightly smaller than that for Moviprep for patients aged greater than 65 year old.

For study BLI-800-301, the adverse event rate for any AE for BLI800 was statistically significantly higher than that for Moviprep for patients in the high risk status since the 95% confidence interval of treatment difference does not contain zero. But for study BLI-800-302, the adverse event rate for any AE for BLI800 was statistically significantly smaller than those for Moviprep for patients in the high risk status.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATION

4.1 Gender, Race and Age

No conclusion on efficacy in racial subgroup can be drawn due to lack of representation of Black and other races.

Results from subgroup analyses of primary efficacy endpoint by gender and age (aged <65 years vs. ≥65 years) given below for true ITT analysis. In this true analysis, patients with missing data were considered to “failure”.

**Number and Percent of Successful Preparations
Protocol BLI800-301
True ITT Analysis**

Subgroup	BLI800	MoviPrep	Diff	95% CI
Gender				
Male	73/90 (81.1%)	71/94 (75.5%)	5.6%	(-6.3%, 17.4%)
Female	86/114 (75.4%)	84/110 (76.4%)	-0.9%	(-12.1%, 10.3%)
Age (yrs)				
< 65	116/150 (77.3%)	120/150 (80.0%)	-2.7%	(-11.9%, 6.6%)
≥ 65	43/54 (79.6%)	35/54 (64.8%)	14.8%	(-1.9%, 31.5%)

Complied by this reviewer.

**Number and Percent of Successful Preparations
Protocol BLI800-302
True ITT Analysis**

Subgroup	BLI800	MoviPrep	Diff	95% CI
Gender				
Male	81/87 (93.1%)	82/87 (94.3%)	-1.1%	(-8.4%, 6.1%)
Female	94/103 (91.3%)	93/102 (91.2%)	0.1%	(-7.7%, 7.8%)
Age (yrs)				
< 65	134/144 (93.1%)	141/150 (94.0%)	-0.9%	(-6.6%, 4.7%)
≥ 65	41/46 (89.1%)	34/39 (87.2%)	1.9%	(-11.9%, 15.8%)

As seen from the table above, treatment differences were consistent among subgroups of gender and age.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

For quality of colonic purgation, in both studies ((BLI800-301, one-day preparation) and (BLI800-302, a split dose, 2 day preparation), the 95% confidence lower limits of the differences between BLI800 and MoviPrep of the proportion of subjects with successful preparation were -5.7% and -2.2%, respectively.

For both studies, the sponsor proposed the 15% of non-inferiority marginal without any justification. The sponsor needs provide more detailed justification on the selection of non-inferiority margin of 15%.

For Study BL800-301, the margin of 15% implies that as much as a 20.5% relative decrease of assumed expect event rate of 73% might occur in patients prepared with BLI800. It may not have been acceptable. If a maximum of a 10% relative decrease as acceptable, then the more appropriate margin would have been 7%.

Based on an ITT analysis which included all randomized subjects, BL800 patients experienced similar preparation success to MoviPrep. The confidence interval of the treatment difference in success rates falls between the predetermined equivalence margin of $\pm 15\%$. Furthermore, the absolute value of the lower limit of the confidence interval was 6.2% which is less than 7%, the non-inferiority margin recommended by this reviewer.

Furthermore, in order to determine whether BLI800 would be superior to placebo if placebo arm were included in this study, the reviewer computed 95% confidence interval on the success rate of BLI800 for true ITT population. This resulted in a lower limit of 71.6%. If the medical division determines that the upper limit of 95% confidence interval of the historical success rate for placebo would be less than 71.6%, then BLI800 could be considered effective from that perspective.

For Study BLI800-302, the expected event for control was larger (89%) and thus the non-inferiority margin should have been much less than sponsor's 15%. A margin of 15% implies that as much as a 16.8% relative decrease of assumed expected event rate of 89% might occur in patients prepared with BLI800. This may not have been acceptable. If a maximum of a 5% relative decrease as acceptable, then the more appropriate margin would have been 4%.

Based on ITT analysis which included all randomized subjects, BLI800 patients experienced similar preparation success rates to MoviPrep. The confidence interval of the treatment difference falls between the predetermined equivalence margin of $\pm 15\%$. Furthermore, the absolute value of the lower limit of the confidence interval (4.9%) is slightly greater than 4%, the non-inferiority margin recommended by this reviewer.

This reviewer performed a statistical analysis of preparation cleansing score using CMH (Cochran-Mantel-Haenszel) method for ordinal data with modified ridit scores. Result from this analysis showed that BLI800 was slightly better than MoviPrep in preparation cleansing score ($p=0.0340$).

Furthermore, in order to determine whether BLI800 would be superior to placebo if placebo arm were included in this study, the reviewer computed 95% confidence interval on the success rate of BLI800 for true ITT population. This resulted in a lower limit of 87.3%. If the medical division determines that the upper limit of 95% confidence interval on the historical success rate for placebo would be less than 87.3%, then BLI800 could be considered effective from that perspective.

For Study BLI-800-301, the adverse event rate for any AE for BLI800 was statistically significantly higher than that for MoviPrep for patients aged greater than 65 year old since the 95% confidence interval of treatment difference does not contain zero. But for study BLI-800-302, the adverse event rate for any AE for BLI800 was slightly smaller than that for MoviPrep for patients aged greater than 65 year old.

For study BLI-800-301, the adverse event rate for any AE for BLI800 was statistically significantly higher than that for MoviPrep for patients in the high risk status since the 95% confidence interval of treatment difference does not contain zero. But for study BLI-800-302, the adverse event rate for any AE for BLI800 was statistically significantly smaller than that for MoviPrep for patients in the high risk status.

5.2 Conclusions and Recommendations

The sponsor conducted two adequate and well-controlled studies to assess the efficacy of SuPrep colonic purgation: BLI800-301, one-day preparation; and BLI800-302, a split dose, 2 day preparation. In both studies, the SuPrep and MoviPrep formulations performed similarly.

In Study BLI800-301 the percent of successful preparations for SuPrep and MoviPrep were 82% and 80%, respectively, and the lower limit of the 95% confidence interval of

the difference in rates was -5.7%. For Study BLI800-302, the percent of successful preparations for SuPrep and MoviPrep was 97% and 96%, respectively, with a lower limit of the 95% confidence interval of the difference of -2.2%.

Although the sponsor did not adequately justify their choice of a 15% non-inferiority margin, the resulting lower confidence limits of -5.7% and -2.2% are sufficiently above the -15% threshold to support non-inferiority.

For Study BLI-800-301, the adverse event rate for any AE for SuPrep was statistically significantly higher than that for Moviprep, for patients aged greater than 65 year old and for patients in the high risk status.

6. Appendix

Table 1 Summary of Demographic and Baseline Characteristics --- Protocol BL800-301

All Randomized Patients			
Characteristics	BL800 (N=204)	MoviPrep (N=204)	Between Treatment p-value
Sex			
Male	90 (44.1%)	94 (46.1%)	0.6906
Female	114 (55.9%)	110 (53.9%)	
Race			
N	202	203	0.5341
White	178 (88.1%)	178 (87.7%)	
Black	22 (10.9%)	25 (12.3%)	
Asian	1 (0.5%)	0 (0.0%)	
Other Races	1 (0.5%)	0 (0.2%)	
Age (yr)			
Mean (SD)	57.7 (10.9)	57.2 (11.9)	0.6622
Age			
<65	150 (73.5%)	150 (73.5%)	1.000
≥65	54 (26.5%)	54 (26.5%)	
High Risk			
Yes	88 (43.1%)	109 (53.4%)	0.0375
No	116 (56.9%)	95 (46.6%)	

Compiled by this reviewer

P-values were computed by this reviewer.

P-value for categorical data was obtained using Chi-square test.

P-value for continuous data was obtained using t-test.

Table 2 Summary of Demographic and Baseline Characteristics --- Protocol BL800-302

All Randomized Patients			
Characteristics	BL800 (N=190)	MoviPrep (N=189)	Between Treatment p-value
Sex			
Male	87 (45.8%)	87 (46.0%)	0.9623
Female	103 (54.2%)	102 (54.0%)	
Race			
N	190	185	0.0952
White	160 (84.2%)	166 (89.7%)	
Black	19 (10.0%)	16 (8.6%)	
Asian	8 (4.2%)	2 (1.1%)	
Native American	0 (0.0%)	1 (0.5%)	
Other Races	3 (1.6%)	0 (0.0%)	
Age (yr)			
Mean (SD)	55.9 (12.3)	55.9 (10.8)	0.9749
Age			
<65	144 (75.8%)	150 (79.4%)	0.4040
≥65	46 (24.2%)	39 (20.6%)	
High Risk			
Yes	88 (46.3%)	86 (45.5%)	0.8738
No	102 (53.7%)	103 (54.5%)	

Compiled by this reviewer

P-values were computed by this reviewer.

P-value for categorical data was obtained using Chi-square test.

P-value for continuous data was obtained using t-test.

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/s/

Milton Fan
7/7/2009 04:07:04 PM
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Mike Welch
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Concur with review