CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

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

ADDENDUM

NDA/Serial Number:	203595/000
Drug Name:	BLI-850 (oral sulfate solution-polyethylene glycol 3350 electrolyte solution)
Applicant:	Braintree Laboratories, INC.
Date(s):	Submission: 12/19/2011; Consult received from DGIEP: 03/1/2012; PDUFA: 10/19/2012 Extended PDUFA: 01/19/2013
Review Priority	Standard
Biometrics Division:	Division of Biometrics 7
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Medical Division:	Division of Gastroenterology and Inborn Error Products
Clinical Team:	Medical Reviewer: Jessica Lee, MD; Medical Team Lead: Robert Fiorentino, MD
Project Manager:	Matthew Scherer

Keywords: Laboratory parameters, shift analysis, safety analysis, RCTs

Background

This addendum updates select Table entries and Figures for the statistical safety review of BLI-850 (oral sulfate solution-polyethylene glycol 3350 electrolyte solution) submitted to DARRTS 9/12/2012 (NDA 203595/000). Braintree Laboratories, Inc., submitted the NDA on 12/17/2011 seeking the indication of cleansing of the colon as a preparation for colonoscopy in adults.

Results for two laboratory parameters presented in the 9/12/2012 statistical safety review are corrected in this addendum. The first correction is for analyses of estimated glomerular filtration rate (eGFR) based on the Modification of Diet in Renal Disease (MDRD) formula. In the 9/12/2012 review eGFR values were calculated using an incorrect MDRD formula; this addendum revises the results for studies BLI850-301 (301) and BLI850-302 (302) using the correct formula.

The second correction revises shift analysis results for eGFR analyses in study 302 based on the Cockcroft-Gault (CG) equation. In the 9/12/2012, one subject who was missing data at visit 2 was incorrectly included in the analysis. An updated analysis omitting this subject is presented in this addendum.

Estimates of the laboratory parameters presented in this addendum replace previous estimates provided in the 9/12/2012 review.

Amended eGFR MDRD Estimates

The 9/12/2012 review used an incorrect formula to estimate eGFR using the MDRD method. Specifically, the 9/12/2012 review estimated eGFR using the following equation

$$175 \times \text{Serum Creatinine (in mg/dL)}^{-1.154} \times \text{Age}^{-0.203} \times [1.212 \text{ if Black}] \times [0.742 \text{ if Female}].$$

The correct equation is

$$\mathbf{186} \times \text{Serum Creatinine (in mg/dL)}^{-1.154} \times \text{Age}^{-0.203} \times [1.212 \text{ if Black}] \times [0.742 \text{ if Female}].$$

Under the corrected equation, compared to the equation used in the 9/12/2012 review, eGFR values will increase by a factor of 1.063 (=186/175), thus impacting mean eGFR levels and the number of subjects classified as normal at baseline (eGFR >90).

The revised eGFR MDRD results are provided below according to whether the analysis dealt with the comparison of shifts (Table 1) or mean levels (Table 2). *Note that the means in Table 27 of the 9/12/2012 review are not included in this addendum as the baseline means for both studies are presented in Table 2.* Updated scatterplots of baseline versus day of colonoscopy eGFR values are shown in Figure 1 for study 301 and in Figure 2 for study 302.

Importantly, use of the revised equation does not impact findings from the hypothesis testing (and confidence interval evaluation) for the comparison of mean change from baseline between groups since the statistical inferences are invariant to scalar transformations. However, results and conclusions for the shift analysis (i.e., the comparison between treatment groups of the number of subjects with an abnormal value at visit 2 among those with normal baseline) are sensitive to use of new the equation.

Two notable changes are observed for this analysis. First, in Table 22 for study 302, the number of subjects with an abnormal value in the BLI-850 compared to MoviPrep group went from being greater though not statistically significant in the analysis in the 9/12/2012 report (BLI-850: 50.0% vs. MoviPrep: 35.7%), to being similar between groups (BLI-850: 33.9% vs. MoviPrep: 31.5%). Second, in study 301 based on the revised eGFR MDRD values, there appears to be a statistically significant interaction between treatment and gender (Table 30). Specifically, based on the revised values, the percentage of abnormal eGFR MDRD values among females is greater in the BLI-850 group compared to HalfLytely (35.0% vs. 11.1%), while, among males, there were fewer abnormal values in the BLI-850 group compared to HalfLytely (20.0% vs. 50.0%). There was no evidence of an interaction by gender for eGFR when using the prior eGRF MDRD equation (in the 9/12/2012 report).

Table 1. Revised eGFR MDRD analyses: Shift analyses

Table# (Trial): Other/Subgroup	BLI-850 n/N (%)	Comparator n/N (%)	RD (95% CI) (or p-value)
Table 9 (301)	114/159 (71.7)	108/171 (63.1)	p-value=0.10
Table 9 (302)	114/173 (65.9)	111/165 (67.3)	p-value=0.82
Table 14 (301)	12/45 (26.7)	21/63 (33.3)	-6.7 (-24.1, 10.7)
Table 22 (302)	20/59 (33.9)	17/54 (31.5)	2.4 (-14.9, 19.7)
Table 28 (301): Below Normal	12/45 (26.7)	21/63 (33.3)	NP
Table 28 (301): Above Normal	0/45 (0)	0/63 (0)	NP
Table 29 (301): < 65 yrs	11/43 (25.6)	20/57 (35.1)	p-value*=0.26
Table 29 (301): ≥ 65 yrs	1/2 (50.0)	1/6 (16.7)	
Table 30 (301): Females	7/20 (35.0)	3/27 (11.1)	p-value*<0.01
Table 30 (301): Males	5/25 (20.0)	18/36 (50.0)	
Table 31 (301): Non-White	1/16 (6.3)	8/25 (32.0)	p-value*=0.09
Table 31 (301): White	11/29 (37.9)	13/38 (34.2)	
Table 32 (301): Non-high risk	8/28 (28.6)	15/38 (39.5)	p-value*=0.61
Table 32 (301): High risk	4/17 (23.5)	6/25 (24.0)	
Table 33 (302): Below Normal	20/59 (33.9)	17/54 (31.5)	NC
Table 33 (302): Above Normal	0/59 (0)	0/54 (0)	
Table 34 (302): < 65 yrs	18/54 (33.3)	16/50 (32.0)	p-value*=0.68
Table 34 (302): ≥ 65 yrs	2/5 (40.0)	1/4 (25.0)	
Table 35 (302): Females	13/32 (40.6)	9/27 (33.3)	p-value*=0.54
Table 35 (302): Males	7/27 (25.9)	8/27 (29.6)	
Table 36 (302): Non-White	4/15 (26.7)	3/13 (23.1)	p-value*=0.92
Table 36 (302): White	16/44 (36.4)	14/41 (34.1)	
Table 37 (302): Non-high risk	14/34 (41.2)	9/28 (32.1)	p-value*=0.38
Table 37 (302): High risk	6/25 (24.0)	8/26 (30.8)	

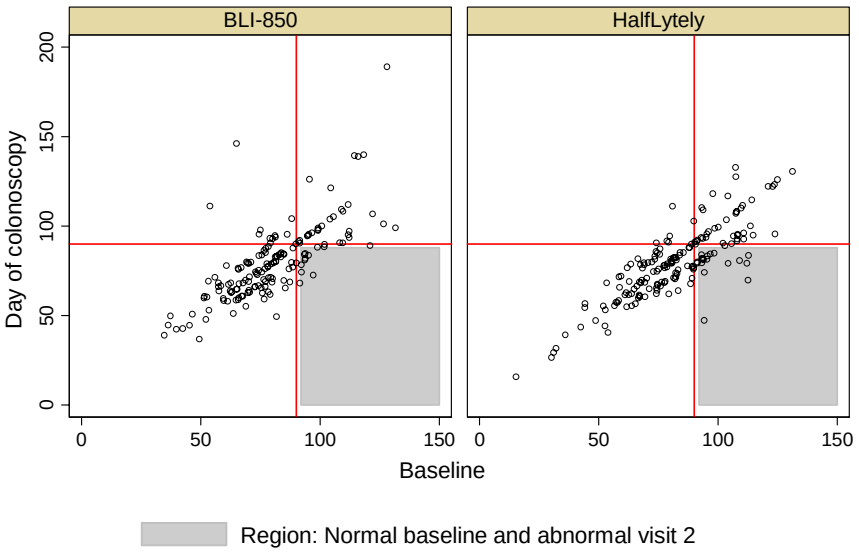
Study 301 Comparator = HalfLytely; Study 302 Comparator = MoviPrep;
#Table from the original statistical review for NDA 203595/000 completed on 9/12/2012
RD = Risk Difference (BLI-850 – Comparator);
* p-value for the test of treatment by subgroup interaction.
NP-comparative summary (p-value or RD and CI) were not presented in 9/12/2012 review, and therefore not included in this addendum
NC-not computed due to zero cells.
Shift analysis compares the proportion of patients between treatment groups with normal baseline values and abnormal visit 2 values

Table 2. Revised eGFR MDRD analyses: Mean value and difference in mean change from baseline

Table# (Trial)	Visit	BLI-850 mean (95% CI)	Comparator mean (95% CI)	DMC from baseline (95% CI)
Table 15 (301)	BL	79.78 (76.80, 82.75)	82.13 (79.05, 85.20)	
	2	79.47 (76.16, 82.78)	79.31 (76.33, 82.29)	2.50 (-0.34, 5.34)
Table 23 (302)	BL	81.30 (78.64, 83.96)	80.13 (77.43, 82.83)	
	2	80.77 (78.43, 83.12)	79.91 (77.36, 82.45)	-0.30 (-2.84, 2.25)

BL=baseline assessment; DMC=difference in mean change (BLI-850 – HalfLytely);
Study 301 Comparator = HalfLytely; Study 302 Comparator = MoviPrep; #Table from the original statistical review for NDA 203595/000 completed on 9/12/2012

Figure 1. Revised eGFR MDRD scatterplot of visit 2 and baseline values with normal range levels overlaid (301). Replaces Figure 7 in 9/12/2012 review for NDA 203595/000.



Lab: eGFR MDRD; Normal Range: > 90
NOTE: points are jittered to reveal frequency

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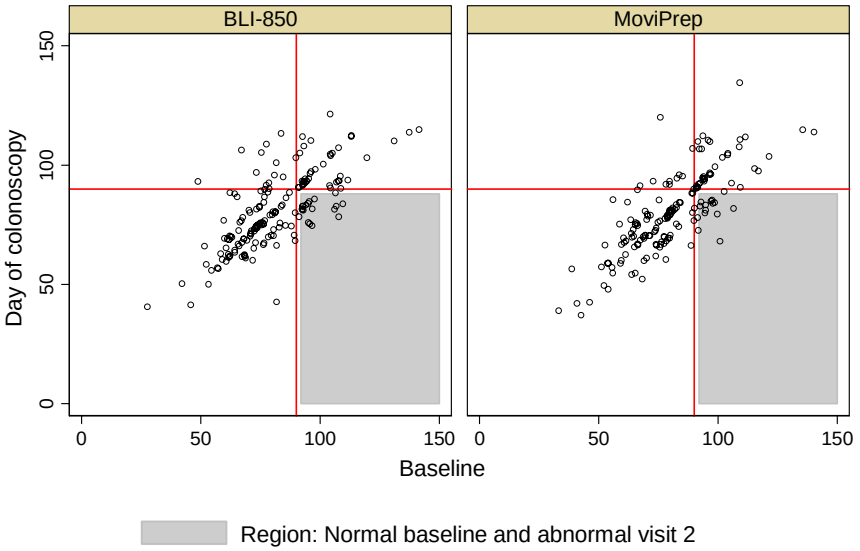
Figure 2. Revised eGFR MDRD scatterplot of visit 2 and baseline values with normal range levels overlaid (302). Replaces Figure 14 in 9/12/2012 review for NDA 203595/000.



APPEARS THIS WAY ON ORIGINAL

Lab: eGFR MDRD; Normal Range: > 90
NOTE: points are jittered to reveal frequency

Amended eGFR CG Estimates

The 9/12/2012 original statistical safety review failed to exclude subject 29013 (randomized to the MoviPrep group) from the eGFR CG shift analyses in study 302. This subject had a missing visit 2 weight and was correctly removed from analyses that investigated means levels. The revised shift related results after excluding this subject are provided in Table 3.

Table 3. Revised eGFR CG shift analyses.

Table#: Other/Subgroup	BLI-850 n/N (%)	MoviPrep n/N (%)	RD (95% CI) (or p-value)
Table 9	71/172 (41)	79/164 (48)	p-value=0.23
Table 22	9/101 (8.9)	9/85 (10.6)	-1.7 (-10.3, 6.9)
Table 33: Below Normal	9/101 (8.9)	9/85 (10.6)	NP
Table 33: Above Normal	0/101 (0)	0/85 (0)	NP
Table 34: < 65 yrs	8/94 (8.5)	9/77 (11.7)	NC
Table 34: ≥ 65 yrs	1/7 (14.3)	0/8 (0.0)	
Table 35: Females	6/64 (9.4)	3/46 (6.5)	p-value*=0.29
Table 35: Males	3/37 (8.1)	6/39 (15.4)	
Table 36: Non-White	4/17 (23.5)	3/14 (21.4)	p-value*=0.64
Table 36: White	5/84 (6.0)	6/71 (8.5)	
Table 37: Non-high risk	7/53 (13.2)	7/45 (15.6)	p-value*=1.0
Table 37: High risk	2/48 (4.2)	2/40 (5.0)	

RD=Risk Difference (BLI-850 – Comparator); NC=Not calculated; * p-value for thest test of treatment by subgroup interaction.
#Table from the original statistical review for NDA 203595/000

Removal of this subject from the analysis of eGFR based on the CG method does not impact, in any substantive way, the findings and conclusions made in the 9/12/2012 statistical reviews for this endpoint.

Conclusions

Results from the revised eGFR MDRD analyses impacted the findings and conclusions made in the 9/12/2012 statistical review for this endpoint in two ways. First, for study 302, the number of subjects with an abnormal value in the BLI-850 compared to MoviPrep group went from being greater, though not statistically significant, in the analysis in the 9/12/2012 report, to being similar without numerical differences between groups. Second, in study 301 based on the revised eGFR MDRD values, there appears to be a statistically significant interaction between treatment and gender. In contrast, there was no evidence of an interaction when using the prior eGRF MDRD equation (in the 9/12/2012 report).

Conclusions from the revised eGFR CG analysis do not impact, in any substantive way, the findings and conclusions presented in the 9/12/2012 statistical safety reviews for this endpoint.

There are no further changes or comments in this safety statistical addendum for NDA 203595/000.

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/s/

BRADLEY W MCEVOY
11/01/2012

LAREE A TRACY
11/02/2012
I concur with this review.

ALOKA G CHAKRAVARTY
11/05/2012

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

STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

NDA/BLA:	20-3595
Drug Name:	(b) (4) (sodium sulfate, potassium sulfate and magnesium sulfate and PEG-3350 (b) (4) for oral solution)
Indication(s):	Cleansing of the colon as a preparation for colonoscopy in adults
Applicant:	Braintree Laboratories, Inc.
Document Reviewed:	Volumes 1 to 22 dated December 16, 2011
Review Priority:	Standard; PDUFA date: January 19, 2013
Biometrics Division:	Division of Biometrics III
Statistical Reviewer:	Wen-Jen Chen, Ph.D., DBIII
Concurring Reviewers:	Mike Welch, PhD, Dep. Dir., DBIII
Medical Division:	Gastroenterology and Inborn Errors Products (DGIEP)
Medical Reviewer:	Jessica Lee, MD.
Medical Team Leader:	Robert Fiorentino, MD.
Project Manager:	Mr. Matthew Scherer

Statistical Keywords: Clinical studies; NDA review, Non-inferiority.

TABLE OF CONTENTS

1.0 EXECTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 Conclusions and Recommendations

From the statistical perspective, the applicant's non-inferiority margin of 15% for the two studies was not supportable and formal statistical testing is compromised. This does not preclude a more general conclusion based on descriptive statistics that the product in each study performed similarly to the active controls.

The two-sided 95% confidence interval for the treatment difference showed that the lower confidence bounds were greater than -15% for both studies (-0.7% for Study BLI850-301 and -5.0% for StudyBLI850-302). However, the reviewer has determined that the NI margin has not been adequately supported (b) (4)

Efficacy analysis for (b) (4) alone shows the lower bounds of the two-sided 95% confidence interval on the proportion of successful bowel cleansings are 84% and 89% for studies BLI850-301 and -302, respectively. Although placebo controlled trials have not been conducted with bowel cleansing preparations, the clinical team should concur that such rates far exceed those possible with placebo.

1.2 Brief Overview of Clinical Studies

(b) (4) is intended to provide an alternative to the Braintree product HalfLytely and Bisacodyl Tablet Bowel Prep Kit (HalfLytely). In particular the bisacodyl component of HalfLytely is replaced by a single dose of sulfate salts (about 22 grams). (b) (4) is intended as a colonic cleansing preparation for colonoscopy. Similar to HalfLytely, the preparation consists of two component steps: a 6 oz bottle of oral sulfate solution (OSS, containing about 22 grams sulfate salts) followed by 2L of a polyethylene glycol and electrolytes solution (PEGELS).

The applicant conducted two randomized, single-blind, active-controlled studies (BLI850-301 and BLI850-302) to compare the safety and efficacy of (b) (4) (BLI850, Oral Sulfate Solution-Polyethylene Glycol 3350 Electrolyte Solution) to HalfLytely (one day preparation regimen) in Study BLI850-301 and to MoviPrep (split dose administration) in Study BLI850-302 for bowel cleansing before colonoscopic examination in adult patients.

In this NDA submission, we note that the applicant conducted a non-inferiority analysis with a pre-specified non-inferiority margin of 15% to establish the efficacy of the study drug. We requested that the applicant provide justification of their non-inferiority margin based on historical studies of the active control. The applicant's response to the information request concerning the non-inferiority margin was received on April 02, 2012 and is a critical part of this review.

For both studies, the primary efficacy endpoint was based on the colonoscopists assessment of colon cleansing using four point scales: 1 – Poor, 2 – Fair, 3 – Good, and 4 - Excellent. For the

primary efficacy analysis, grades 3 and 4 were considered "successes" and grades 1 and 2 were considered "failures". For secondary endpoints, each patient was also rated as to whether or not cleansing was adequate for examination and the need for re-preparation.

The primary efficacy analysis was based upon a modified intent-to-treat (mITT) population which included all patients randomized that took any portion of study preparation. Patients that did not undergo colonoscopy because of inadequate preparation or preparation related adverse events were considered failures for the primary efficacy endpoint. However, patients that took study preparation but withdrew prior to colonoscopy for reasons unrelated to safety or efficacy were excluded from efficacy analyses.

The applicant indicated that success rate for the primary endpoint was analyzed using CMH Chi-square adjusting for the effect of investigator site. The two-sided 95% confidence interval for the treatment difference showed that the lower confidence bounds were greater than -15% for both studies (-0.7 for Study BLI850-301 and -5.0% for StudyBLI850-302). However, the reviewer has determined that the NI margin has not been adequately supported and would be (b) (4) . The lower confidence bounds of the two-sided 95% confidence intervals on the proportions of bowel cleansing success for (b) (4) (BLI850) are not less than 84%. This threshold is likely informative of an efficacious product, as discussed in Section 1.3.

It is noted that a margin of 10% has been employed for approval of INKP-102 (NDA 21-892 on May 17, 2005). In addition, the advice letter sent by the Agency (on June 6, 2009) commented that a margin of 15% has not been justified statistically and has not been considered statistically acceptable as a non-inferiority margin for evaluation of investigational bowel preparation. Accordingly, from a statistical perspective, the non-inferiority margin of 15% selected by the applicant for HalLytely and MoviPrep is questionable and is not acceptable.

1.3 Statistical Issues and Findings

In this section, this reviewer first gives the comments on the non-inferiority margin of 15% and the assessments of colon cleansing quality. Then, the comments on the primary efficacy analysis by center and the efficacy assessments for BLI850 separately for each individual study are followed.

Comments on the issue of non-inferiority margin

As noted by this reviewer, the justification for the non-inferiority margin of 15% submitted by the applicant is for the two active control arms (HalfLytely and MoviPrep) employed by the two studies (BLI850-301 and BLI850-302). Accordingly, the comments made below by this reviewer on the issue of the non-inferiority margin are for both studies.

As noted in the ICH E-10 guidance, the non-inferiority margin chosen should be based on the smallest effect size of the active control arm as shown in the historical well-controlled placebo trials conducted under the conditions similar to that of the current trials.

However, none of the three studies (F38-15, F38-20, and F38-26) submitted by the applicant to support the non-inferiority margin of 15% was a historical placebo-controlled study using HalfLytely or MoviPrep as a treated arm. Since all three studies provided by the applicant did not comply with the ICH E-10 guidance for a non-inferiority margin selection, the justification for the non-inferiority margin of 15% as determined by the applicant is problematic.

We understand that in the bowel cleansing preparation trial, for ethical reason, a placebo controlled study might have never been performed. Success rate for placebo is unknown and may be close to 0% as the applicant stated. However, a margin of 15% has not been justified statistically and has not been considered statistically acceptable as a non-inferiority margin for evaluation of investigational bowel preparation. In addition, recently, a margin of 10% has been employed for approval of INKP-102 (NDA 21-892 submitted on May 17, 2005). Accordingly, from statistical perspective, the non-inferiority margin of 15% selected by the applicant for HalLytely and MoviPrep is questionable and not acceptable.

Finally, no non-inferiority margin was pre-specified for the secondary endpoint "cleansing adequate for evaluation", the results from the secondary endpoints can not be validly assessed. Accordingly, these results are exploratory (b) (4) However, both studies showed that the new treatment BLI850 performed similarly to the active controls. This conclusion is descriptive only and would be more appropriate for labeling.

Comments on the assessments of colon cleansing quality

Based on the applicant's study design, biased assessments on colon cleansing quality may be induced by the following two issues: i) nature of single blinded design and ii) the non-inferiority analysis criterion.

i) Issue on the single blinded design

Since this is a single blinded study, patients knew which drug was used for their bowel preparation. There was possibility for the investigators to be informed of the bowl preparation drug used by patients. Therefore, the single blinded trial had potential to be an open label trial. Furthermore, the ratings of "fair" (enough feces or fluid to prevent a completely reliable exam) and "good" (small amounts of feces or fluid not interfering with exam) in bowel cleansing quality are not completely distinguishable and might be assessed subjectively.

Accordingly, if the investigator realized which drug was used by the patient, the assessment on the successful bowel preparation (scored as "good" by investigators) could be biased in favor of the study drug.

The ICH E10 Guidance for Industry states that for the comparative trial to be informative concerning relative safety and/or efficacy, the trial needs to be fair; i.e., the conditions of the trial should not inappropriately favor one treatment over the other. Accordingly, in order to avoid the potential for biased assessments in this single blinded trial the applicant could have included

another lower dose arm 2L-PEC (2 liters of PEG-ELS - **o**ne component of HalfLytely) in this trial (as was done for Study F38-15). As noted by this reviewer, 2L-PEC used in Study F38-15 by the applicant was to support HalfLytely as an effective bowel preparation drug by showing superiority to the 2L-PEC control. However, a decision to include another lower dose arm in the trial should be based on practical and ethical considerations and is deferred to Medical Division. In addition, this reviewer recommends that in future studies, a more objective colon cleansing rating scale should be employed to enhance the quality of colon cleansing assessments.

ii) Issue on the non-inferiority analysis criterion

Based on the non-inferiority analysis criterion, one notes that if the outcomes of the bowel preparations for the two treatment groups, HalfLytely and (b) (4) are similarly scored by the investigators, then non-inferiority for the two drugs would easily be achieved. Due to the ambiguous definitions of grade 2 and grade 3 scoring, the bowel preparation quality might not be assessed objectively. Therefore, with only two arms (b) (4) and HalfLytely in the trial, it may have been likely for the investigator to assign similar scores to the bowel preparations for the two treatment groups and the likelihood of a conclusion of non-inferiority for the two drugs would be increased. However, such a conclusion would be a biased result.

Comments on the primary efficacy analysis by center

For Study BLI850-301, analysis of the primary endpoint by center indicates that no center was found in the BLI850 group to have an abnormally large proportion of patients judged success in gut cleansing. Thus, no center dominates the comparison of BLI850 to HalfLytely.

Similarly, for Study BLI850-302, no center was found in the BLI850 group to have abnormally large proportion of patients judged success in gut cleansing to dominate the comparison of BLI850 to MoviPrep.

Efficacy of BLI850

Finally, for Study BLI850-301, the efficacy analysis on BLI850 shows that lower bound of the two-sided 95% confidence interval on the success rate of bowel cleansing quality is 0.84 using the ITT patient population.

For Study BLI850-302, the lower bound for the two-sided 95% confidence interval on the success rate of bowel cleansing quality is 0.89 using the ITT patient population.

The lower bounds of the two-sided 95% confidence intervals on the proportions of bowel cleansing success for (b) (4) (BLI850) are not less than 84%. This threshold is consistent with values observed in other bowel cleansing agents and can be used by the Medical Division as an aid in assessing the clinical efficacy of (b) (4) for bowel cleansing.

2.0 INTRODUCTION

2.1 Overview

The applicant conducted two randomized, single-blind, active-controlled studies (BLI850-301 and BLI850-302) to compare the safety and efficacy of BLI850 (Oral Sulfate Solution-Polyethylene Glycol 3350 Electrolyte Solution) to HalfLytely (in one day preparation regimen) in Study BLI850-301 and to MoviPrep (in a split dose administration) in Study BLI850-302 for bowel cleansing before colonoscopic examination in adult patients.

(b) (4) is intended to provide an alternative to the Braintree product HalfLytely and Bisacodyl Tablet Bowel Prep Kit (HalfLytely). In particular the bisacodyl component of HalfLytely is replaced by a single dose of sulfate salts (about 22 grams). (b) (4) is intended as a colonic cleansing preparation for colonoscopy. Similar to HalfLytely, the preparation consists of two component steps: a 6 oz bottle of oral sulfate solution (OSS, containing about 22 grams sulfate salts) followed by 2L of a polyethylene glycol and electrolytes solution (PEGELS).

In this NDA submission, the applicant applied non-inferiority analysis with non-inferiority margin of 15% to establish the efficacy of the study drug (b) (4) in bowel preparation. We noted that the issue on the selection of non-inferiority margin of 15% was commented by the Agency in previous NDAs submitted by the applicant for the bowel cleansing quality and in a letter sent by the Agency on June 6, 2009 for IND 102,894. Accordingly, in order to make sure the Agency has received clear/full justifications of the non-inferiority margin of 15% determined by the applicant for this NDA submission, we requested the applicant provide justification of non-inferiority margin based on historical studies following the principles of the ICH E-10 Guidance. The applicant's response to the information request of the non-inferiority margin was received on April 02, 2012.

2.1.1 Study BLI850-301

The purpose of this study was to evaluate the safety and efficacy of BLI850 (Oral Sulfate Solution-Polyethylene Glycol 3350 Electrolyte Solution) vs. HalfLytely and Bisacodyl Tablets Bowel Prep Kit (HalfLytely) for bowel cleansing before colonoscopic examination in adult patients. The study was designed as a randomized, active-controlled, single-blind, multi-center, pivotal phase-3 trial with two parallel treatment groups, (b) (4) (BLI850) or HalfLytely bowel preparation kits. This study was conducted in USA and 394 patients were randomized. Of the 394 patients, 366 patients took one of the two bowel preparations and 362 underwent colonoscopy.

The primary efficacy endpoint was based on the colonoscopists assessment of colon cleansing using a four point scale: 1 – Poor, 2 – Fair, 3 – Good, and 4 - Excellent.
For the primary efficacy analysis, grades 3 and 4 were considered "successful" and grades 1 and 2 were considered "failures". Each examination was also rated as to whether or not cleansing was adequate for examination and the need for re-preparation.

Secondary efficacy endpoints included the following:

- Adequacy of cleaning (cleaning adequate for evaluation) and need for re-preparation;
- Number of excellent preparations as graded by the blinded colonoscopist;
- Number of examinations in which the colonoscopist reached the cecum.

The primary efficacy analysis was based upon a modified intent-to-treat (mITT) population included all patients randomized that took any portion of study preparation. Patients that did not undergo colonoscopy because of inadequate preparation or preparation related adverse events were considered failures for the primary efficacy endpoint.

The applicant indicated that success rate for the primary endpoint was analyzed using CMH Chi-square adjusting for the effect of investigator site. The formal hypothesis test result (p-value) for treatment difference is presented together with a two-sided 95% confidence interval for the difference. A lower CI bound greater than -15% would establish non-inferiority between BLI850 and HalfLytely for a non-inferiority margin of 15%.

2.1.2 Study BLI850-302

The purpose of this study was to evaluate the safety and efficacy of BLI850 (Oral Sulfate Solution-Polyethylene Glycol 3350 Electrolyte Solution) vs. MoviPrep (active control preparation) administered as split doses for bowel cleansing before colonoscopic examination in healthy adult outpatients requiring colonoscopy. The study was designed as a randomized, active-controlled, single-blind, multi-centre, pivotal phase 3 trial and was conducted in USA. Total 386 patients were randomized. Of the 386 patients, 371 patients took one of the two bowel preparations and 369 underwent colonoscopy.

The primary and secondary efficacy endpoints and analysis methods were the same as that for Study BLI850-301.

2.2 Data Sources

Documents reviewed include NDA volumes 1 to 22 for Module 5 submitted by the applicant on December 16, 2011. The data used in this reviewer's analysis was submitted by the applicant December 20, 2011. The data sets are located at \\cdsesub4\NONECTD\NDA203595\4985472.

3.0 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study BLI850-301

3.1.1.1 Study Design and Endpoints

The purpose of this study was to evaluate the safety and efficacy of BLI850 (Oral Sulfate

Solution-Polyethylene Glycol 3350 Electrolyte Solution) vs. HalfLytely and Bisacodyl Tablets Bowel Prep Kit (HalfLytely) for bowel cleansing before colonoscopic examination in adult patients. The study was designed as a randomized, active-controlled, single-blind, multi-centre, pivotal phase-3 trial with two parallel treatment groups, BLI850 or HalfLytely bowel preparation kits.

In this single blind, active controlled study, BLI850 or HalfLytely bowel preparation kits were provided to patients requiring colonoscopy for routinely accepted indications. The order of preparation assignment was determined according to a computer generated randomization schedule. Patients self-administered the assigned study preparation in two doses on the day before their scheduled colonoscopy. All study medications were provided to patients in identically labeled outer packages to eliminate unintentional un-blinding.

Based on the sample size calculation, it was intended to recruit up to 360 in-patients in order to obtain 300 efficacy-evaluable patients. All patients had to be scheduled to undergo complete colonoscopy at up to 15 hospital centers with specialized gastroenterology departments. For the assignment of patients to test or reference treatment during the single-blind treatment period, (b) (4) had prepared a randomization list with a block size of 4 and passed it on to the (b) (4) responsible for packaging of the investigational drugs.

Patients were randomly assigned in a 1:1 ratio to receive either BLI850 or HalfLytely bowel preparation kits within each participating site. The randomization schedule for this study was created by StatNet Statistical Services Network and was constructed using random blocks of 2 balanced treatment assignments at each site. The randomization schedule was implemented by Braintree Laboratories prior to kit distribution to the site. Following receipt of a sequential series of drug kits, site personnel dispensed the lowest numbered kit available to patients who met eligibility criteria in order to maintain the randomization schedule.

On the day of their colonoscopy, patients were instructed to return all used and unused drug supplies to the clinic. In order to maintain the blinding, only the un-blinded staff members processed drug returns. The un-blinded staff members performed drug accountability by measuring and counting the remaining amounts of unused study medication returned, and by querying study patients for compliance.

Patients maintained a treatment questionnaire that was completed over the course of their bowel preparation which recorded the times at which the patient took each dose of their preparation, the date and time of any vomiting episodes which may have occurred, and a description of what they ate and drank on the day of the preparation up until their colonoscopy. Finally, patients filed out an overall symptom questionnaire at Visit 2 (prior to colonoscopy) where they rated symptoms typically associated with bowel preparations.
The primary efficacy endpoint was based on the colonoscopist's assessment of colon cleansing using a four point scale. This scale is shown below in Table 3.1.1.1.1.

Table 3.1.1.1.1 (Applicant's) Colonoscopist colon cleansing assessment scores - Study BLI850-301

Score	Grade	Description
1	**Poor**	**Large amounts of fecal residue, additional cleansing**
2	**Fair**	**Enough feces or fluid to prevent a completely**
3	**Good**	**Small amounts of feces or fluid not interfering with exam**
4	**Excellent**	**No more than small bits of adherent feces/fluid**

For the primary efficacy analysis, grades 3 and 4 were considered "successful" and grades 1 and 2 were considered "failures". Each examination was also rated as to whether or not cleansing was adequate for examination and the need for re-preparation.

Secondary efficacy endpoints included the following:

- Adequacy of cleaning (cleaning adequate for evaluation) and need for re-preparation;
- Number of excellent preparations as graded by the blinded colonoscopist;
- Number of examinations in which the colonoscopist reached the cecum.

3.1.1.2 Statistical Methods

The primary efficacy analysis was based upon a modified intent-to-treat (mITT) population which included all patients randomized that took any portion of study preparation. Patients that did not undergo colonoscopy because of inadequate preparation or preparation related adverse events were considered failures for the primary efficacy endpoint. However, patients that took study preparation but withdrew prior to colonoscopy for reasons unrelated to safety or efficacy were excluded from efficacy analyses.

The applicant indicated that success rate for the primary endpoint was analyzed using CMH Chi-square adjusting for the effect of investigator site. The formal hypothesis test result (p-value) for treatment difference is presented together with a two-sided 95% confidence interval for the difference. The applicant stated that a lower CI bound greater than -15% would establish non-inferiority between BLI850 and HalfLytely for a non-inferiority margin of 15%.

Secondary endpoints were analyzed in a manner similar to the primary analysis 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 responses. No adjustment was made for multiplicity testing of secondary endpoints. Results are presented for the effect results (p-values) and two-sided 95% confidence intervals for the-treatment difference. The primary efficacy analysis and selected secondary efficacy analyses were descriptively summarized by gender, race and age group (< 65, ≥ 65 and < 75, ≥ 75 years of age). These selected subgroup analyses were also tested to identify any significant treatment group differences. In addition,

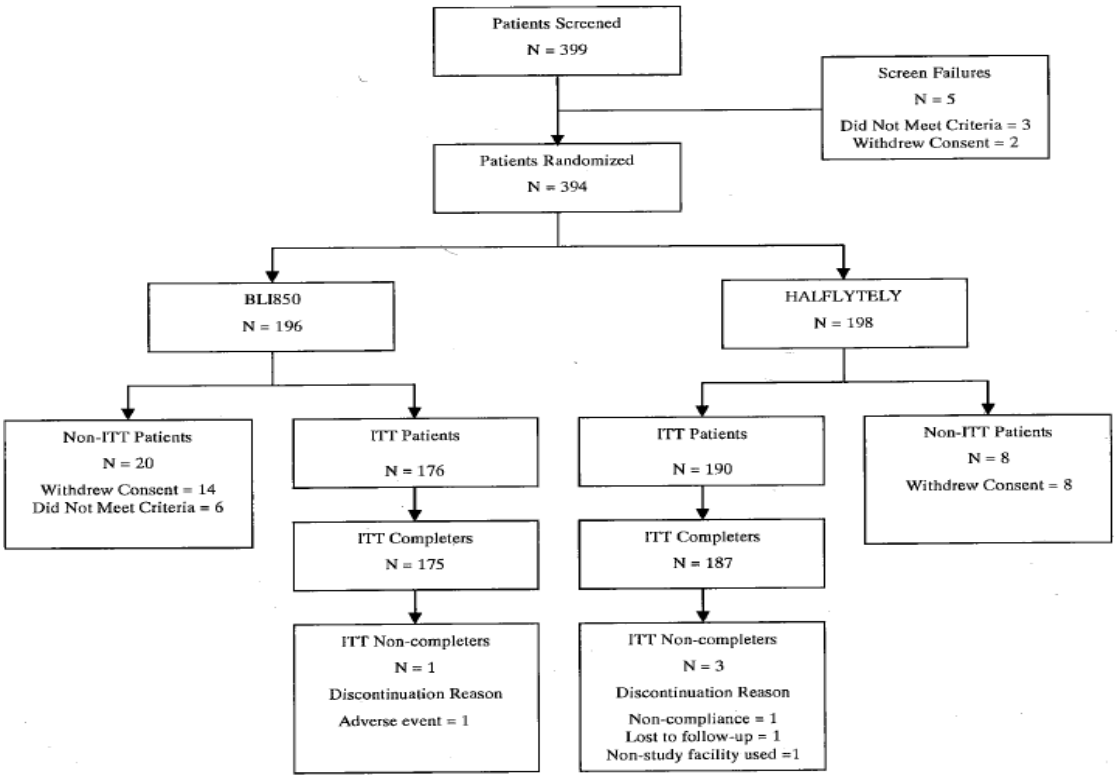
symptom questionnaire data for patient reported individual symptoms for Overall Experience (nausea, stomach cramping, stomach bloating and overall discomfort) were tested using ANOVA with terms for treatment, site, and their interaction.

For the sample size determination, the applicant indicated that the protocol planned study size was three hundred sixty (360) patients. Patients were randomly assigned to one of the two preparations in a ratio of 1:1 (180 patients per group). A dropout rate of approximately 5% per treatment group was expected. The efficacy of HalfLytely administered as a one-day preparation has been previously reported as 87%. Assuming a success rate for BLI850 of ≥ 81% based on results of a similar sulfate based 1-day preparation, a two-sided 95% confidence interval (asymptotic Pearson Chi-square method) for the between group success rates (BLI850 - HalfLytely) will result in a lower CI bound greater than -15%. This result will establish non-inferiority between BLI850 and HalfLytely for a non-inferiority margin of 15%.

3.1.1.3 Patient Disposition

This study was conducted at 12 centers. 399 patients were screened and 394 were randomized and dispensed study medication. 366 patients took the study preparation and were included in the Intent-to-Treat (ITT) analysis, including 97 elderly. Non-ITT patients included 22 patients that withdrew consent prior to receiving study preparation, and 6 patients that were found to have not met inclusion/exclusion criteria after being dispensed study preparation. All Non-ITT patients were confirmed to have not taken any study preparation. Figure 3.1.1.3.1 displayed the diagram of the patient disposition.

Figure 3.1.1.3.1 (Applicant's) Patient Disposition Diagram – Study BLI850-301



In addition, the reasons for discontinuation in the ITT group are given below in Table 3.1.1.3.1.

Table 3.1.1.3.1 (Applicant's) Reasons for Patient Discontinuation using Intent-to-Treat Population – Study BLI850-301

	BLISSO n(%)	**MoviPrep** n(%)
Total ITT Patients	176 (100%)	190 (100%)
Completing Patients	175 (99.4%)	187 (98.4%)
Patients Discontinued	1 (0.6%)	3 (1.6%)
Reasons for discontinuation:		
Adverse event	1 (100%)	0 (0%)
Non-compliance	0 (0%)	1 (33%1
Lost to follow-up	0 (0%)	1 (33%)
Non-study facility used	0 (O)	1 (33%)

Based upon Table 3.1.1.3.1, the applicant indicated that 362 patients of the 366 patients that received their study preparation fully completed the study (defined as patients that had a colonoscopy). Four patients (numbers 05006, 05040, 06027, 10003) took their assigned preparation but were withdrawn prior to colonoscopy. Patient 05006 (BLI850) experienced atrial fibrilation and was discontinued from the study prior to colonoscopy. Patient 05040 (HalfLytely) had their colonoscopy performed at a non-study facility due to patient concerns about anesthesia administration. This patient did not report any adverse events. Patient 06027 (HalfLytely)

discontinued taking the preparation because they did not have a bowel movement within 6 hours following the bisacodyl dose. This patient did not report any adverse events. Patient 10003 (HalfLytely) was unable to obtain transportation to the facility for colonoscopy. This patient did not report any adverse events.

The applicant further indicated that the primary efficacy analysis was based on 364 patients in ITT population. All patients enrolled that took the study preparation and underwent colonoscopy (n=362) were included. Patients 05006 and 06027 were also included in the primary efficacy responder analyses as failures because they could not undergo colonoscopy due to a concurrent adverse event (05006) or non-compliance with preparation administration (06027). Patients 05040 and 10003 completed the preparation but are not included in any efficacy analyses. Patient 05040 had their colonoscopy at a non-study facility due to patient concerns about anesthesia. Patient 10003 was unable to return for colonoscopy due to transportation issues. Neither patient reported any adverse events.

3.1.1.4 Demographic and other Baseline Characteristics

For the structures of the demographics, the applicant indicated that the overall study population included slightly more female patients (55%) than males, although no difference was detected in the gender distribution between the two treatment groups. The treatment groups were similar with respect to age, racial distribution and baseline weight.

The average age of study participants was about 57 years, ranging from 22 to 86 years of age. There were 97 ITT patients age 65 or older (48 BLI850, 49 HalfLytely), and 32 patients 75 years of age or older (16 BLI850, 16 HalfLytely). About 83% of ITT patients were Caucasian and 15% were African American, approximately reflecting the national racial population distribution. Study patients weighed an average of about 181 lbs. No demographic related statistically significant differences were noted between the treatment groups. The study population demographics are summarized in Table 3.1.1.4.1 below.

Table 3.1.1.4.1 (Applicant's) Study Demographics using ITT population- Study BLI850-301

	BLI850	HalfLytely	p[1]
Age (years)[2]			
n	176	190	0.935
Mean (SD)	56.8 (13.1)	56.9 (12.3)	
Gender			
Female	97 (55%)	104 (55%)	1.000
Male	79 (45%)	86 (45%)	
Race[3]			
White	143 (81%)	145	0.662
A.Am.	25 (14%)	(76%)	
Other	4 (2%)	28 (15%)	
Ethnicity			
Hispanic	4 (2%)	10 (5%)	0.176
Non Hispanic	172 (98%)	180 (95%)	
Weight (lbs)			
Mean(SD	181 (42)	181 (42)	0.982

(1) P-value from exact Chi-Square test for the categorical variables and from an ANDV A with term for treatment for the continuous variables,
(2) Age is calculated using of date of birth and screening visit (Visit 1) date.
(3) Percentage for race does not equal 100% since Hispanic or Latino patients may not have reported a race.
SD = standard deviation; A. Am. = African American

3.1.1.5 Applicant's Efficacy Analysis Results and Conclusions

Primary endpoint analysis

The examining physician rated each colonoscopy for cleansing according to a four point scale where a score of 1= "poor" and a score of 4= "excellent" as described above in Section 3.1.1.1. Cleansing scores for the BLI850 and HalfLytely bowel preparations are shown in Table3.1.1.5.1.

Table 3.1.1.5.1 (Applicant's) Preparation Cleansing Score – Study BLI850-301

Score	**BLI850** n (%)	**HalfLytely** n (%)	**p[1,2]**
4 Excellent	84 (47.7%)	67 (35.6%)	**0.010**
3 Good	74 (42.0%)	90 (47.9%)	
2 Fair	13 (7.4%)	25 (13.3%)	
1 Poor	4 (2.3%)	5 (2.7%)	
Missing	1 (0.6%)	1 (0.5%)	
Mean Score[3]	3.36	3.17	**0.016**

1) P-value comparing excellent preps is from a CMH, controllng for site;
2) P-value for mean score is from a one-way ANDVA with term for treatment;
3) patients 05040 and 10003 were excluded as non-evaluable for efficacy analysis while 05006 and 06027 are included as "missing"

Based upon Table 3.1.1.5.1, the applicant indicated that all 364 patients included by this table had a colonoscopy or withdrew due to safety or non-compliance. BLI850 achieved significantly

more "Excellent" preparations than HalfLytely (p = 0.010). In addition, the average cleansing score was also significantly higher for BLI850 (p = 0.016).

The applicant further indicated that as might be expected from the cleansing score results, analysis of the number of "successful" preparations (the primary efficacy variable), where a colonoscopy cleansing score of 3 or 4 was considered as “successful” and scores of 1 and 2 were considered as "failures", showed no difference between the two preparations, shown in Table 3.1.1.5.2.

Table 3.1.1.5.2 (Applicant’s) Analysis on percent of successful endoscopy exam by treatment groups Study BLI850-301

Responder[1]	BLI850 n (%)	HalfLytely n (%)	95% CI[2]	p[3]	p[4]
All Patients[5]	176	190			
Success	158 (89.8%)	157 (83.5%)	-0.7, 13.2	0.065	**<0.001**
Fail	18 (10.2%)	31 (16.5%)			
Elderly (≥65 y)	48	49			
Success	41 (85.4%)	42 (85.7%)	-14.3, 13.7	0.951	-
Fail	7 (14.6%)	7 (14.3%)			
Males	79	84			
Success	69 (87.3%)	66 (78.6%)	-2.7, 20.2	0.211	-
Fail	10 (12.7%)	18 (21.4%)			
Females	97	104			
Success	89 (91.8%)	91 (87.5%)	-4.1, 12.6	0.283	-
Fail	8 (8.2%)	13 (12.5%)			

(1) A successful treatment is defined as bowel cleansing graded either excellent or good by the blinded colonoscopist (grading score = 3 or 4).
(2) Confidence interval (CI) for the difference between treatments was by Chi-Square Test.
(3) P-value for the difference between treatments is from a CMH, controllng for site.
(4) P-value for the non-inferiority hypothesis using an equivalence margin of 15 percent
(5) Patients 05040 and 10003 were excluded as non-evaluable for efficacy analysis.

Based upon Table 3.1.1.5.2, the applicant indicated that this table includes the 364 patients that underwent colonoscopy as well as the two patients that were counted as failures due to a concurrent adverse event (05006) or noncompliance with preparation administration (06027).

Although not statistically significant, BLI850 patients tended to have a higher percentage of successful preparations compared to HalfLytely patients (90% to 84%, respectively). The applicant indicated that non-inferiority testing showed that the lower confidence bound of -.7% was greater than -15% thus supporting the hypothesis that split dose preparation with BLI850 is non-inferior to MoviPrep.

The applicant further indicated that a sensitivity analysis of the primary endpoint using a true ITT population (all randomized subjects) confirms the previous conclusion that BLI850 (success rate 80.6%) is non-inferior to HalfLytely (success rate 79.3%).

Secondary efficacy endpoint analysis

The analysis results on the secondary endpoints "adequacy of cleansing" and "cecum reached" are presented in Table 3.1.1.5.3.

Table 3.1.1.5.3 (Applicant's) Number and Percent of Adequate Preparations – Study BLI850-301

	BLI850 n (%)	**HalfLytely** n(%)	**95% CI[1]**	p[1]
Adequate? (n)	175	187		
Yes	170 (97%)	183 (98%)	-3.9, 2.5	0.744
No	5 (3%)	4 (2%)		
Cecum reached? (n)	172	184		
Yes	170 (99%)	184 (100%)	-2.8, 0.4	0.157
No	2 (1%)	0 (0%)		

(1) Confidence interval (CI) and p-value for the difference between treatments was by Chi-Square Test.
Note: Patients 05006, 05040, 06027 and 10003 are not included because they did not undergo colonoscopy.

Based upon Table 3.1.1.5.3, the applicant indicated that most preparations for either treatment were considered to be adequate. In addition, in nearly all procedures for either preparation, examining physicians were able to reach the cecum.

The proportions of excellent preparations are shown in Table 3.1.1.5.1.

3.1.1.6 Reviewer's Comments and Analysis

In order to validate the sponsor's (b) (4) this reviewer first comments on the following three issues: 1) non-inferiority margin of 15%, 2) assessments of colon cleansing quality, and 3) primary efficacy analysis by center. Then, the reviewer's efficacy analysis is presented.

3.1.1.6.1 Reviewer's Comments

1) Comments on the applicant's non-inferiority margin

The documents provided by the applicant to support the selection of the non-inferiority margin of 15% first indicated that a non-inferiority margin of 15% had been used for controlled studies performed in support of FDA approved applications including previous applications for HalfLytety and MoviPrep. In addition, the applicant stated that the HalfLytely control agent with 15% margin is clearly distinguishable from placebo which would reasonably be expected to have a nearly 0% success rate. Finally, the applicant justifies the 15% margin using three studies: F38-15, F38-20, and F38-26.

- Contents of studies F38-15, F38-20, and F38-26

Study F38-15

Study F38-15 was submitted through NDA 21551, approved in 2003, as a supportive study together with Study F38-20 to support HalfLytely for bowel cleansing prior to colonscopy. In

this study, the applicant compared each of the individual components of HalfLytely (20 mg of bisacodyl and 2 liters of PEG-ELS, "2LPEG") to a 4 liter polyethylene glycol and electrolytes preparation (NuLYTELY). The goal of this study was to show that NuLYTELY (the 4L standard preparation) was statistically significantly superior to each individual components of HalfLytely (20 mg of bisacodyl and 2L-PEG) for the primary endpoint of preparation success.

The rationale for comparing NuLYTELY to each individual components of HalfLytely was that due to ethical reasons, placebo could not be utilized as a negative control in bowel preparation studies. In addition, the applicant further emphasized that the high failing rates of the two components showed that each component could not be used as a bowel preparation drug. The applicant however used the difference between NuLYTELY and the 2L-PEG preparation (15.4%) to estimate the smallest effect size that NuLYTELY would be reliably expected to have when compared to any failed preparation. Thus, the applicant declared that a 15 percent non-inferiority margin for bowel preparation studies is justified.

Study F38-20

Study F38-20 was submitted through NDA 21551 as a pivotal phase 3 trial to support the original approval of HalfLytely for bowel cleansing prior to colonscopy in 2003. The studied drug HalfLytely 20 mg/2L Tablets is a reduced volume preparation and consisted of 20 mg bisacodyl (four 5 milligram tablets) followed several hours later by 2 liters of NuLytely.

The primary endpoint of cleansing success as presented in the NDA study report was originally tested for a null hypothesis of no effect difference ($p = 0.90$). Then, this data was reanalyzed to test a non-inferiority hypothesis using 15% non-inferiority margin. Based upon the non-inferiority result, the applicant stated that the analysis result showed that HalfLytely was confirmed to be non-inferior to NuLYTELY, with the lower limit of the 95% confidence interval -12.8% within the 15% margin.

Study F38-26

Study F38-26 was submitted through NDA 21551 as a pivotal phase 3 trial to compare the safety and efficacy of HalfLytely with 10 mg bisacodyl (the test drug) to HalfLytely with 20 mg bisacodyl (the approved product) in normal adult outpatients requiring colonoscopy.

The applicant indicated that a similar reanalysis to Study F38-20 was performed for Study F38-26. Original testing of the null hypothesis of no effect difference performed for Study F38-26 indicated no difference between the two HalfLytety treatment groups (bisacodyl dose 10 mg versus bisacodyl dose 20 mg; $p = 0.521$). Then, testing of a non-inferiority hypothesis using the 15% margin resulted in a significant result ($p < 0.001$). Based upon this result, the applicant emphasized that the non-inferiority of HalfLytety with 10 mg bisacodyl to HalfLytety with 20 mg is supported by the lower limit of the 95% confidence interval of -7.6%, which is well within the 15% margin.

- Comments on studies F38-15, F38-20, and F38-26

Since the justification for the non-inferiority margin of 15% submitted by the applicant is for both active control arms (HalfLytely and MoviPrep) employed by the two studies (BLI850-301 and BLI850-302), the following comments made by this reviewer on the non-inferiority margin are also for both studies.

First, ICH E10, "Guidance for Industry, E10 choice of Control Group and Related Issues in Clinical Trials", indicates that the non-inferiority trials are designed to show that the new drug is not less effective than the active control arm by more than a defined amount, generally called margin. This margin is the degree of inferiority of the test treatment to the control that the trial will attempt to exclude statistically.

As to the principle of margin selection, ICH E10 states that the margin chosen for a non-inferiority trial cannot be greater than the smallest effect size that the active drug would be reliably expected to have compared with placebo in the setting of the planned trial. However, usually, for ethical reasons, no placebo arms were planned to be included in the new trials. Accordingly, identification of the smallest effect size that the active drug would be reliably expected to have is only possible when there is historical evidence of sensitivity to drug effects and, indeed, identification of the margin is based upon that evidence. Thus, the margin generally is identified based on past experience (historical studies) in placebo-controlled trials of adequate design under conditions similar to those planned for the new trials.

Based upon the principles stated in ICH E-10, the comments regarding inadequate evidence provided by the three studies used to support the choice of non-inferiority margin of 15% are given below.

Study F38-15

As indicated by the applicant, the goal of this study was to show that NuLYTELYwas superior to each of the two components of HalfLytely. Then, the applicant used the rate difference (15.4%) estimated between NuLYTELY and 2L-PEG to support the non-inferiority margin of 15% for HalfLytely.

Since neither placebo arm nor the active control arm (HalfLytely or MoviPrep) used in Study BLI850-301 or BLI850-302 was included in this study (F38-15), the information provided by this study can not be used to estimate the effect size of HalfLytely or MoviPrep based upon the criteria of ICH E-10. Data evidence provided by the study (F38-15) is not acceptable to justify the non-inferiority margin of 15% determined for HalfLytely and MoviPrep.

Study F38-20

As mentioned by the applicant in the submitted non-inferiority margin justification documents, the goal of Study F38-20 was to apply non-inferiority (NI) analysis to compare the effects of bowel cleansing for HalfLytely to NuLYTELY using a non-inferiority margin of 15%. Therefore,

in this study, no data was used to justify the selection of 15% NI margin selected for HalfLytely or MoviPrep.

Study F38-26

Similar to Study F38-20, Study F38-26 applied non-inferiority analysis to compare the effects of bowel cleansing between the two HalfLytety treatment groups (bisacodyl dose 10 mg versus bisacodyl dose 20 mg). Therefore, in this study, no data was used to justify the selection of 15% NI margin selected for HalfLytely bisacodyl dose 20 mg.

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Accordingly, based upon this reviewer's review on the three studies, none of these three studies was a historical well-controlled placebo study using HalfLytely or MoviPrep as the treated arm. However, as this reviewer stated in the beginning of this sub-section of reviewer's comments, the margin chosen should be based on the efficacy evidence of the active control arm shown in the historical trials following the guidance of ICH E-10. Since all three studies provided by the applicant did not comply with the guidance from ICH E-10, the justification for NI margin of 15% determined by the applicant is not acceptable to this reviewer.

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This reviewer understands that in bowel cleansing preparation trials, a placebo-controlled study might have never been performed due to ethical concerns. The success rate for placebo is unknown, and it may be close to 0% as the sponsor stated. However, a margin of 15% has not been justified statistically and has not been considered statistically acceptable as a non-inferiority margin for evaluation of investigational bowel preparation products. In addition, a margin of 10% has been employed for approval of INKP-102 (NDA 21-892 on May 17, 2005). Accordingly, from a statistical perspective, the non-inferiority margin of 15% selected by the applicant for HalLytely and MoviPrep is questionable and not acceptable.

2) Comments on the assessments of colon cleansing quality

Based on the applicant's study design, biased assessments on the colon cleansing quality are possibly induced by the following two issues: i) nature of single blinded design and ii) non-inferiority analysis criterion.

i) Issue on the single blinded design

As indicated by the applicant, this trial was conducted as a single blinded study in which investigators were blinded as to the methods of preparation. However, since patients knew which drugs were used for their bowel preparations, it might have been easy for the investigators to recognize the bowel preparation drug used by patients. Therefore, in reality, the single blinded trial had potential to be an open label trial for the investigator. Furthermore, the definitions of "grade 2" (Enough feces or fluid to prevent a completely reliable exam) and "grade 3" (Small amounts of feces or fluid not interfering with exam) in bowel cleansing quality are not clear cut and may be assessed subjectively. Accordingly, as long as the investigator comprehended which

drug was used by the patient, the assessment on the successful bowel preparation could have been biased in favor of study drug.

In ICH E10, Section 1.4.3, it states that for the comparative trial to be informative concerning relative safety and/or efficacy, the trial needs to be fair; i.e., the conditions of the trial should not inappropriately favor one treatment over the other. In order to avoid the potential biased assessments, in Study BLI850-301, the applicant could have included another lower dose arm 2L-PEC (2 liters of PEG-ELS - one component of HalfLytely) in this trial. As noted by this reviewer, 2L-PEC was used in Study F38-20 by the applicant to show that NuLYTELY was an effective bowel preparation drug. However, there are practical and ethical issues regarding a decision to include another lower dose arm in bowel preparation cleansing trials, and this consideration is deferred to the Medical Division. In addition, in the future studies, this reviewer recommends that a more objective colon cleansing rating scale be employed to enhance the quality of colon cleansing assessments.

ii) Issue on the non-inferiority analysis criterion

Based on the efficacy non-inferiority analysis criteria, one notes that if the outcomes of the bowel preparations for the two treatment groups, HalfLytely and (b) (4) are assessed similarly then non-inferiority for the two drugs would be a likely result. As indicated in the above sub-section i), due to the ambiguous definition on the "grade 2" and "grade 3" of the bowel cleansing quality, the bowel preparation quality might not be assessed objectively. Therefore, with only two arms (b) (4) and HalfLytely in the trial, it may have been likely for the investigator to assign similar scores to the bowel preparations for the two treatment groups. As long as the investigator assessed the outcomes of the bowel preparations for the two treatment groups in a similar fashion, the chance of the non-inferiority for the two drugs is increased. However, the non-inferiority of the two treatment groups established by the above assessments would be a biased result.
Thus, as commented by this reviewer in the above sub-section, in order to prevent the potentially biased assessments, the applicant could have included another arm of 2L-PEC in the trial. However, as stated in the above sub-section, the consideration to include another lower dose arm in these trials is deferred to Medical Division, and the use of a more objective colon cleansing rating scale is recommended.

3) Primary efficacy analysis by center

The 12 study centers analyzed individually by the applicant for the primary efficacy variable are shown below in Table 3.1.1.6.1.

Table 3.1.1.6.1 (Applicant's) Analysis on the percent of successful endoscopy exam by site – Study BLI850-301

Site	Score[2]	BLI850 n(%)	HalfLytely n (%)	95% CI[3]	p3
01	Success Fail	11 (92%) 1 (8%)	8 (73%) 3 (27%)	-11.7, 49.6	0.317
02	Success Fail	19 (95%) 1 (5%)	16 (76%) 5 (24%)	-1.8, 39.4	0.184
03	Success Fail	23 (77%) 7 (23%)	23 (74%) 8 (26%)	-19.1, 24.1	1.000
04	Success Fail	10 (100%) 0	9 (90%) 1 (10%)	-8.6, 28.6	1.000
05	Success Fail	15 (94%) 1 (6%)	16 (100%) 0 (0%)	-18.1, 5.6	1.000
06	Success Fail	21(81%) 5 (19%)	21 (72%) 8 (28%)	-13.9, 30.6	0.537
07	Success Fail	4 (80%) 1 (20%)	4 (80%) 1 (20%)	-49.6, 49.6	1.000
08	Success Fail	12 (100%) 0	14 (93%) 1 (7%)	-6.0, 19.3	1.000
09	Success Fail	25 (96%) 1 (4%)	27 (93%) 2 (7%)	-8.8, 14.9	1.000
10	Success Fail	6 (100%) 0	3 (60%) 2 (40%)	-2.9, 82.9	0.182
11	Success Fail	3 (75%) 1 (25%)	6 (100%) 0	-67.4, 17.4	0.400
12	Success Fail	9 (100%) 0	10 (100%) 0	-	-

(1) Patients 05006 and 06027 are included as failures in this table. Patients 05040 and 10003 are not included.
(2) A success.ful preparation was defined as as colonoscopy cleansing score of 3 or 4.
(3) Confidence interval and P-value for the difference between BLI850 and MoviPrep are from a Chi Square test.

Table 3.1.1.6.1 indicates that of the twelve centers, only two centers (5 and 11) for the BLI850 ((b) (4) group show numerically lower proportions of patients judged success in gut cleansing than HalfLytely. However, of the ten centers which BLI850 shown higher gut cleansing success rate, no center is found in the BLI850 group to have abnormally large proportion of patients judged success in gut cleansing to dominate the non-inferiority of BLI850 to HalyteLty.

3.1.1.6.2 Reviewer's Analysis

As noted in the comments (stated in Sub-section 3.1.1.6.1) on the applicant's non-inferiority margin, since the justification for the non-inferiority margin of 15% provided by the applicant is not statistically persuasive, (b) (4) However this does not preclude a more general conclusion based on descriptive statistics that the two products performed numerically similarly.

In order to judge if the test drug BLI850 has efficacy that would be superior to placebo, this reviewer calculated the two-sided 95% confidence interval on the success rate of BLI850 (P_{BLI850}). Since the definition of the per-protocol population was not given in the study report and no variable for the per-protocol population was provided in the original data set submitted by the sponsor, the two-sided 95% confidence interval on the success rate of BLI 850 is shown only for the ITT population. Table 3.1.1.6.2 presents this result.

Table 3.1.1.6.2 (Reviewer's) 95% two-sided confidence intervals on P_{BLI850} – Study BLI850-301

	BLI850		95% Confidence Interval on
Patient Population	No. Success	Success Rate (n/N)	P_{BLI850}
Intent-to-Treat Population	158	0.90 (158/176)	(0.84, 0.94)

Table 3.1.1.6.2 shows the lower bound for the two-sided 95% confidence interval on the success rate of bowel cleansing quality is 0.84 using ITT patient population. Since the assessments on the bowel preparations could potentially be biased in favor of the test drug BLI850, the lower bound of the 95% two-sided interval for BLI850 calculated using the data from a double-blind study may be expected to be smaller than 0.84 presented in Table 3.1.1.6.2. From a statistical perspective, BLI850 can be considered effective if the lower bound of the CIs in the table exceed any expectation for a placebo response rate.

3.1.2 Study BLI850-302

3.1.2.1 Study Design and Endpoints

The purpose of this study was to evaluate the safety and efficacy of BLI850 (Oral Sulfate Solution-Polyethylene Glycol 3350 Electrolyte Solution) vs MoviPrep (active control preparation) administered as split doses for bowel cleansing before colonoscopic examination in adult patients. The study was designed as a randomized, active-controlled, single-blind, multi-centre, pivotal phase 3 trial

In this study, BLI850 or MoviPrep kits were provided to patients requiring colonoscopy for routinely accepted indications. The order of preparation assignment was determined according to a computer generated randomization schedule. Patients began administration of the study preparation on the evening prior to their colonoscopy, and completed the morning of the procedure.

In order to maintain blinding of the treatment, the colonoscopist was not allowed to perform any drug related activities (randomization, dispensing or accountability). Investigators who were blinded to the patient's bowel preparation allocation performed colonoscopies according to the site's standard procedures and evaluated cleansing efficacy using a 4-point scale.

Study patients were provided with a treatment questionnaire to record food consumption, any vomiting episodes and the date and time of preparation. Prior to the colonoscopy, study patients

also completed a symptom questionnaire to report their overall experience with the preparation. Blood samples were collected at baseline and pre-colonoscopy for chemistry and hematology analysis.

Patients were dispensed MoviPrep and BLI850 in identically labeled kits and given instructions on dosing and dietary restrictions. Instructions specific to each preparation are noted below. For BLI850, dose one was started at about 6 pm on the evening prior to colonoscopy. At dose one, patients were instructed to pour the contents of the 6 ounce bottle of study preparation into the provided mixing cup and to fill the cup with water to the fill line (16 oz) and then drink the entire cup of solution. Patients were further instructed to drink one additional 16 ounce glass of water over the next two hours. In addition, patients were recommended to drink at least one additional 16 ounce glass of water on the evening prior to colonoscopy.

Then, dose two was started at about 6 am in the morning of colonoscopy. At dose 2, patients were instructed to begin drinking the 2 liters of PEGELS solution at a rate of one 16 ounce glass every 20 minutes until the jug was empty.

For dietary restrictions, patients who took BLI850 were instructed to consume clear liquids only on the day prior to colonoscopy. This clear liquid diet continued until after completion of the colonoscopy.

For MoviPrep, dose one was started at about 6pm on the evening prior to colonoscopy. At dose one, patients were instructed to pour the contents of pouch A and B into the one Liter container and fill with water to the fill line. Patients were instructed to drink the solution over one hour at a rate of 8 ounces every 15 minutes until complete. Patients were required to drink another 0.5 liters of clear liquid that evening.

Then, dose two was started at about 6 am in the morning of colonoscopy. At dose 2, patients were instructed to prepare the second liter of solution and drink the solution over one hour at a rate of 8 ounces every 15 minutes until complete. Patients were required to drink another 0.5 liters of clear liquid that morning.

The dietary restrictions for patients who took MovPrep instructed that for the day before colonoscopy, patients took normal breakfast, light lunch, and clear soup and/or plain yogurt for dinner. Clear liquids only from the time the MoviPrep preparation is started until after completion of the colonoscopy.

Eligible patients were randomly assigned in a 1:1 ratio within each participating site. The randomization schedule for this study was created by StatNet Statistical Services Network and was constructed using random blocks of 2 balanced treatment assignments at each site. The randomization schedule was implemented by Braintree Laboratories prior to kit distribution to the site. Following receipt of a sequential series of drug kits, site personnel dispensed the lowest numbered kit available to patients that met eligibility criteria in order to maintain the randomization schedule.

On the day of their colonoscopy, patients were instructed to return all used and unused drug supplies to the clinic. In order to maintain the blinding, only the un-blinded staff members processed drug returns. The un-blinded staff members performed drug accountability by measuring and counting the remaining amounts of unused study medication returned, and by querying study patients for compliance.

Patients maintained a treatment questionnaire that was completed over the course of their bowel preparation which recorded the times at which the patient took each dose of their preparation, the date and time of any vomiting episodes which may have occurred, and a description of what they ate and drank on the day of the preparation up until their colonoscopy. Finally, patients filed out an overall symptom questionnaire at Visit 2 (prior to colonoscopy) where they rated symptoms typically associated with bowel preparations.

The primary efficacy endpoint was based on the colonoscopists assessment of colon cleansing using a four point scale. This scale is shown below in Table 3.1.2.1.1.

Table 3.1.2.1.1 (Applicant's) Colonoscopist colon cleansing assessment scores - Study BLI850-302

Score	Grad	Description
1	**Poor**	**Large amounts of fecal residue, additional cleansing required**
2	**Fair**	**Enough feces or fluid to prevent a completely reliable exam**
3	**Good**	**Small amounts of feces or fluid not interfering with exam**
4	**Excellent**	**No more than small bits of adherent feces/fluid**

For the primary efficacy analysis, grades 3 and 4 were considered "successful" and grades 1 and 2 were considered "failures". Each examination was also rated as to whether or not cleansing was adequate for examination and the need for re-preparation.
Secondary efficacy endpoints included the following:

- Adequacy of cleaning (cleaning adequate for evaluation) and need for re-preparation;
- Number of excellent preparations as graded by the blinded colonoscopist;
- Number of examinations in which the colonoscopist reached the cecum.

3.1.2.2 Statistical Methods

The primary efficacy analysis was based upon a modified intent-to-treat (mITT) analysis and included all patients randomized that took any portion of study preparation. Patients that did not undergo colonoscopy because of inadequate preparation or preparation related adverse events were considered failures for the primary efficacy endpoint. However, patients that took study preparation but withdrew prior to colonoscopy for reasons unrelated to safety or efficacy were excluded from efficacy analyses.

The applicant indicated that success rate for the primary endpoint was analyzed using CMH Chi-square adjusting for the effect of investigator site. The formal hypothesis test result (p-value) for treatment difference is presented together with a two-sided 95% confidence interval for the difference. A lower CI bound greater than -15% would, according to the sponsor, establish non-inferiority between BLI850 and MoviPrep for a non-inferiority margin of 15%.

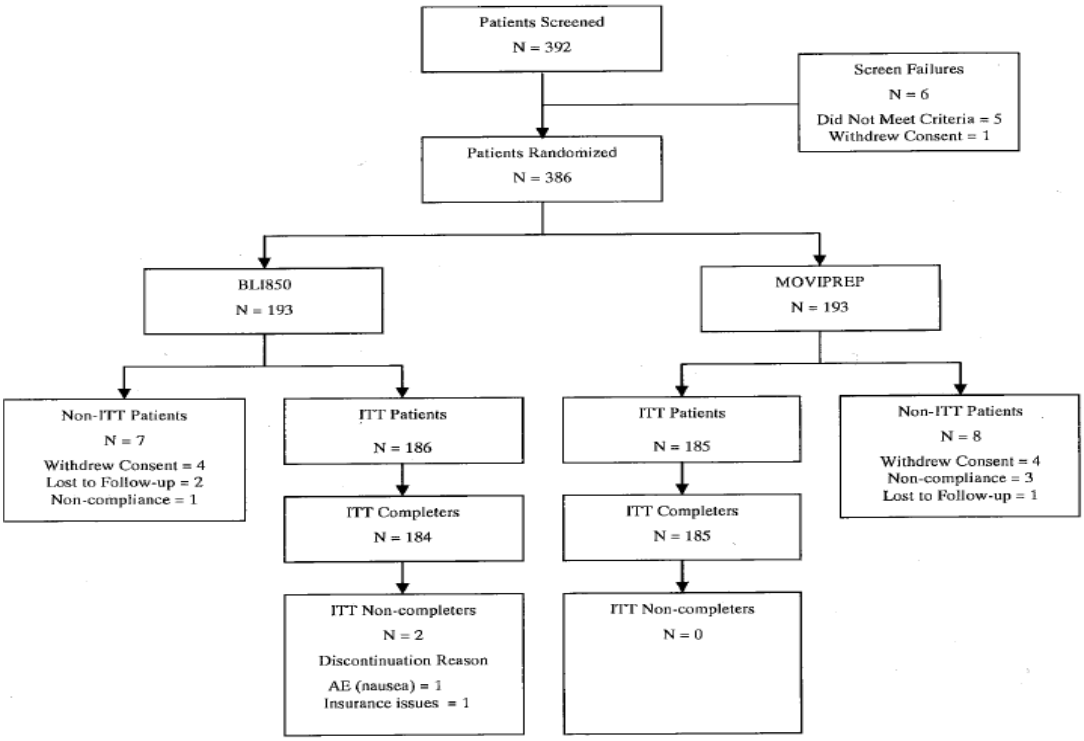
Secondary endpoints were analyzed in a manner similar to the primary analysis using CMH Chi-Square adjusting for any site effects for counts (percentage) of responses and two-way ANOVA with terms for treatment, site, and their interaction for mean responses. No adjustment was made for multiplicity testing of secondary endpoints. Results are presented for the effect results (p-values) and two-sided 95% confidence intervals for the-treatment difference. The primary efficacy analysis and selected secondary efficacy analyses were descriptively summarized by gender, race and age group (< 65, ≥ 65 and < 75, ≥ 75 years of age). These selected subgroup analyses were also tested to identify any significant treatment group differences.
In addition, symptom questionnaire data for patient reported individual symptoms for Overall Experience (nausea, stomach cramping, stomach bloating and overall discomfort) were tested using ANOVA with terms for treatment, site, and their interaction.

For the sample size determination, the applicant indicated that the protocol planned study size was three hundred sixty (360) patients. Patients were randomly assigned to one of the two preparations in a ratio of 1:1 (180 patients per group). A dropout rate of approximately 5% per treatment group was expected. The efficacy of MoviPrep administered as a two-day preparation has been previously reported as 89%. Assuming a success rate for BLI850 of $\geq 85\%$ based on results of a similar sulfate based 2-day preparation, a two-sided 95% confidence interval (asymptotic Pearson Chi-square method) for the between group success rates (BLI850 - MoviPrep) will result in a lower CI bound greater than -15%.

3.1.2.3 Patient Disposition

This study was conducted at 12 centers. 392 patients were screened and 386 were randomized and dispensed study medication. 371 patients took the study preparation and were included in the Intent-to-Treat (ITT) analysis, including 91 elderly. Non-ITT patients included 8 patients that withdrew consent prior to receiving study medication, 4 that were withdrawn due to non-compliance, and 3 patients that were lost to follow-up. All Non-ITT patients were confirmed to have not taken study medication. Figure 3.1.2.3.1 displayed the diagram for the patient disposition.

Figure 3.1.2.3.1 (Applicant's) Diagram for Patient Disposition- Study BLI850-302



In addition, the reasons for discontinuation in the ITT group are given below in Table 3.1.2.3.1.

Table 3.1.2.3.1 (Applicant's) Reasons for Patient Discontinuation using Intent-to-Treat Population - Study BLI850-302

	BLI850 n (%)	MoviPrep n (%)
Total ITT Patients	186 (100%)	185(100%)
Completing Patients	184 (98.9%)	185 (100%)
Patients Discontinued	2(1.1%)	0
Reasons for discontinuation:		
Adverse event (nausea)	1 (50%)	
Lack of insurance coverage	1 (50%)	

Based upon Table 3.1.2.3.1, the applicant indicated that 369 patients of the 371 patients that received their study preparation fully completed the study (defined as patients that had a colonoscopy). Two patients (numbers 25063 and 26002) took their assigned preparation but were withdrawn prior to colonoscopy. Patient 25063 (BU850) experienced moderate nausea and decided to discontinue the preparation and withdraw from the study. The nausea had resolved when the patient returned for Visit 2 the following day. Patient 26002 (BLI850) completed the preparation but withdrew from the study after learning that the colonoscopy would not be covered by her insurance. This patient did not experience any adverse events.

The applicant further indicated the primary efficacy analysis was based on 370 patients. All patients enrolled that took the study preparation and underwent colonoscopy (n=369) were included. Patient 25063 was also included in the primary efficacy responder analyses as a failure because she did not undergo colonoscopy due to a concurrent adverse event (nausea). Patient 26002 completed the preparation but was not included in any efficacy analyses because she withdrew due to insurance issues, not because of safety or efficacy.

3.1.2.4 Demographic and other Baseline Characteristics

The applicant indicated that the overall study population was gender balanced (52% female, 48% male). However a difference was detected in the gender distribution between treatment groups, with BLI850 group comprised of significantly more male patients (54%) than MoviPrep (42%, P = 0.017). In addition, the treatment groups were similar with respect to age, racial distribution and baseline weight. The average age of study participants was about 56 years, ranging from 21 to 86 years of age.

There were 91 ITT patients age 65 or older (42 BLI850, 49 MoviPrep), and 23 patients 75 years of age or older (13 BLI850, 10 MoviPrep). About 86% of ITT patients were White and 6% were African American. Study patients weighed an average of about 186 lbs. With the exception of gender, no demographic related statistically significant differences were noted between the treatment groups. The study population demographics are summarized in Table 3.1.2.4.1.

Table 3.1.2.4.1 (Applicant's) Study Demographics using ITT Population - Study BLI850-302

	BLI850	MoviPrep	p[1]
Age (years)[2]			
n	186	185	0.903
Mean (SD)	56.9 (11.4)	56.8 (11.0)	
Gender			
Female	85 (46%)	108 (58%)	**0.017**
Male	101 (54%)	77 (42%)	
Race[3]			
White	160 (86%)	159 (86%)	0.582
A. Am.	9 (5%)	13 (7%)	
Other	6 (3%)	5 (3%)	
Ethnicity			
Hispanic	11 (6%)	8 (4%)	0.639
Non Hispanic	175 (94%)	177 (96%)	
Weight (lbs)			
Mean (SD)	188 (44)	183 (46)	0.229

(1) P-value from exact Chi-Square test for the categorical variables and from an ANOV A with term for treatment for the continuous variables
(2) Age is calculated using of date of birth and screening visit (Visit 1) date.
(3) Percentage for race does not equal 100% since Hispanic or Latino patients may not have reported a race.
SD = standard deviation; A. Am. = African American

3.1.2.5 Applicant's Efficacy Analysis Results and Conclusions

Primary endpoint analysis

The applicant indicated that the examining physician rated each colonoscopy for cleansing according to a four point scale where a score of 1= "poor", 2= "fair", 3="good", and 4= "excellent" as described above in Section 3.1.2.1. Cleansing scores for the BLI850 and MoviPrep bowel preparations are shown in Table 3.1.2.5.1.

Table 3.1.2.5.1 (Applicant's) Preparation Cleansing Score - Study BLI850-302

Score	**BLI850** n (%)	**MoviPrep** n (%)	**p**[1,2]
4 Excellent	96 (51.9%)	95 (51.4%)	0.986
3 Good	77 (41.6%)	78 (42.2%)	
2 Fair	10 (5.4%)	10 (5.4%)	
1 Poor	1 (0.5%)	2 (1.1%)	
Missing	1 (0.5%)	0	
Mean Score[3]	3.46	3.44	0.779

1) P-value comparing excellent preps is from a CMH, controlling for site;
2) P-value for mean score is from a one-way ANDVA with term for treatment;
3) Patient 26002 was excluded as non-evaluable for efficacy analysis. Patient 25063 is included as "missing".

Based upon Table 3.1.2.5.1, the applicant indicated that all 370 patients included by this table had a colonoscopy or withdrew due to safety or non-compliance. No difference was seen between BLI850 and MoviPrep in the number of "Excellent" preparations or average cleansing score.
The applicant further indicated that as might be expected from the cleansing score results, analysis of the number of "successful" preparations (the primary efficacy variable), where a colonoscopy cleansing score of 3 or 4 was considered as "successful" and scores of 1 or 2 was considered as "failures", showed no difference between the two preparations.

Table 3.1.2.5.2 presented the results of bowel cleansing comparisons between BLI850 and MoviPrep.

Table 3.1.2.5.2 (Applicant's) Analysis on the percent of successful endoscopy exam - Study BLI850-302

Responder[1]	BLI850 n (%)	MoviPrep n (%)	95% CI[2]	p[3]	p[4]
All Patients[5]	186	185			
Success	173 (93.5%)	173 (93.5%)	-5.0, 5.0	0.947	**<0.001**
Fail	12 (6.5%)	12 (6.5%)			
Elderly (≥65 y)	42	49			
Success	39 (92.9%)	42 (85.7%)	-5.4, 19.7	0.318	-
Fail	3 (7.1%)	7 (14.3%)			
Males	101	77			
Success	95 (94.1%)	73 (94.8%)	-7.5, 6.0	0.780	-
Fail	6 (5.9%)	4 (5.2%)			
Females	84	108			
Success	78 (92.9%)	100 (92.6%)	-7.1, 7.7	0.987	-
Fail	6 (7.1%)	8 (7.4%)			

(1) A successful treatment is defined as bowel cleansing graded either excellent or good by the blinded colonoscopist (grading score = 3 or 4).
(2) Confidence interval (CI) for the difference between treatments was by Chi-Square Test.
(3) P-value for the difference between treatments is from a CMH, controllng for site.
(4) P-value for the non-inferiority hypothesis using an equivalence margin of 15 percent
(5) Patient 26002 was excluded as non-evaluable for efficacy analysis.

Based upon Table 3.1.2.5.2, the applicant indicated that this table includes the 370 patients that underwent colonoscopy as well as the patient that was counted as a failure due to a concurrent adverse event (25063).

BLI850 patients had an identical percentage of successful preparations compared to MoviPrep patients (93.5%). The sponsor's non-inferiority testing showed that the lower confidence bound of -5% was greaster than -15% thus supporting the hypothesis that split dose preparation with BLI850 is non-inferior to MoviPrep.

The applicant further indicated that a sensitivity analysis of the primary endpoint using a true ITT population (all randomized subjects) confirms the previous conclusion that BLI850 is non-inferior to MoviPrep, with 89.6% of ITT patients in both groups having a successful preparation.

Secondary efficacy endpoint analysis

The analysis results on the secondary endpoints "adequacy of cleansing" and "cecum reached" are presented in Table 3.1.2.5.4.

Table 3.1.2.5.4 (Applicant's) Number and Percent of Adequate Preparations - Study BLI850-302

	BLI850 n (%)	MoviPrep n (%)	95% CI[1]	P
Adequate?[2] (n)	184	185		
Yes	181 (98%)	180 (97%)	-1.9, 4.0	0.724
No	3 (2%)	5 (3%)		
Cecum reached?[2] (n)	181	182		
Yes	181 (100%)	182 (100%)	-	-
No	0 (0%)	0 (0%)		

(1) Confidence interval (CI) and p-value for the difference between treatments was by Chi-Square Test.
(2) Patients 25063 and 26002 are not included because they did not undergo colonoscopy.

Based upon Table 3.1.2.5.4, the applicant indicated that most preparations for either treatment were considered to be adequate. In addition, in nearly all procedures for either preparation, examining physicians were able to reach the cecum.

The proportions of excellent preparations are shown in table 3.1.2.5.1.

3.1.2.6 Reviewer's Comments and Analysis

In order to validate the applicant's (b) (4) this reviewer first comments on the following three issues: 1) non-inferiority margin of 15%, 2) assessments of colon cleansing quality, and 3) primary efficacy analysis by center. Then, this reviewer performs the efficacy analysis on BLI850.

However, the comments on the issues of the non-inferiority margin of 15% and the assessments of colon cleansing quality for this study (Study PLI850-302) are the same as that for Study BLI850-301. Please refer these two comments to Section. 3.1.1.6.

Reviewer's Comments on the primary efficacy analysis by center

The 12 study centers analyzed individually by the applicant for the primary efficacy variable are shown below in Table 3.1.2.6.1.

Table 3.1.2.6.1 (Applicant's) Analysis on the percent of successful endoscopy exam by site – Study BLI850-302

Site	Score[2]	BLI850 n (%)	MoviPrep n (%)	95% CI[3]	p[3]
21	Success Fail	13 (100%) 0	12 (100%) 0	-	-
22	Success Fail	20 (83%) 4 (17%)	23 (92%) 2 (8%)	-27.0, 9.6	0.417
23	Success Fail	29 (97%) 1 (3%)	28 (97%) 1 (3%)	-9.1, 9.4	1.000
24	Success Fail	13 (100%) 0	12 (100%) 0	-	-
25	Success Fail	30 (97%) 1 (3%)	28 (85%) 5 (15%)	-1.8, 25.6	0.198
26	Success Fail	3 (75%) 1 (25%)	6 (100%) 0	-67.4, 17.4	0.400
27	Success Fail	13 (93%) 1 (7%)	11 (79%) 3 (21%)	-11.1, 39.7	0.596
28	Success Fail	15 (100%) 0	13 (100%) 0	-	-
29	Success Fail	9 (90%) 1 (10%)	9 (90%) 1 (10%)	-26.3, 26.3	1.000
30	Success Fail	12 (92%) 1 (8%)	14 (100%) 0	-22.2, 6.8	0.481
31	Success Fail	14 (93%) 1 (7%)	15 (100%) 0	-19.3, 6.0	1.000
32	Success Fail	2 (67%) 1 (33%)	2 (100%) 0	-86.7, 20.0	1.000

(1) Patient 25063 is included as a failures in this table. Patient 26002 is not included.
(2) A success ful preparation was defined as as colonoscopy cleansing score of 3 or 4.
(3) Confidence interval and P-value for the difference between BLI850 and MoviPrep are from a Chi Square test.

Table 3.1.2.6.1 indicates that of the twelve centers, only five centers (22, 26, 30, 31, and 32) for the (b) (4) group show numerically lower proportions of patients judged success in gut cleansing than MoviPrep. However, no center is found in the BLI850 group to have abnormally large proportion of patients judged success in gut cleansing to dominate the non-inferiority of BLI850 to MoviPrep.

Reviewer's Efficacy Analysis of BLI850

Similar to Study BLI850-301, (b) (4) To support the contention that the test drug (b) (4) has efficacy superior to placebo, in this sub-section, this reviewer computed the two-sided 95% confidence interval on the success rates of (b) (4) . Since the definition of the per-protocol population was not given in the study report and no variable for the per-protocol population was provided in the original data set submitted by the applicant, the two-sided 95% confidence interval on the success rate of BLI850 is calculated by ITT population. Table 3.1.2.6.2 presents the result.

Table 3.1.2.6.2 (Reviewer's) 95% two-sided confidence intervals on P_{PLI850} - Study BLI850-302

	BLI850		95% Confidence Interval on
Patient Population	No. Success	Success Rate (n/N)	P_{PLI850}
Intent-to-Treat Population	173	0.940 (173/185)	(0.890, 0.970)

Table 3.1.2.6.2 shows the lower bounds for the two-sided 95% confidence interval on the success rate of bowel cleansing quality is 0.890 using ITT patient population. Since the assessments on the bowel preparations could potentially be biased in favor of the test drug BLI850, the lower bound of the 95% two-sided interval for BLI850 calculated using the data from a double-blind study may be expected to be smaller than 0.89. From a statistical perspective, BLI850 can be considered effective if the lower bound of the CIs in the table exceed any expectation for a placebo response rate. Since the NI margin of 15% was not acceptable, this does not preclude a more general conclusion based on descriptive statistics that the two products performed similarly.

3.2 Evaluation of Safety

3.2.1 Study BLI850-301

For the safety assessments, the applicant indicated that 394 patients were randomized and 366 were prepared for colonoscopy with either the approved HalfLytely or BLI850. Gastrointestinal complaints represented the majority of adverse events. Most of these reports were mild to moderate in intensity and quickly resolved. No difference was seen in the frequency of adverse event reports between preparation groups in the overall population or any of the demographic or high-risk subgroup.

Patient symptoms reported following completion of the preparation showed that there was a slightly higher intensity in overall discomfort score in the BLI850 group (2.06) than in the HalfLytely-treated group (1.76) on a scale of 1 to 5 (p= 0.032). Analysis of the elderly population revealed slightly higher nausea and overall discomfort scores in the BLI850 group (1.61 vs. 1.27 with p = 0.005 and 2.07 vs. 1.58 with p = 0.012, respectively).

Finally, the applicant concluded that no difference was seen between groups for the other preparation related symptoms (bloating and cramping). These differences were not considered clinically significant; symptom averages were between "None" and "Mild". These averages were consistent with symptom reports from previous studies of approved preparations and may be due to the somewhat larger required volume for BLI850 preparation. There were no on-study deaths and no serious adverse events reported during the study.

3.2.2 Study BLI850-302

For the safety assessments, the applicant indicated that 386 patients were randomized and 371 were prepared for colonoscopy with either the approved MoviPrep or BLI850. There were slight differences between preparations with respect to patient reported symptoms. BLI850 patients reported a slightly higher frequency of vomiting compared to MoviPrep patients (p=0.042).

In addition, when analyzed by demographic sub-group, MoviPrep patients reported a higher frequency of abdominal pain (high-risk patients, p = 0.041) and bloating (females, p = 0.015). In the general population, MoviPrep patients also reported a higher intensity of bloating symptoms (p = 0.025). Average symptom scores for all symptoms fell in the range between "None" and "Mild" and the statistically significant differences do not appear to be clinically important.

Finally, the applicant concluded that there were no on-study deaths. One BLI850 patient was hospitalized post-colonoscopy with abdominal pain, secondary to a possible infection. The patient's symptoms resolved within days of treatment. The investigator concluded this SAE was unrelated to the BLI850 preparation.

4.0 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 GENDER, RACE, AND AGE

In order to assess the consistency of the treatment effect of (b) (4) versus HalfLytely/MoviPrep across subgroups, this reviewer performed the subgroup analyses for the primary endpoint (percentage of patients achieving successful bowel preparation “Good or Excellent” with score of 3 or 4) using ITT patient population. It is noted that the percentages of Non-White patients are 21.5% and less than 15%, respectively for Studies BLI850-301 and BLI850-302. Accordingly, the analyses on the successful rates of bowel preparations are performed only for Gender (Male and Female) and Age group (age ≤ 65 and age > 65).

4.1.1 Study BLI850-301

i) Gender

Table 4.1.1.1 presents the results of treatment efficacy comparisons for BLI850 versus HalfLytely by gender.

Table 4.1.1.1 (Reviewer's) Results by Gender analysis using the ITT population – Study BLI850-301

Female

	BLI850 (B) % (n/m)	HalfLytely (H) % (n/m)	Difference ($P_B - P_H$) %	95% CI
Primary Endpoint[a]	92.0% (89/97)	88.0% (91/104)	4.0%	(-4.5%, 13.1%)

Male

	BLI850 (B) % (n/m)	HalfLytely (H) % (n/m)	Difference ($P_B - P_H$)	95% CI
Primary Endpoint	88.0% (69/78)	80.0% (66/83)	8.0%	(-2.6%, 20.5%)

[a]: percentage of patients achieving successful bowel preparation "Good or Excellent" with score of 3 or 4.

Table 4.1.1.1 indicates that the lower limit of the two-sided 95% confidence interval on the proportion difference of the success rate (rate score 3 or 4) of gut cleansing for BLI850 minus HalfLytely are greater than the negative value of the non-inferiority margin (-15%) for both females (-4.5%) and males (-2.60%).

ii) Age group (age ≤ 65 and age > 65)

Table 4.1.1.2 presents the results of treatment efficacy comparisons for BLI850 versus HalfLytely by age group.

Table 4.1.1.2 (Reviewer's) Results by Age group analysis using ITT population – Study BLI850-301

Age > 65

	BLI850 (B) % (n/m)	HalfLytely (H) % (n/m)	Difference ($P_B - P_H$) %	95% CI
Primary Endpoint[a]	87.0% (40/46)	86.0% (38/44)	1.0%	(-14.0%, 15.7%)

Age ≤ 65

	BLI850 (B) % (n/m)	HalfLytely (H) % (n/m)	Difference ($P_B - P_H$) %	95% CI
Primary Endpoint	91.0% (118/129)	83.0% (119/143)	8.0%	(-0.3%, 16.0%)

[a]: percentage of patients achieving successful bowel preparation "Good or Excellent" with score of 3 or 4.

Table 4.1.1.2 indicates that the lower limit of the one-sided 97.5% lower confidence interval on the proportion difference of the success rate (rate score 3 or 4) of gut cleansing for BLI850 minus HalfLytely are greater than the negative value of the non-inferiority margin (-15%) for both groups with age greater than 65 (-14.0%) and with age less than or equal to 65 (-0.3%).

4.1.2 Study BLI850-302

i) Gender

Table 4.1.2.1 presents the results of treatment efficacy comparisons for BLI850 versus MoviPrep by gender.

Table 4.1.2.1 (Reviewer's) Results by Gender analysis using ITT population – Study BLI850-302

Female

	BLI850 (B) % (n/m)	MoviPrep (M) % (n/m)	Difference ($P_B - P_H$) %	95% CI
Primary Endpoint	94.0% (78/83)	93.0% (100/108)	1.0%	(-6.8%, 8.9%)

Male

	BLI850 (B) % (n/m)	MoviPrep (M) % (n/m)	Difference ($P_B - P_H$) %	95% CI
Primary Endpoint[a]	94.1% (95/101)	95.0% (73/77)	-0.9%	(-8.0%, 7.4%)

[a]: percentage of patients achieving successful bowel preparation "Good or Excellent" with score of 3 or 4.

Table 4.1.2.1 indicates that the lower limit of the one-sided 97.5% lower confidence interval on the proportion difference of the success rate (rate score 3 or 4) of gut cleansing for BLI850 minus MoviPrep are greater than the negative value of the non-inferiority margin (-15%) for both females (-6.8%) and males (-8.0%).

ii) Age group (age ≤ 65 and age > 65)

Table 4.1.2.2 presents the results of treatment efficacy comparisons for moviprep versus Nap by age group.

Table 4.1.2.2 (Reviewer's) Results by Age group analysis using ITT population – Study BLI850-302

Age > 65

	BLI850 (B) % (n/m)	MoviPrep (M) % (n/m)	Difference ($P_B - P_H$) %	95% CI
Primary Endpoint[a]	92.0% (34/37)	85.0% (34/40)	7.0%	(-8.8%, 22.7%)

Age ≤ 65

	BLI850 (B) % (n/m)	MoviPrep (M) % (n/m)	Difference ($P_B - P_H$) %	95% CI
Primary Endpoint	95.0% (139/147)	96.0% (139/145)	-1.0%	(-6.8%, 4.0%)

[a]: percentage of patients achieving successful bowel preparation "Good or Excellent" with score of 3 or 4.

Table 4.1.2.2 indicates that the lower limit of the one-sided 97.5% lower confidence interval on the proportion difference of the success rate (rate score 3 or 4) of gut cleansing for BLI850 minus MoviPrep are greater than the negative value of the non-inferiority margin (-15%) for both groups with age greater than 65 (-8.8%) and with age less than or equal to 65 (-6.8%).

4.2 Other Special/Subgroup Populations - Not applicable

5.0 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

In this section, this reviewer first gives the comments on the non-inferiority margin of 15% and the assessments of colon cleansing quality. Then, the comments on the primary efficacy analysis by center and the efficacy assessments for BLI850 separately for each individual study are followed.

Comments on the issue of non-inferiority margin

As noted by this reviewer, the justification for the non-inferiority margin of 15% submitted by the applicant is for the two active control arms (HalfLytely and MoviPrep) employed by the two studies (BLI850-301 and BLI850-302). Accordingly, the comments made below by this reviewer on the issue of the non-inferiority margin are for both studies.

As noted in the ICH E-10 guidance, the non-inferiority margin chosen should be based on the smallest effect size of the active control arm as shown in the historical well-controlled placebo trials conducted under the conditions similar to that of the current trials.
However, none of the three studies (F38-15, F38-20, and F38-26) submitted by the applicant to support the non-inferiority margin of 15% was a historical placebo-controlled study using HalfLytely or MoviPrep as a treated arm. Since all three studies provided by the applicant did

not comply with the ICH E-10 guidance for a non-inferiority margin selection, the justification for the non-inferiority margin of 15% as determined by the applicant is problematic.

We understand that in the bowel cleansing preparation trial, for ethical reason, a placebo controlled study might have never been performed. Success rate for placebo is unknown and may be close to 0% as the applicant stated. However, a margin of 15% has not been justified statistically and has not been considered statistically acceptable as a non-inferiority margin for evaluation of investigational bowel preparation. In addition, recently, a margin of 10% has been employed for approval of INKP-102 (NDA 21-892 submitted on May 17, 2005). Accordingly, from statistical perspective, the non-inferiority margin of 15% selected by the applicant for HalLytely and MoviPrep is questionable and not acceptable.

Finally, no non-inferiority margin was pre-specified for the secondary endpoint "cleansing adequate for evaluation", the results from the secondary endpoints can not be validly assessed. Accordingly, these results are exploratory (b) (4) However, both studies showed that the new treatment BLI850 performed similarly to the active controls. This conclusion is descriptive only and would be more appropriate for labeling.

Comments on the assessments of colon cleansing quality

Based on the applicant's study design, biased assessments on colon cleansing quality may be induced by the following two issues: i) nature of single blinded design and ii) the non-inferiority analysis criterion.

i) Issue on the single blinded design

Since this is a single blinded study, patients knew which drug was used for their bowel preparation. There was possibility for the investigators to be informed of the bowl preparation drug used by patients. Therefore, the single blinded trial had potential to be an open label trial. Furthermore, the ratings of "fair" (enough feces or fluid to prevent a completely reliable exam) and "good" (small amounts of feces or fluid not interfering with exam) in bowel cleansing quality are not completely distinguishable and might be assessed subjectively.

Accordingly, if the investigator realized which drug was used by the patient, the assessment on the successful bowel preparation (scored as "good" by investigators) could be biased in favor of the study drug.

The ICH E10 Guidance for Industry states that for the comparative trial to be informative concerning relative safety and/or efficacy, the trial needs to be fair; i.e., the conditions of the trial should not inappropriately favor one treatment over the other. Accordingly, in order to avoid the potential for biased assessments in this single blinded trial the applicant could have included another lower dose arm 2L-PEC (2 liters of PEG-ELS **-** **o**ne component of HalfLytely) in this trial (as was done for Study F38-15). As noted by this reviewer, 2L-PEC used in Study F38-15 by the applicant was to support HalfLytely as an effective bowel preparation drug by showing

superiority to the 2L-PEC control. However, a decision to include another lower dose arm in the trial should be based on pracitical and eithical considerations and is deferred to Medical Division. However, this reviewer recommends that in future studies, a more objective colon cleansing rating scale should be employed to enhance the quality of colon cleansing assessments.

ii) Issue on the non-inferiority analysis criterion

Based on the non-inferiority analysis criterion, one notes that if the outcomes of the bowel preparations for the two treatment groups, HalfLytely and (b) (4) are similarly scored by the investigators, then non-inferiority for the two drugs would easily be achieved. Due to the ambiguous definitions of grade 2 and grade 3 scoring, the bowel preparation quality might not be assessed objectively. Therefore, with only two arms (b) (4) and HalfLytely in the trial, it may have been likely for the investigator to assign similar scores to the bowel preparations for the two treatment groups and the likelihood of a conclusion of non-inferiority for the two drugs would be increased. However, such a conclusion would be a biased result.

Comments on the primary efficacy analysis by center

For Study BLI850-301, analysis of the primary endpoint by center indicates that no center was found in the BLI850 group to have an abnormally large proportion of patients judged success in gut cleansing. Thus, no center dominates the non-inferiority of BLI850 to HalfLytely.

Similarly, for Study BLI850-302, no center was found in the BLI850 group to have abnormally large proportion of patients judged success in gut cleansing to dominate the non-inferiority of BLI85 to MoviPrep.

Efficacy of BLI850

Finally, for Study BLI850-301, the efficacy analysis on BLI850 shows that lower bound of the two-sided 95% confidence interval on the success rate of bowel cleansing quality is 0.84 using the ITT patient population.

For Study BLI850-302, the lower bound for the two-sided 95% confidence interval on the success rate of bowel cleansing quality is 0.89 using the ITT patient population.

The lower bounds of the two-sided 95% confidence intervals on the proportions of bowel cleansing success for (b) (4) (BLI850) are not less than 84%. This threshold is consistent with values observed in other bowel cleansing agents and can be used by the Medical Division as an aid in assessing the clinical efficacy of (b) (4) for bowel cleansing.

5.2 Conclusions and Recommendations

From the statistical perspective, the applicant's non-inferiority margin of 15% for the two studies was not supportable and formal statistical testing is compromised. This does not preclude a

more general conclusion based on descriptive statistics that the product in each study performed similarly to the active controls.

The two-sided 95% confidence interval for the treatment difference showed that the lower confidence bounds were greater than -15% for both studies (-0.7% for Study BLI850-301 and -5.0% for StudyBLI850-302). However, the reviewer has determined that the NI margin has not been adequately supported (b) (4)

Efficacy analysis for (b) (4) alone shows the lower bounds of the two-sided 95% confidence interval on the proportion of successful bowel cleansings are 84% and 89% for studies BLI850-301 and -302, respectively. Although placebo controlled trials have not been conducted with bowel cleansing preparations, the clinical team should concur that such rates far exceed those possible with placebo.

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/s/

WEN JEN CHEN
10/31/2012

MICHAEL E WELCH
10/31/2012

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:	203595-000
Drug Name:	BLI-850 (oral sulfate solution-polyethylene glycol 3350 electrolyte solution)
Applicant:	Braintree Laboratories, INC.
Date(s):	Submission: 12/19/2011; Consult request: 03/1/2012; PDUFA: 10/19/2012
Review Priority	Standard
Biometrics Division:	Division of Biometrics 7
Statistical Reviewer:	Bradley McEvoy, MS, DrPH
Concurring Reviewers:	LaRee Tracy, MA, PhD, Team Leader Aloka Chakravarty, PhD, Division Director
Medical Division:	Division of Gastroenterology and Inborn Error Products
Clinical Team:	Medical Reviewer: Jessica Lee, MD; Medical Team Lead: Robert Fiorentino, MD
Project Manager:	Matthew Scherer

Keywords: Laboratory parameters, shift analysis, safety analysis, RCTs

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1 EXECUTIVE SUMMARY

The Division of Gastroenterology and Inborn Error Products (DGIEP) consulted the Division of Biometrics VII requesting a statistical safety review for BLI-850 (oral sulfate solution-polyethylene glycol 3350 electrolyte solution). This product is for cleansing of the colon as a preparation for colonoscopy in adults (NDA# 203595). The consult requested a targeted review focusing on changes in chemistry laboratory parameters in both pivotal trials submitted in the NDA. This review is in response to the consult and has a primary focus to assess whether differences between the trial treatments in laboratory parameters exist following administration of trial drug.

The statistical safety review was performed using data from two phase III, assessor-blinded, multi-center, randomized, active-controlled, non-inferiority clinical trials designed to investigate the efficacy, safety and tolerability of BLI-850 compared to a marketed bowel prep. Both trials share a similar trial design differing with respect to the comparator bowel prep and timing of the administration of the bowel preps (i.e., split-dose or day before). Specifically, in trial BLI850-301 (301), BLI-850 was administered as a split-dose (over two days) and compared to HalfLytely (PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution and bisacodyl delayed-release tablets). In trial BLI850-302 (302), BLI-850 was administered the day before the colonoscopy and was compared to MoviPrep (PEG-3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate, and ascorbic acid for oral solution). Both trials were conducted in generally healthy male and female subjects at least 18 years of age undergoing an elective colonoscopy.

In trial 301, 160 of 196 subjects randomized to BLI-850 (81.6%) and 173 of the 198 subjects randomized to HalfLytely (87.3%) were included in at least one of the statistical reviewer's lab analysis. In trial 302, 174 of 193 subjects randomized to BLI-850 (90.2%) and 167 of the 193 subjects randomized to MoviPrep (86.5%) were included in at least one of the lab analyses.

Neither trial was powered nor designed to test safety-related hypotheses concerning specific laboratory parameters. Therefore, results from analyses should not be considered confirmatory. However, given that the submission includes two trials, with similar designs and patient population, it is reasonable to assess for trends only within the BLI-850 group where feasible; comparison of the experimental and comparator effect across studies is problematic as the two studies included different comparator agents.

In trial 301, compared to HalfLytely, BLI-850 had a greater percentage of subjects who switched from normal at baseline to above the normal range on the day of the colonoscopy (visit 2) for calcium (8.6% vs. 3.6%) and total protein (4.5% vs. 0.6%). Based on the comparison of the change in means from baseline to visit 2, the only statistically significant difference between groups was for serum glucose, where the mean increased slightly in the BLI-850 group (104.5 mg/dL to 105.4 mg/dL) and decreased in the HalfLytely group (105.9 mg/dL to 100.4 mg/dL).

In trial 302, compared to MoviPrep, BLI-850 had a statistically significantly greater number of subjects who switched from normal at baseline to above the normal range at visit 2 for total

bilirubin (11.2% vs. 3.7%). Laboratory parameters in which there were a greater non-statistically significant percentage of values above the normal range in the BLI-850 group compared to MoviPrep were albumin (7.3% vs. 3.8%) and ALT (6.2% vs. 3.3%). Statistically significant differences between BLI-850 and MoviPrep in the mean change (day of colonoscopy) from baseline were observed for the following laboratory parameters: bicarbonate, chloride, sodium, total bilirubin, urea (BUN), serum osmolality, and uric acid; however, the mean levels were of similar magnitude at baseline and visit 2 in the BLI-850 group for bicarbonate, chloride, and sodium, suggesting that the difference between groups for these labs was driven by changes in mean levels for MoviPrep.

In conclusion, while both trials revealed that select laboratory parameters measured on the day of the colonoscopy differed between BLI-850 and the respective comparator, there was no consistent or large signal for any specific laboratory parameter associated with the use of BLI-850 between trials. This lack of a consistent signal should be interpreted cautiously as 1) neither trial was powered to show a difference in laboratory parameters, 2) the trials used different comparator agents, and 3) 13-18% of subjects in study 301 and 10-13% of subjects in study 302 that were randomized to a study treatment were excluded from the laboratory analyses. Despite the lack of a marked safety signal, a significant limitation of the two trials is that follow-up did not extend beyond the day of the colonoscopy thus preventing a long-term safety assessment of BLI-850. To fully evaluate the long-term safety of this product, the reviewer recommends a large randomized clinical trial to evaluate safety with follow-up assessments up to 30 days post-treatment.

2 INTRODUCTION

2.1 Overview

On 17 December 2011, Braintree Laboratories, Inc., submitted NDA (203-595) for BLI-850 (oral sulfate solution-polyethylene glycol 3350 electrolyte solution) for cleansing of the colon as a preparation for colonoscopy in adults. On 1 March 2012, the Division of Gastroenterology and Inborn Error Products (DGIEP) consulted the Division of Biometrics VII to provide a targeted statistical safety review of the submission's clinical trial data.

Specific laboratory parameters that were investigated in this review include those related to electrolytes, liver function, and renal function. Of primary interest is the assessment of potential significant changes in laboratory values from baseline overall, in subjects greater than 64 years of age, and those considered high risk.

The statistical review is supported by laboratory data collected in the following two phase 3, randomized clinical trials:

- BLI850-301: "A Safety and Efficacy Evaluation of BLI850 vs. HalfLytely® and Bisacodyl Bowel Prep Kit as Bowel Cleansing Preparations in Adult Subjects."
- BLI850-302: "A Safety and Efficacy Evaluation of BLI850 vs. MoviPrep® as Bowel Cleansing Preparations in Adult Subjects."

For the statistical review of the clinical efficacy data refer to the statistical review by Dr. Wen Jen Chen (DB3/OB).

2.2 Data Sources

Datasets for the two trials are available in the EDR and are located at:
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3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

3.1.1 Data Quality

The datasets submitted were not in CDISC format.

3.1.1.1 Data Quality: Follow-up Assessments

The statistical reviewer identified subject 9057 (HalfLytely group) who had several liver function laboratory values outside the normal range on the day of the colonoscopy. This subject's baseline and visit 2 values are presented in Table 1. *Unlike subjects 30028 and 31027 in trial 302 (see Table 4) that had a blood redraw due to elevated liver function tests at visit 2, subject 9057 did not have a redraw despite having higher liver levels. This case underscores the trial design limitation of not having predefined criteria for a follow-up laboratory assessment in the case of highly abnormal values.*

Table 1. Subject 9057 liver function laboratory values

Laboratory Parameter	Normal Range	Visit 1	Visit 2
Albumin	3.7 - 4.9	4.6	4.4
ALP	40 - 135	73	227
ALT	0 - 47	26	680
AST	0 - 37	17	221
Direct Bilirubin	0 - 0.2	0.1	0.2
Gamma GT	0 - 33	13	243
Total Bilirubin	0 - 1.1	0.3	0.8

3.1.1.2 Unscheduled and Missing Laboratory Assessments

Trial 301

Unscheduled Laboratory Assessments

Among subjects in the safety analysis population, defined as subjects that were randomized to and took any amount of the preparation, 8 had unscheduled laboratory values (subject IDs: 10001, 2004, 5013, 5038, 8007, 8013, 9031, and 9040). Of these subjects, only the redraw for subject 9040 was for the baseline assessment (visit 1—09/25/2008; redraw–10/01/2008); values from the redraw were used (by the sponsor and FDA reviewer) to replace the original values. Subject 2004 received BLI-850 and had a redraw for visit 2 due to reported suspected pre-analytical contamination (visit 2—09/03/2008; redraw—09/05/2008). ***While the sponsor used this subject's redraw values in their analysis, this subject is excluded from the FDA analysis since the redraw did not occur on the day of the colonoscopy (visit 2).***

The six other subjects had an unscheduled laboratory assessment based on the laboratory sample collected at visit 2. The reasons for their redraws are as follows. The sample for subject 10001 was considered invalid due to suspected pre-analytical contaminants. The samples for subjects 8007 and 8013 were reported to be moderately or grossly hemolyzed. Subjects 5013 and 5038 did not get blood drawn at visit 2. Subject 9031 (HalfLytely group) had a redraw due to an abnormal CK value (baseline =88; visit 2 =1381 (09/24/2008); redraw =538 (09/26/2008)). None of the values from the redraw samples were used by the sponsor or by the FDA statistician in the analysis of the laboratory parameters. Subjects with a visit 2 sample that was either contaminated or hemolyzed were excluded from the analysis.

Missing Laboratory Assessments

Of the 176 subjects in the BLI-850 safety population, 16 had missing laboratory values on all laboratory parameters that were investigated in this review. The reason these exclusions are listed below (Table 2).

Table 2. Reason excluded from Chemistry Laboratory analysis for BLI-850 group (Trial 301)

Reason	Frequency
Visit 1 sample moderately or grossly hemolyzed	1
Visit 2 invalid due to suspected pre-analytical contaminants	2
Visit 2 sample moderately or grossly hemolyzed	10
No visit 2 value	2
Unable to take sample at visit 2	1

Of the 190 subjects in the HalfLytely safety population, 22 were excluded from at least one of the laboratory parameters examined. Seventeen (17) of these subjects were excluded from every chemistry laboratory investigation; refer to Table 3 for the reasons for exclusion. The IDs of the five subjects that were included in some but not all laboratory analyses are: 9040 (excluded only from serum osmolality), 3028 (excluded only from CK and serum glucose), 6054 (included only in amylase), 5034 (included only in serum osmolality), and 9031 (included only in serum osmolality).

Table 3. Reason excluded from Chemistry Laboratory analysis for HalfLytely (Trial 301). Table does not include subjects that were not included every laboratory analysis.

Reason	Frequency
Visit 1 sample moderately or grossly hemolyzed	3
Visit 2 sample moderately or grossly hemolyzed	9
No visit 2 value	4
Unable to take sample at visit 2	1

Trial 302

Unscheduled Laboratory Assessments

Among subjects in the safety population for both treatment groups, 10 had an unscheduled chemistry laboratory value (subject IDs: 22011, 22025, 23001, 23004, 23009, 30017, 30028, 31004, 31021, and 31027). Subjects 22025 and 23009 had redraws that replaced their original baseline (visit 1) sample. The redraw for subject 22025 was due to visit 1 being greater than from 30 days from colonoscopy (visit 1—09/09/08; redraw—10/17/08; visit 2—10/20/08). Subject 23009 had invalid visit 1 results due to suspected pre-analytical contaminates (visit 1—09/02/08; redraw—09/04/08); note this subject's visit 2 sample was classified as gross or moderately hemolyzed.

The other 8 subjects had redraws based on findings/results from the sample taken on the day of the colonoscopy. The following subjects had a redraw due to an out of range value on at least one parameters: 30017 (out of range phosphate value), 31021 (out of range creatinine), 31004 (out of range creatinine), 30028 (elevated liver function tests), and 31027 (elevated liver function tests); information on these subjects laboratory measurements are presented in Table 4. Subjects 22011, 23001, and 23004 each had a redraw due to their visit 2 sample being classified as moderately or grossly hemolyzed.

Table 4. Laboratory values for subjects with redraw due to abnormal visit 2 values (Trial 302)

Subject ID	Treatment	Laboratory Parameter	Normal Range	Visit 1	Visit 2 (date)	Redraw (date)
30017	BLI-850				(9/25/08)	(10/9/08)
		Phosphate	2.4-4.9	2.8	1.8	2.9
31021	MoviPrep				(9/30/08)	(10/16/08)
		Creatinine	0.5-1.0	1.1	1.2	1.0
31004	BLI-850				(9/3/08)	(9/17/08)
		Creatinine	0.6-1.4	1.2	2.1	1.2
30028†	BLI-850				(10/3/08)	(10/10/08)
		ALP	40-135	64	160	93
		ALT	0-47	28	327	47
		AST	0-37	27	98	21
		Gamma GT	0-33	21	61	38
31027†	MoviPrep				(9/29/08)	(10/21/08)
		ALT	0-47	116	114	84
		AST	0-37	103	143	60
		Gamma GT	0-33	144	157	78

†-Liver functions tests with visit 2 values outside the normal range are presented

Missing Laboratory Assessments

Of the 186 subjects in the BLI-850 safety population, 174 were included in the analysis of at least one chemistry laboratory parameter. Twelve (12) subjects were excluded from the chemistry laboratory investigation; see Table 5 for the reason these subjects were excluded. Subjects 31008 and 28005 were included in some but not all of the analyses. Subject 31008 was only excluded from the serum osmolality analysis (visit 1 sample insufficient for testing). Subject 28005 was only included in the serum osmolality analysis (no visit 2 values for other labs).

Table 5. Reason excluded from Chemistry Laboratory analysis for BLI-850 (Trial 302). Table does not include subjects that were not included every laboratory analysis.

Reason	Frequency
Visit 1 sample moderately or grossly hemolyzed	2
Visit 2 sample moderately or grossly hemolyzed	9
No visit 2 value	1

Of the 185 subjects in the MoviPrep safety population, 167 were included in the analysis of one laboratory parameter. The reason 18 subjects were excluded from the chemistry are tabulated Table 6. Subjects 25016, 25036, 30020, and 30027 were included in some but not all of the analyses. Subject 25036 was only included in the serum osmolality analysis (no visit 2 values reported). Subject 25016 was only included in the amalyze and serum osmolality analysis (other visit 2 labs invalid due to hemolysis). Subject 30020 was only excluded from the CK and Serum glucose analysis (other visit 2 samples invalid due to hemolysis). Subject 30027 was only excluded from the serum glucose analysis (visit 1 sample moderately or grossly hemolyzed).

Reviewer Comment: Although the amount of missing laboratory assessments in both studies was moderate (~10%), the statistical reviewer did not consider it necessary to either perform sensitivity analyses that investigated the impact of missing data or apply missing data techniques since the missing data were primarily due to the quality of the laboratory sample.

Table 6. Reason excluded from Chemistry Laboratory analysis for MoviPrep (Trial 302). Table does not include subjects that were not included every laboratory analysis.

Reason	Frequency
Visit 1 sample moderately or grossly hemolyzed	2
Visit 2 sample moderately or grossly hemolyzed	14
No visit 2 value	2

3.2 Evaluation of Efficacy

This review does not include an assessment of efficacy.

3.3 Evaluation of Safety

3.3.1 Design and Endpoints

Trial Design

Studies BLI850-301 (301) and BLI850-302 (302) are Phase III, randomized, assessor-blinded, parallel, active-controlled non-inferiority trials designed to investigate the safety and efficacy of

BLI-850 for cleansing the colon as a preparation for colonoscopy in adult patients. Both studies shared similar designs, but differed in comparator prep and timing of administration; other minor differences existed and are noted below.

In both studies subjects who were undergoing colonoscopy for routinely accepted indications were screened for trial inclusion at visit 1. In Trial 301, subjects that satisfied the entry criteria were randomized using a 1:1 randomization to one of the following treatment arms:

- BLI-850: Each subject will receive a 6 ounce bottle containing an oral sulfate solution (OSS) and a 2.5L polyethylene bottle containing PEG and electrolytes. At approximately 6:00pm the day before the colonoscopy, patients will drink 6 ounces of OSS diluted with 16 ounces of water. After completing the OSS, patients must drink a 16 ounce glass of water over the next two hours. At approximately 6:00am on the morning of the colonoscopy patients will start to drink 2L PEG and electrolyte solution at a rate of 16 ounce glass every 20 minutes until complete.
- HalfLytely and bisacodyl tablet (PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution and bisacodyl delayed-release tablets): Between approximately 12:00 and 3:00pm on the day before the colonoscopy subjects were instructed to take two 5mg bisacodyl tablets with water. Following a bowel movement (or maximum of 6 hours after taking the two bisacodyl tablets) patients were to drink 2L of HalfLytely solution at a rate of 8 ounces every 10 minutes.

In Trial 302, subjects that satisfied the entry criteria were randomized using a 1:1 randomization to one of the following treatment arms:

- BLI-850: Each subject will receive a 6 ounce bottle containing an OSS and a 2.5L polyethylene bottle containing PEG and electrolytes. At approximately 6:00pm the day before the colonoscopy, patients will drink 6 ounces of OSS diluted with 16 ounces of water. After completing the OSS, patients must drink a 16 ounce glass of water over the next two hours. Two hours after beginning the OSS dose of BLI850 preparation, patients will start to drink 2L PEG and electrolyte solution at a rate of 16 ounce glass every 20 minutes until complete.
- MoviPrep (PEG-3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate, and ascorbic acid for oral solution): Subjects will be instructed to follow the evening-morning regimen (i.e., split-dose). At approximately 6:00pm the day before the colonoscopy, patients will take the first liter of MoviPrep solution (one 8 ounce glass every 15 minutes) and then drink 16 ounces of clear liquid. At approximately 6:00am on the morning of the colonoscopy, patients will take the second liter of MoviPrep solution over one hour and then drink 16 ounces of clear liquid at least one hour prior to the start of the colonoscopy.

Subjects were instructed not to discuss their treatment assignment with any staff member. A subject was considered to have completed the trial if they took the randomized treatment and received a colonoscopy (regardless of whether or not the colonoscopy was completed).

Subjects at least 18 years of age undergoing colonoscopy for a routinely accepted indication that were in otherwise good-health were included subject to the Investigator's judgment. Females of

child-bearing potential had to use an acceptable form of birth control and have a negative urine pregnancy test to participate.

In trial 301, subjects were excluded if they were undergoing a colonoscopy for foreign body removal or decompression, if they had known or suspected ileus, severe ulcerative colitis, gastrointestinal obstruction, gastric retention, bowel perforation, toxic colitis, megacolon, significant gastrointestinal surgery, deficiency, allergic to any preparation components, pregnant or planning to become pregnant, child-bearing potential that refused pregnancy test, recent participation in an investigational trial, clinically significant electrolyte abnormalities at visit 1, or impaired consciousness that predisposes them to pulmonary aspirations. The clinically significant electrolyte abnormalities is determined by the opinion of the Investigator and there is not formal standard across sites (e.g., potassium > 3 upper limit of normal).

Trial 302 also excluded subjects with phenylketonuria or who were glucose-6-phospate dehydrogenase deficient.

At visit 1 each subject provided their medical history, had a physical examination and collected vital signs, and had blood samples collected for serum chemistry and hematology testing. At visit 2 bloods samples were also collected. Testing was performed at ICON Central Laboratories.

Adverse event (AE) collection began when the subject provided informed consent to participate in the trial and concluded at the completion of visit 2. Telephone follow-up was performed for ongoing AEs at visit 2 that were deemed possibly, probably or definitely related to the trial preparation. The telephone follow-up was to occur 2 weeks after visit 2. Subjects with clinically significant laboratory results at visit 2 which were classified by the Investigator as an AE were to return approximately 2 weeks later for a redraw.

Reviewer Comment: It is not possible to infer the safety of BLI-850 (based on AEs or laboratory abnormalities) from the two trials being reviewed beyond the day of the colonoscopy. The inability to establish long-term safety of BLI-850 is a considerable limitation of both trials given the potential long-term safety associated with bowel preps. Further, not having predefined criteria to identify clinically significant laboratory parameters at visit 2 is another trial design limitation that might introduce biases associated with Investigator judgment in reporting events.

Trial Endpoints

Laboratory analyses are performed on the laboratory analysis set, defined as subjects that received at least one dose of trial medication and there were available laboratory measurements for that subject collected at both baseline and visit 2. Treatment assignment is based on treatment received. Note that inclusion into the laboratory analysis set includes subjects that had laboratory values for some but not all of the laboratory parameters investigated in this review. **Importantly, for trial 301, the laboratory analysis set used by the statistical reviewer to analyze the laboratory data differs from the analysis set used by sponsor. The sponsor includes subject 2004 whereas this review excludes this subject. This subject was excluded since the blood redraw following a contaminated visit 2 sample was performed after the day of the colonoscopy**.

The number and reasons for missing laboratory parameters were discussed for both studies in Section 3.1.

The 22 chemistry laboratory parameters and 4 derived parameters were grouped by the statistical reviewer per direction of the medical officer into one of the following groups based on functionality: electrolyte, liver function, renal function, and other. The labs that comprise each group are listed below.

- Electrolyte laboratory parameters: bicarbonate, calcium, chloride, magnesium, phosphate, potassium, sodium, serum glucose and anion gap.
- Liver function laboratory parameters: albumin, ALP, ALT, AST, gamma GT, total protein, total bilirubin, and direct bilirubin.
- Renal function laboratory parameters: urea (BUN), creatinine, estimated glomerular filtration rate (eGFR, calculated by 3 separate formulas per request of the medical officer: Cockcroft-Gault (CG), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), and Modification of Diet in Renal Disease (MDRD)).
- Other laboratory parameters: amylase, CK, serum osmolality, and uric acid.

Formulas used to calculate anion gap and eGFR are given in Section 6.1. Per communication with the medical officer, the eGFR calculated using the MDRD and CKD-EPI formulas are preferred over CG. Although the CG formula is the most commonly used approach to calculate eGFR, having body weight in the numerator of the formula may be problematic as a decrease in eGFR can result from a loss of weight associated with the cleansing of the colon.

3.3.2 Statistical Methodologies

To evaluate whether differences in laboratory parameters exist between treatment arms after administration of the trial treatment, the following analyses were conducted by the sponsor and redone by the statistical reviewer in this review using laboratory values collected at visit 2 (day of colonoscopy):

- *Shift analysis*: Compare the incidence of laboratory values outside the normal range among subjects that were normal at baseline. For comparative purposes, risk differences (RD) for BLI-850 compared to the control arm (HalfLytely or MoviPrep) and 95% confidence intervals (CI) are included. Refer to Table 26 (in Section 6.1) for normal range reference values.
- *Mean Analysis:*
    - Calculated mean laboratory value and 95% CI.
    - Calculated the difference in mean change (DMC) from baseline for BLI-850 compared to the control arm and 95% CI.

Note that the mean analysis was not limited to the subset of subjects with baseline laboratory values that are within the normal range.

3.3.3 Patient Disposition, Demographics & Baseline Characteristics

Table 7 summarizes patient disposition and laboratory samples for subjects in the two studies. In trial 301, 196 and 198 subjects were randomized to BLI-850 and HalfLytely, respectively. Among these subjects, 20 (10.2%) randomized to BLI-850 and 8 (4.0%) of the 198 randomized to HalfLytely were excluded from the all randomized set. Of the 176 subjects and 190 subjects in

the BLI-850 and HalfyLytely that were randomized and took any amount of the preparation, defined as the safety population by the sponsor, 160 subjects in the BLI-850 group and 173 in the HalfLytely group were included in the statistical reviewer's laboratory analysis set. As stated previously, the sponsor's laboratory analysis population differs from the statistical reviewer's population as it includes the redraw value for subject 2004 that was not performed on the day of the colonoscopy.

In study 301, 6 subjects (all in the BLI-850 group) were removed from the all randomized analysis set due to not meeting study criteria. The reasons provided for why these subjects were excluded are: clinically significant electrolyte abnormalities at visit 1 (subjects 2018 and 2048); investigator discretion: clinically significant liver function values (subject 9025), subject was coordinator actively involved in the study (11005), and unable to draw laboratory sample (subject 3002); and previous significant gastrointestinal surgery (8023).

Reviewer Comment: In study 301, subjects knew treatment assignment (investigator blinded to treatment). Therefore, there is a possibility that the consent withdrawals for which there were more of in the BLI-850 group (7% vs. 4%), could be related to the subject knowing treatment received, thus potentially resulting in a biased analysis population

In trial 302, 193 subjects were randomized to each of the two treatment groups of which 7 (3.6%) were excluded from the BLI-850 group (4 withdrew consent prior to receiving study treatment, 2 lost to follow-up, 1 non-compliance) and 8 (4.1%) were excluded in the MoviPrep group (4 withdrew consent prior to receiving study treatment, 3 non-compliance, 1 lost to follow-up). Of the 186 subjects and 185 subjects in the BLI-850 and MoviPrep groups respectively that were included in the safety analysis population, 174 subjects in the BLI-850 group and 167 in the HalfLytely group were included in the statistical reviewer's laboratory analysis set.

Table 7. Laboratory assessments and patient disposition by study

	Trial 301		Trial 302	
	BLI-850 n (%=n/196)	**HalfLytely n (%=n/198)**	**BLI-850 n (%=n/193)**	**MoviPrep n (%=n/193)**
All randomized	196	198	193	193
*Withdrew consent**	*14 (7)*	*8 (4)*	*4 (2)*	*4 (2)*
*Did not meet criteria**	*6 (3)*	*0 (0)*	*0 (0)*	*0 (0)*
*Lost to follow-up**	*0 (0)*	*0 (0)*	*2 (1)*	*1 (1)*
*Non-compliance**	*0 (0)*	*0 (0)*	*1 (1)*	*3 (2)*
Safety population†	176 *(90)*	190 *(96)*	186 *(96)*	185 *(96)*
Missing laboratory assessment: all labs	16 *(8)*	17 *(9)*	12 *(6)*	18 *(9)*
Visit 1 or visit 2 sample hemolyzed	*11 (6)*	*12 (6)*	*11 (6)*	*16 (8)*
Visit 1 or visit 2 sample contaminated	*2 (1)*	*0 (0)*	*0 (0)*	*0 (0)*
No visit 2 value	*2 (1)*	*4 (2)*	*1 (1)*	*2 (1)*
Unable to take sample at visit 2	*1 (1)*	*1 (1)*	*0 (0)*	*0 (0)*
Missing laboratory assessment: at least 1 lab	0 *(0)*	5 *(3)*	2 *(1)*	4 *(2)*
Laboratory redraw	4 *(2)*	4 *(2)*	4 *(2)*	6 *(3)*
Related to visit 1 sample	*0 (0)*	*1 (1)*	*0 (0)*	*2 (1)*
Related to visit 2 sample	*4 (2)*	*3 (2)*	*4 (2)*	*4 (2)*
Included in at least one lab analysis				
Sponsor's laboratory analysis set	161 *(82)*‡	173 *(87)*	174 *(90)*	167 *(87)*
FDA laboratory analysis set	160 *(82)*	173 *(87)*	174 *(90)*	167 *(87)*

* Subjects did not reportedly take any amount of study treatment; †Randomized and received treatment; ‡ Includes subject 2004 with visit 2 redraw that was not performed on the day of the colonoscopy.

Table 8 displays the baseline characteristics by trial and treatment group of subjects included in at least one laboratory analyses in the statistical reviewer's laboratory analysis set. In Trial 302 not all baseline characteristics were balanced between treatment groups. Specifically, the BLI-850 group had statistically significantly more males (56%) compared to the MoviPrep group (42%); this statistically significant imbalance was also present in the safety analysis set. Trial 301 had more females than males but percentages were similar between treatment groups.

Both trials had more subjects that were less than 65 years of age than patients greater than 65 years. Trial 301 has slightly fewer subjects classified as high risk, defined as subjects with a medical history of cardiac, renal or vascular problems (hypertension), or diabetes. *Reviewer Comment: This subgroup was not specified in either the study protocol or statistical analysis plan, and is therefore a post-hoc subgroup.* The majority of subjects were White in both trials. Note that all of the subjects with a missing value for Race were reported to be of Hispanic or Latino ethnicity.

Table 8. Demographic and baseline characteristics for subjects included in at least one laboratory analysis

	Trial 301		Trial 302	
Demographic & Baseline Characteristics	**BLI-850 (N=160) n (%)**	**HalfLytely (N=173) n (%)**	**BLI-850 (N=174) n (%)**	**MoviPrep (N=167) n (%)**
Sex				
Male	71 (44)	77 (45)	97 (56)	70 (42)
Age (years)				
Age >= 65	41 (26)	43 (25)	37 (21)	46 (28)
mean (sd)	56 (13)	56 (12)	57 (11)	57 (11)
Race				
White	129 (80)	131 (76)	150 (86)	143 (86)
Black	23 (14)	27 (16)	9 (5)	12 (7)
Asian	4 (3)	4 (2)	2 (1)	3 (2)
Indian or Alaskan Native	0 (0)	2 (1)	1 (1)	2 (1)
Other	-	-	3 (2)	0 (0)
Missing	4 (3)	9 (5)	9 (5)	7 (4)
High Risk†	68 (43)	76 (44)	84 (48)	89 (53)
Weight (lbs)				
Missing	1 (1)	0 (0)	1 (1)	0 (0)
mean (sd)	180 (42)	180 (41)	189 (43)	181 (42)

† High risk defined as patients with medical history of cardiac, renal or vascular problems (hypertension), or diabetes.

3.3.4 Results and Conclusion

Baseline Assessment

In trial 301, there were no statistically significant differences at baseline between the BLI-850 and HalfLytely groups with regard to either the mean laboratory value (Table 27 in Section 6.2.1) or in the proportion of subjects with an abnormal laboratory value (Table 9). There were several subjects with abnormal eGFR values at baseline, which varied considerably according to the formula used. Approximately half of the subjects had abnormal eGFR values based on the CG formula, and notably more abnormal using the others (MDRD and CKD-EPI). In addition to eGFR, the following laboratory parameters had at least 10% of the subjects in a treatment arm with laboratory value outside the normal range: amylase, calcium, CK, GGT, serum osmolality, urea, and uric acid. These findings and general trends were observed for trial 302.

Table 9. Summary of baseline laboratory values outside the normal range

	Study 301			Study 302	
Laboratory Parameter	**BLI-850 n/N (%)**	**HalfLytely n/N (%)**	**p-value**	**BLI-850 n/N (%)**	**MoviPrep n/N (%)**
Albumin	7/159 (4)	7/171 (4)	1	9/173 (5)	6/165 (4)
ALP	6/159 (4)	9/171 (5)	0.6	7/173 (4)	3/165 (2)
ALT	11/159 (7)	10/171 (6)	0.82	11/173 (6)	15/165 (9)
Amylase	24/159 (15)	28/172 (16)	0.88	23/174 (13)	24/166 (14)
Anion Gap	4/159 (3)	1/171 (1)	0.20	7/173 (4)	10/165 (6)
AST	8/159 (5)	10/171 (6)	0.81	12/173 (7)	11/165 (7)
Bicarbonate	3/159 (2)	4/171 (2)	1	3/173 (2)	4/165 (2)
Calcium	20/159 (13)	32/171 (19)	0.13	32/173 (18)	21/165 (13)
Chloride	2/159 (1)	0/171 (0)	0.23	0/173 (0)	2/165 (1)
CK	21/159 (13)	19/170 (11)	0.62	26/173 (15)	21/164 (13)
Creatinine	14/159 (9)	16/171 (9)	1	6/173 (3)	12/165 (7)
eGFR CG	74/158 (47)	83/171 (49)	0.83	71/172 (41)	79/165 (48)
eGFR CKI-EPI	113/159 (71)	104/171 (61)	0.06	112/173 (65)	109/165 (66)
eGFR MDRD	130/159 (82)	131/171 (77)	0.28	141/173 (82)	137/165 (83)
Direct Bilirubin	2/159 (1)	4/171 (2)	0.69	4/173 (2)	2/165 (1)
Gamma GT	33/159 (21)	31/171 (18)	0.58	24/173 (14)	31/165 (19)
Glucose, Serum	13/159 (8)	14/170 (8)	1	13/173 (8)	13/163 (8)
Magnesium	1/159 (1)	2/171 (1)	1	4/173 (2)	2/165 (1)
Osmolality, Serum	21/160 (13)	18/171 (11)	0.5	22/173 (13)	22/167 (13)
Phosphate	4/159 (3)	3/171 (2)	0.71	2/173 (1)	5/165 (3)
Potassium	15/159 (9)	11/171 (6)	0.41	11/173 (6)	6/165 (4)
Sodium	2/159 (1)	2/171 (1)	1	4/173 (2)	2/165 (1)
Total Bilirubin	2/159 (1)	1/171 (1)	0.61	3/173 (2)	3/165 (2)
Total Protein	2/159 (1)	8/171 (5)	0.11	6/173 (3)	4/165 (2)
Urea (BUN)	12/159 (8)	19/171 (11)	0.35	11/173 (6)	12/165 (7)
Uric Acid	16/159 (10)	11/171 (6)	0.32	10/173 (6)	11/165 (7)

3.3.4.1 Trial 301

Refer to Table 28 in Section 6.2.2 for the classification (above or below normal) of visit 2 abnormal values.

3.3.4.1.1 Electrolytes Laboratory Parameters

The shift summaries for the electrolyte parameters by treatment group are displayed in Table 10. The only differences between groups for these parameters were for calcium and serum glucose; however, none were statistically significant. For calcium, the BLI-850 group had a greater number of subjects with an above normal value compared HalfLytely (8.6% vs. 3.6%; RD=5.0, 95% CI=-0.6, 10.6). Despite this greater percentage of abnormal calcium values in the BLI-850 group, none of the abnormal values were large in magnitude (see Figure 4 in Section 6.2.2).

For serum glucose the proportion of patients with abnormal values at visit 2 was 6.8% in the BLI-850 group compared 3.2% in the HalfLytely group (RD=3.6, 95% CI (-1.3, 8.6)). The majority of these subjects' values were above normal; one subject in the HalfLytely group had an abnormal value that was below normal. It is apparent from Figure 1 that the abnormal values at

visit 2 among those that were normal at baseline were not clustered around the upper limit of the normal range and differed slightly from how they were distributed in the HalfLytely group.

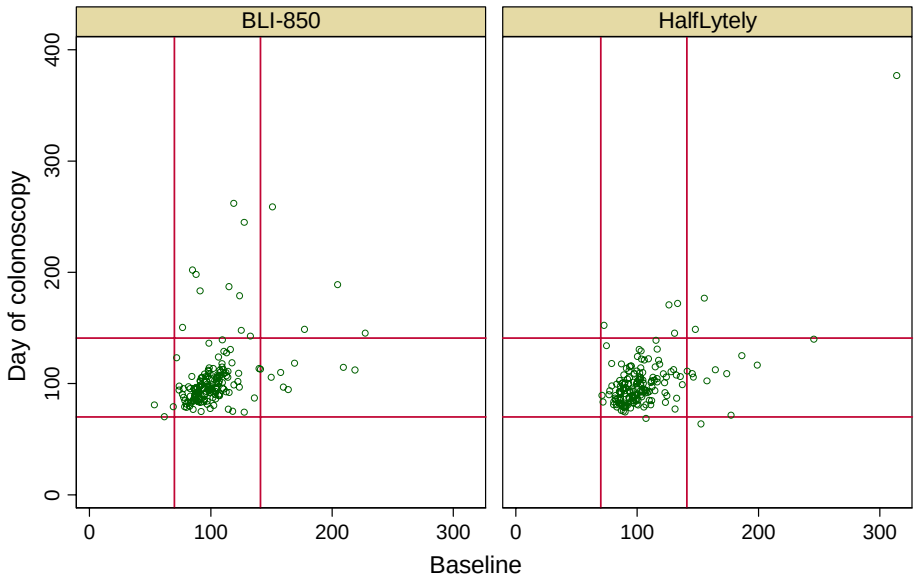
Table 10. Proportion of subjects with abnormal electrolyte values (normal baseline) (Trial 301)

Laboratory Parameter	BLI-850 n/N (%)	HalfLytely n/N (%)	RD (95% CI)
Anion Gap	5/155 (3.2)	10/170 (5.9)	-2.7 (-7.2, 1.8)
Bicarbonate	5/156 (3.2)	5/167 (3.0)	0.2 (-3.6, 4.0)
Calcium	12/139 (8.6)	5/139 (3.6)	5.0 (-0.6, 10.6)
Chloride	1/157 (0.6)	0/171 (0.0)	0.6 (-0.6, 1.9)
Magnesium	1/158 (0.6)	1/169 (0.6)	0.0 (-1.7, 1.7)
Phosphate	2/155 (1.3)	2/168 (1.2)	0.1 (-2.3, 2.5)
Potassium	6/144 (4.2)	4/160 (2.5)	1.7 (-2.4, 5.7)
Glucose, Serum	10/146 (6.8)	5/156 (3.2)	3.6 (-1.3, 8.6)
Sodium	1/157 (0.6)	0/169 (0.0)	0.6 (-0.6, 1.9)

†Refer to Table 28 in Section 6.2.2 for the classification (above or below normal) of visit 2 abnormal values.

Based on the analysis between groups in change in mean levels from baseline to visit 2, serum glucose was the only parameter that was statistically significantly different between groups (see Table 11). Compared to baseline, the visit 2 mean serum glucose level was slightly larger for the BLI-850 group (104.2 vs. 105.4) and smaller in the HalfLytely group (105.9 vs. 100.4). This difference resulted in a statistically significant change between groups (DMC=6.36 mg/dL; 95% CI =0.11, 12.61).

Figure 1. Scatterplot of visit 2 and baseline serum glucose values with normal range levels overlaid (301)



Lab: GLUCOSE, SERUM (mg/dL); Normal Range: 70 - 141
NOTE: points are jittered to reveal frequency

Table 11. Mean electrolyte laboratory values and difference in mean change from baseline (Trial 301)

Laboratory Parameter	Visit	BLI-850 mean (95% CI)	HalfLytely mean (95% CI)	DMC from baseline (95% CI)
Anion Gap	BL	11.72 (11.41, 12.02)	11.96 (11.66, 12.26)	
	2	12.43 (12.11, 12.76)	12.49 (12.15, 12.84)	0.18 (-0.41, 0.78)
Bicarbonate	BL	25.18 (24.80, 25.56)	24.94 (24.59, 25.30)	
	2	24.30 (23.93, 24.66)	24.43 (24.08, 24.78)	-0.37 (-0.92, 0.19)
Calcium	BL	9.84 (9.78, 9.90)	9.90 (9.83, 9.97)	
	2	9.75 (9.69, 9.82)	9.76 (9.70, 9.82)	0.05 (-0.04, 0.14)
Chloride	BL	102.60 (102.19, 103.01)	102.78 (102.42, 103.14)	
	2	103.23 (102.82, 103.63)	103.05 (102.69, 103.42)	0.35 (-0.17, 0.87)
Magnesium	BL	1.77 (1.74, 1.79)	1.77 (1.75, 1.79)	
	2	1.76 (1.74, 1.78)	1.74 (1.72, 1.76)	0.03 (-0.00, 0.05)
Phosphate	BL	3.52 (3.43, 3.61)	3.60 (3.52, 3.69)	
	2	3.45 (3.36, 3.53)	3.59 (3.50, 3.67)	-0.06 (-0.19, 0.07)
Potassium	BL	4.29 (4.22, 4.37)	4.36 (4.29, 4.43)	
	2	4.10 (4.04, 4.16)	4.12 (4.06, 4.18)	0.05 (-0.05, 0.14)
Glucose, serum	BL	104.52 (100.42, 108.61)	105.91 (101.53, 110.29)	
	2	105.36 (100.52, 110.20)	100.39 (96.16, 104.63)	6.36 (0.11, 12.61)
Sodium	BL	139.49 (139.12, 139.86)	139.68 (139.35, 140.01)	
	2	139.96 (139.60, 140.31)	139.97 (139.65, 140.29)	0.17 (-0.30, 0.64)

BL=baseline assessment; DMC=Difference in mean change (BLI-850 – HalfLytely)

3.3.4.1.2 Liver Function Tests

There were no notable differences between treatment groups in the proportion of subjects with an abnormal value (Table 12) or change in mean levels (Table 13) at visit 2.

No subjects simultaneously had significantly elevated ALT/AST and total bilirubin at visit 2; therefore there are no potential Hy's Law cases.

Table 12. Proportion of subjects with an abnormal liver function value (normal baseline) (Trial 301)

Laboratory Parameter	BLI-850 n/N (%)	HalfLytely n/N (%)	RD (95% CI)
Albumin	7/152 (4.6)	9/164 (5.5)	-0.9 (-5.7, 3.9)
ALP	0/153 (0.0)	5/162 (3.1)	-3.1 (-5.7, -0.4)
ALT	8/148 (5.4)	5/161 (3.1)	2.3 (-2.2, 6.8)
AST	9/151 (6.0)	7/161 (4.3)	1.6 (-3.3, 6.5)
Direct Bilirubin	14/157 (8.9)	18/167 (10.8)	-1.9 (-8.3, 4.6)
Gamma GT	2/126 (1.6)	5/140 (3.6)	-2.0 (-5.8, 1.8)
Total Bilirubin	12/157 (7.6)	17/170 (10.0)	-2.4 (-8.5, 3.8)

†Refer to Table 28 in Section 6.2.2 for the classification (above or below normal) of visit 2 abnormal values.

Table 13. Liver function tests: Mean values and difference in mean change from baseline (Trial 301)

Laboratory Parameter	Visit	BLI-850 mean (95% CI)	HalfLytely mean (95% CI)	DMC from baseline (95% CI)
Albumin	BL	4.49 (4.45, 4.52)	4.50 (4.46, 4.54)	
	2	4.52 (4.47, 4.56)	4.50 (4.46, 4.54)	0.03 (-0.01, 0.08)
ALP	BL	71.41 (68.14, 74.68)	71.82 (67.85, 75.79)	
	2	72.89 (69.10, 76.67)	73.78 (69.36, 78.20)	-0.48 (-3.17, 2.21)
ALT	BL	26.82 (23.73, 29.92)	26.89 (23.74, 30.03)	
	2	27.75 (24.92, 30.57)	31.09 (23.27, 38.91)	-3.28 (-11.32, 4.76)
AST	BL	23.50 (22.10, 24.90)	23.73 (22.21, 25.25)	
	2	26.13 (24.32, 27.94)	26.35 (23.72, 28.97)	0.01 (-2.78, 2.81)
Direct Bilirubin	BL	0.12 (0.11, 0.13)	0.12 (0.12, 0.13)	
	2	0.17 (0.16, 0.18)	0.17 (0.16, 0.18)	0.00 (-0.01, 0.02)
Gamma GT	BL	35.66 (29.21, 42.11)	30.24 (26.32, 34.16)	
	2	34.27 (28.75, 39.79)	30.96 (26.41, 35.52)	-2.12 (-5.58, 1.35)
Total Bilirubin	BL	0.44 (0.41, 0.48)	0.44 (0.41, 0.47)	
	2	0.72 (0.67, 0.77)	0.72 (0.66, 0.77)	0.00 (-0.04, 0.05)

BL=baseline assessment; DMC=Difference in mean change (BLI-850 – HalfLytely)

3.3.4.1.3 Renal Function

For the shift analysis of laboratory parameters listed in Table 16, the only statistically significant difference between groups was in total protein (4.5% vs. 0.6%; RD = 3.8; 95% CI = 0.4, 7.3); all abnormal values were above normal. From the scatterplot of total protein values (Figure 8 in Section 6.2.2), the above normal values in the BLI-850 group were not markedly larger than the upper limit of normal.

Using the CG formula for eGFR, there is a greater percentage of abnormal values in the BLI-850 group compared to HalfLytely (25% vs. 13.6%). However, using the other formulas to estimate eGFR, there are fewer patients in the BLI-850 group with an abnormal value (e.g., CKD-EPI: 30.4% vs. 41.8%). In addition to previously noted limitations of the CG formula to estimate eGFR, the comparison of percentage across the separate formula should be interpreted cautiously as the analyses are not performed on the same subjects.

Table 14. Proportion of subjects with an abnormal renal function value (normal baseline) (Trial 301)

Laboratory Parameter	BLI-850 n/N (%)	HalfLytely n/N (%)	RD (95% CI)
Creatinine	3/145 (2.1)	4/155 (2.6)	-0.5 (-3.9, 2.9)
eGFR CG	21/84 (25.0)	12/88 (13.6)	11.4 (-0.3, 23.1)
eGFR CKD-EPI	14/46 (30.4)	28/67 (41.8)	-11.4 (-29.1, 6.4)
eGFR MDRD	9/29 (31.0)	18/40 (45.0)	-14.0 (-36.8, 8.9)
Total Protein	7/157 (4.5)	1/163 (0.6)	3.8 (0.4, 7.3)
Urea (BUN)	17/147 (11.6)	17/152 (11.2)	0.4 (-6.8, 7.6)

†Refer to Table 28 in Section 6.2.2 for the classification (above or below normal) of visit 2 abnormal values.

There are no statistically significant differences between groups in the change in mean levels from baseline to visit 2 (Table 15). For each of the eGFR formulas, the decrease in mean at visit 2 from baseline is greater but not statistically significant in the HalfLytely group compared to BLI-850. Scatterplots of visit 2 and baseline eGFR values for each of the three eGFR are provided in Section 6.2.2.

Table 15. Renal function tests: Mean values and difference in mean change from baseline (Trial 301)

Laboratory Parameter	Visit	BLI-850 mean (95% CI)	HalfLytely mean (95% CI)	DMC from baseline (95% CI)
Creatinine	BL	0.97 (0.93, 1.00)	0.97 (0.91, 1.02)	
	2	0.97 (0.93, 1.01)	0.99 (0.94, 1.05)	-0.02 (-0.05, 0.01)
eGFR CG	BL	94.74 (89.44, 100.04)	97.31 (91.84, 102.78)	
	2	93.01 (87.87, 98.16)	93.51 (88.12, 98.89)	2.07 (-0.89, 5.04)
eGFR CKI-EPI	BL	80.52 (77.45, 83.60)	82.86 (79.66, 86.06)	
	2	79.78 (76.69, 82.88)	79.94 (76.92, 82.96)	2.18 (-0.29, 4.65)
eGFR MDRD	BL	75.06 (72.26, 77.86)	77.27 (74.37, 80.16)	
	2	74.77 (71.65, 77.88)	74.62 (71.81, 77.43)	2.35 (-0.32, 5.02)
Total Protein	BL	7.09 (7.03, 7.14)	7.13 (7.07, 7.20)	
	2	7.15 (7.08, 7.22)	7.14 (7.07, 7.20)	0.06 (-0.02, 0.14)
Urea (BUN)	BL	16.40 (15.69, 17.12)	16.71 (15.67, 17.75)	
	2	13.29 (12.57, 14.01)	13.12 (12.22, 14.02)	0.48 (-0.34, 1.30)

BL=baseline assessment; DMC=Difference in mean change (BLI-850 – HalfLytely)

3.3.4.1.4 Other Laboratory Tests

There were no statistically significant differences in the proportion of subjects who were normal at baseline and abnormal at visit 2 (Table 16) or change in mean levels from baseline to visit 2 (Table 17) for amylase, CK, serum osmolality and uric acid. However, several subjects in both groups had notably large visit 2 CK values (Figure 2).

Table 16. Proportion of subjects with an abnormal value on "Other" laboratory tests (normal baseline) (Trial 301)

Laboratory Parameter	BLI-850 n/N (%)	HalfLytely n/N (%)	RD (95% CI)
Amylase	4/135 (3.0)	8/144 (5.6)	-2.6 (-7.3, 2.1)
CK	10/138 (7.2)	7/151 (4.6)	2.6 (-2.9, 8.1)
Osmolality, Serum	5/139 (3.6)	9/153 (5.9)	-2.3 (-7.1, 2.6)
Uric Acid	8/143 (5.6)	11/160 (6.9)	-1.3 (-6.7, 4.2)

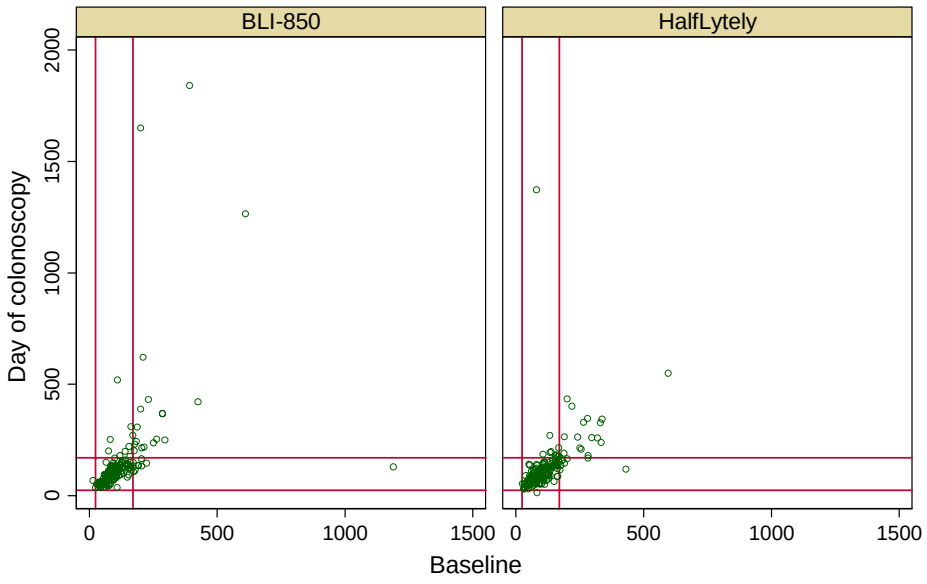
†Refer to Table 28 in Section 6.2.2 for the classification (above or below normal) of visit 2 abnormal values.

Table 17. Other Laboratory Tests: Mean values and difference in mean change from baseline (301)

Laboratory Parameter	Visit	BLI-850 mean (95% CI)	HalfLytely mean (95% CI)	DMC from baseline (95% CI)
Amylase	BL	69.84 (65.70, 73.97)	78.73 (64.27, 93.18)	
	2	58.65 (55.18, 62.12)	62.20 (57.27, 67.14)	5.33 (-10.01, 20.68)
CK	BL	122.09 (104.25, 139.92)	118.17 (106.47, 129.87)	
	2	151.23 (117.03, 185.43)	124.35 (105.69, 143.02)	22.96 (-11.57, 57.48)
Osmolality, Serum	BL	288.21 (287.19, 289.22)	287.98 (287.05, 288.91)	
	2	287.32 (286.45, 288.20)	287.80 (286.82, 288.78)	-0.71 (-2.26, 0.85)
Uric Acid	BL	5.43 (5.19, 5.66)	5.33 (5.11, 5.54)	
	2	5.82 (5.59, 6.05)	5.82 (5.62, 6.02)	-0.10 (-0.27, 0.07)

BL=baseline assessment; DMC=Difference in mean change (BLI-850 – HalfLytely)

Figure 2. Scatterplot of visit 2 and baseline CK values with normal range levels overlaid (301).



Lab: CK (U/L); Normal Range: 24 - 170
NOTE: points are jittered to reveal frequency

3.3.4.2 Trial 302

Refer to Table 33 in Section 6.2.3 for the classification (above or below normal) of visit 2 abnormal values.

3.3.4.2.1 Electrolyte Laboratory Parameters

There were no statistically significant differences in proportion of subjects with abnormal visit 2 value among those with a normal baseline value for any of the measured electrolytes (Table 18). For anion gap, the BLI-850 group had a greater percentage of overall abnormal (above or below normal range) values compared to MoviPrep (11.4% vs. 7.7%); however, considering values only above the normal range, the difference between groups is not as large (10.2% vs. 7.7%).

Table 18. Proportion of subjects with an abnormal electrolyte value (normal baseline) (Trial302)

Laboratory Parameter	BLI-850 n/N (%)	MoviPrep n/N (%)	RD (95% CI)
Anion Gap	19/166 (11.4)	12/155 (7.7)	3.7 (-2.7, 10.1)
Bicarbonate	7/170 (4.1)	20/161 (12.4)	-8.3 (-14.2, -2.4)
Calcium	6/141 (4.3)	7/144 (4.9)	-0.6 (-5.4, 4.2)
Chloride	1/173 (0.6)	0/163 (0.0)	0.6 (-0.6, 1.7)
Magnesium	0/169 (0.0)	2/163 (1.2)	-1.2 (-2.9, 0.5)
Phosphate	6/171 (3.5)	4/160 (2.5)	1.0 (-2.7, 4.7)
Potassium	6/162 (3.7)	8/159 (5.0)	-1.3 (-5.8, 3.1)
Glucose, Serum	6/160 (3.8)	8/150 (5.3)	-1.6 (-6.2, 3.1)
Sodium	1/169 (0.6)	1/163 (0.6)	-0.0 (-1.7, 1.6)

†Refer to Table 33 in Section 6.2.3 for the classification (above or below normal) of visit 2 abnormal values.

As shown in Table 19, statistically significant differences in the change in mean from baseline between BLI-850 and MoviPrep was observed for bicarbonate, chloride, and sodium. The statistically significant differences between groups for chloride and bicarbonate were driven by a mean increase and decrease, respectively, from baseline in the MoviPrep group. For sodium, the difference was driven by the BLI-850 group, which had a significantly smaller change from baseline compared to MoviPrep.

Table 19. Mean electrolyte laboratory values and difference in mean change from baseline (302)

Laboratory Parameter	Visit	BLI-850 mean (95% CI)	MoviPrep mean (95% CI)	DMC from baseline (95% CI)
Anion Gap	BL	12.97 (12.65, 13.29)	12.75 (12.43, 13.08)	
	2	13.36 (13.01, 13.72)	13.67 (13.30, 14.05)	-0.53 (-1.16, 0.10)
Bicarbonate	BL	24.28 (23.92, 24.63)	24.25 (23.88, 24.62)	
	2	24.05 (23.68, 24.42)	22.56 (22.15, 22.98)	1.46 (0.85, 2.07)
Calcium	BL	9.88 (9.81, 9.96)	9.80 (9.74, 9.86)	
	2	9.74 (9.68, 9.80)	9.63 (9.57, 9.69)	0.02 (-0.08, 0.12)
Chloride	BL	102.61 (102.27, 102.95)	102.53 (102.14, 102.92)	
	2	102.60 (102.22, 102.97)	104.11 (103.62, 104.59)	-1.59 (-2.11, -1.08)
Magnesium	BL	1.76 (1.73, 1.78)	1.76 (1.73, 1.78)	
	2	1.75 (1.73, 1.77)	1.72 (1.69, 1.74)	0.03 (0.00, 0.06)
Phosphate	BL	3.56 (3.48, 3.64)	3.53 (3.44, 3.62)	
	2	3.35 (3.27, 3.44)	3.39 (3.32, 3.47)	-0.07 (-0.20, 0.06)
Potassium	BL	4.23 (4.17, 4.30)	4.30 (4.24, 4.36)	
	2	4.08 (4.03, 4.13)	4.19 (4.12, 4.26)	-0.04 (-0.13, 0.05)
Glucose, serum	BL	102.18 (97.46, 106.91)	101.95 (97.99, 105.91)	
	2	98.40 (95.11, 101.70)	96.98 (92.94, 101.01)	1.20 (-4.59, 6.98)
Sodium	BL	139.86 (139.50, 140.21)	139.53 (139.21, 139.86)	
	2	140.01 (139.71, 140.30)	140.35 (139.98, 140.72)	-0.66 (-1.18, -0.15)

BL=baseline assessment; DMC=Difference in mean change (BLI-850 – HalfLytely)

3.3.4.2.2 Liver Function Tests

From the results of the shift analysis in Table 20, total bilirubin is the only laboratory parameter with statistically significantly more subjects with abnormal values in the BLI-850 group compared to control (11.2% vs. 3.7%; RD = 7.5; 95% CI = 1.9, 13.0). There is no evidence of extreme values for visit 2 and baseline total bilirubin (Figure 9 in Section 6.2.3).

The following laboratory parameters had a greater but not statistically significant percentage of abnormal values in the BLI-850 group compared to MoviPrep: albumin (7.3% vs. 3.8), ALT (6.2% vs. 3.3%), and direct bilirubin (9.5% vs. 6.1%). A few subjects in the BLI-850 group with normal baseline laboratory values had visibly large visit 2 values for ALT (Figure 10 in Section 6.2.3) and AST (Figure 11 in Section 6.2.3).

No subjects simultaneously had significantly elevated ALT/AST and total bilirubin at visit 2; therefore there are no potential Hy's Law cases.

Table 20. Proportion of subjects with an abnormal liver function value (normal baseline) (Trial 302)

Laboratory Parameter	BLI-850 n/N (%)	MoviPrep n/N (%)	RD (95% CI)
Albumin	12/164 (7.3)	6/159 (3.8)	3.5 (-1.4, 8.5)
ALP	1/166 (0.6)	1/162 (0.6)	-0.0 (-1.7, 1.7)
ALT	10/162 (6.2)	5/150 (3.3)	2.8 (-1.8, 7.5)
AST	13/161 (8.1)	14/154 (9.1)	-1.0 (-7.2, 5.2)
Direct Bilirubin	16/169 (9.5)	10/163 (6.1)	3.3 (-2.4, 9.1)
Gamma GT	4/149 (2.7)	3/134 (2.2)	0.4 (-3.2, 4.1)
Total Bilirubin	19/170 (11.2)	6/162 (3.7)	7.5 (1.9, 13.0)

†Refer to Table 33 in Section 6.2.3 for the classification (above or below normal) of visit 2 abnormal values.

The change in mean levels from baseline to visit 2 in direct bilirubin, total bilirubin, and GGT were statistically significantly different between groups (see Table 21). For direct bilirubin and total bilirubin, differences were largely driven by a larger mean change from baseline in the BLI-850 group compared to MoviPrep. For GGT, the difference between groups was driven by an increase at visit 2 in the MoviPrep group.

Table 21. Liver function tests: Mean values and difference in mean change from baseline (302)

Laboratory Parameter	Visit	BLI-850 mean (95% CI)	MoviPrep mean (95% CI)	DMC from baseline (95% CI)
Albumin	BL	4.52 (4.48, 4.56)	4.49 (4.46, 4.53)	
	2	4.59 (4.55, 4.63)	4.55 (4.51, 4.59)	0.01 (-0.03, 0.06)
ALP	BL	71.71 (68.23, 75.18)	73.27 (70.19, 76.34)	
	2	73.83 (70.00, 77.67)	73.94 (70.67, 77.21)	1.45 (-0.58, 3.49)
ALT	BL	25.90 (23.88, 27.92)	26.70 (23.98, 29.41)	
	2	30.23 (26.08, 34.38)	30.56 (27.18, 33.94)	0.47 (-3.40, 4.35)
AST	BL	23.93 (22.73, 25.13)	24.42 (22.61, 26.23)	
	2	28.04 (26.29, 29.79)	28.64 (26.19, 31.08)	-0.11 (-1.80, 1.58)
Direct Bilirubin	BL	0.12 (0.11, 0.13)	0.12 (0.11, 0.12)	
	2	0.17 (0.16, 0.18)	0.15 (0.14, 0.16)	0.01 (0.00, 0.03)
Gamma GT	BL	29.50 (24.99, 34.00)	35.38 (28.03, 42.73)	
	2	29.50 (25.23, 33.78)	37.33 (29.01, 45.66)	-1.95 (-3.81, -0.08)
Total Bilirubin	BL	0.49 (0.45, 0.54)	0.45 (0.41, 0.48)	
	2	0.77 (0.68, 0.85)	0.60 (0.55, 0.64)	0.13 (0.07, 0.19)

BL=baseline assessment; DMC=Difference in mean change (BLI-850 – HalfLytely)

3.3.4.2.3 Renal Function

Except for urea (BUN), the percentages of subjects with an abnormal value in both treatment groups were similar (Table 22). For urea, the BLI-850 group had a greater (not statistically significant) percentage of subjects with an abnormal value compared MoviPrep (13.6% vs. 9.8%; RD=3.8, 95% CI=-3.3, 10.8); however, none of the values were notable (see Figure 15 in Appendix).

Using either the CKD-EPI or the MDRD formula to estimate eGFR, the BLI-850 group had a greater percentage of subjects with abnormal values at visit 2 compared to MoviPrep. Using the

CG formula, the percentage of subjects with abnormal values was similar for the two groups (BLI-850: 8.9%; MoviPrep: 11.6%).

Table 22. Proportion of subjects with an abnormal renal function value (normal baseline) (Trial 302)

Laboratory Parameter	BLI-850 n/N (%)	MoviPrep n/N (%)	RD (95% CI)
Creatinine	2/167 (1.2)	1/153 (0.7)	0.5 (-1.5, 2.6)
eGFR CG	9/101 (8.9)	10/86 (11.6)	-2.7 (-11.5, 6.0)
eGFR CKD-EPI	20/61 (32.8)	15/56 (26.8)	6.0 (-10.5, 22.5)
eGFR MDRD	16/32 (50.0)	10/28 (35.7)	14.3 (-10.5, 39.1)
Total Protein	2/167 (1.2)	8/161 (5.0)	-3.8 (-7.5, -0.0)
Urea (BUN)	22/162 (13.6)	15/153 (9.8)	3.8 (-3.3, 10.8)

†Refer to Table 33 in Section 6.2.3 for the classification (above or below normal) of visit 2 abnormal values.

The only renal parameter that was statistically significant in the analysis of change in mean levels from baseline to visit 2 was urea (DMC=-0.91 mg/dL; 95% CI =-1.69, -0.12) (Table 23). This difference was driven by a larger decrease in the BLI-850 group compared to MoviPrep. Scatterplots of visit 2 and baseline eGFR values for each of the three eGFR are provided in Section 6.2.3.

Table 23. Renal function tests: Mean values and difference in mean change from baseline (Trial 302)

Laboratory Parameter	Visit	BLI-850 mean (95% CI)	MoviPrep mean (95% CI)	DMC from baseline (95% CI)
Creatinine	BL	0.95 (0.92, 0.98)	0.93 (0.90, 0.96)	
	2	0.95 (0.92, 0.98)	0.93 (0.90, 0.96)	0.00 (-0.03, 0.03)
eGFR CG	BL	100.81 (96.10, 105.52)	96.52 (91.72, 101.31)	
	2	98.49 (94.21, 102.77)	95.01 (90.28, 99.74)	-0.81 (-3.66, 2.04)
eGFR CKI-EPI	BL	81.69 (79.10, 84.27)	81.17 (78.46, 83.88)	
	2	81.69 (79.29, 84.09)	80.90 (78.36, 83.44)	0.27 (-2.00, 2.55)
eGFR MDRD	BL	76.49 (73.99, 78.99)	75.39 (72.85, 77.93)	
	2	76.00 (73.79, 78.20)	75.18 (72.78, 77.58)	-0.28 (-2.68, 2.12)
Total Protein	BL	7.04 (6.98, 7.10)	7.02 (6.96, 7.08)	
	2	7.17 (7.10, 7.23)	7.12 (7.06, 7.19)	0.03 (-0.04, 0.10)
Urea (BUN) (mg/dL)	BL	16.68 (15.87, 17.48)	15.98 (15.20, 16.77)	
	2	12.76 (12.16, 13.37)	12.98 (12.31, 13.64)	-0.91 (-1.69, -0.12)

BL=baseline assessment; DMC=Difference in mean change (BLI-850 – HalfLytely)

3.3.4.2.4 Other Laboratory Tests

There were no statistically significant differences between groups in the proportion of subjects who were normal at baseline and abnormal at visit 2 for amylase, CK, serum osmolality and uric acid (Table 24).

Table 24. Proportion of subjects with an abnormal value on "Other" laboratory tests (normal baseline) (Trial 302)

Laboratory Parameter	BLI-850 n/N (%)	MoviPrep n/N (%)	RD (95% CI)
Amylase	6/151 (4.0)	4/142 (2.8)	1.2 (-3.0, 5.3)
CK	10/147 (6.8)	7/143 (4.9)	1.9 (-3.5, 7.3)
Osmolality, Serum	9/151 (6.0)	15/145 (10.3)	-4.4 (-10.6, 1.8)
Uric Acid	7/163 (4.3)	4/154 (2.6)	1.7 (-2.3, 5.7)

†Refer to Table 33 in Section 6.2.3 for the classification (above or below normal) of visit 2 abnormal values.

Based on the analysis of the change between groups in mean levels from baseline to visit 2, the change in amylase, serum osmolality, and uric acid were statistically significant different between groups (see Table 25). For amylase, the BLI-850 group had a greater decrease from baseline compared to the MoviPrep group (DMC=-3.43 U/L; 95% CI =-6.16, -0.70). This finding was consistent after removing one subject (ID 32006) who had a large amylase value at baseline (1467 U/L) and at visit 2 (1470 U/L) (outlier illustrated in Figure 16 in Section 6.2.3).

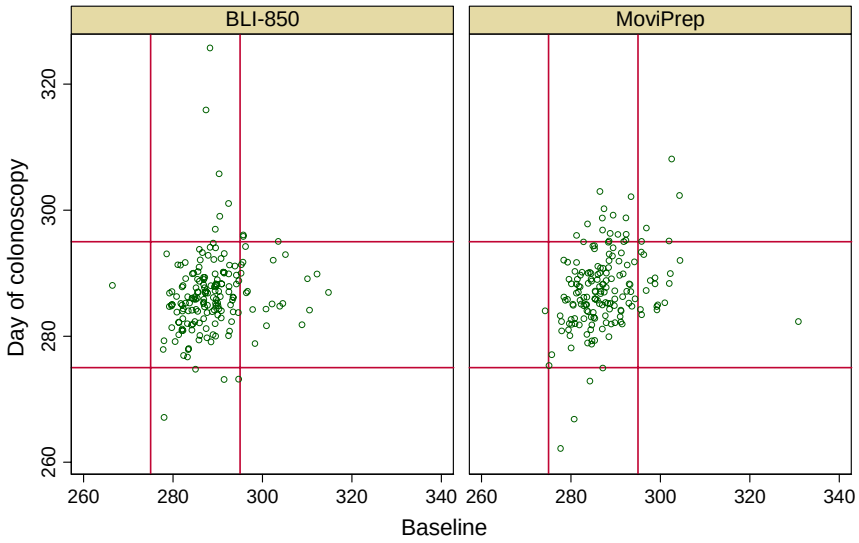
For serum osmolality the mean level in the BLI-850 group decreased slightly from baseline to visit 2 with no change noted in the MoviPrep group. From the scatterplot of visit 2 and baseline laboratory values in Figure 3, a few subjects in the BLI-850 group that were abnormal at visit 2 (normal at baseline) had serum osmolality values that were visibly larger than those in the MoviPrep group.

Table 25. Other laboratory tests: Mean values and difference in mean change from baseline (302)

Laboratory Parameter	Visit	BLI-850 mean (95% CI)	MoviPrep mean (95% CI)	DMC from baseline (95% CI)
Amylase	BL	74.83 (58.58, 91.09)	66.25 (62.13, 70.37)	
	2	64.86 (48.61, 81.10)	59.70 (55.89, 63.50)	-3.43 (-6.16, -0.70)
CK	BL	129.54 (114.57, 144.51)	120.35 (105.66, 135.03)	
	2	124.46 (111.18, 137.73)	124.55 (97.22, 151.89)	-9.29 (-36.34, 17.77)
Osmolality, Serum	BL	288.70 (287.65, 289.75)	287.51 (286.44, 288.57)	
	2	286.58 (285.63, 287.54)	287.40 (286.45, 288.34)	-2.00 (-3.77, -0.24)
Uric Acid	BL	5.68 (5.47, 5.90)	5.46 (5.24, 5.69)	
	2	6.01 (5.80, 6.23)	5.47 (5.23, 5.70)	0.33 (0.17, 0.48)

BL=baseline assessment; DMC=Difference in mean change (BLI-850 – HalfLytely)

Figure 3. Scatterplot of visit 2 and baseline serum osmolality values with normal range levels overlaid (302)



Lab: OSMOLALITY,SERUM (mOsm/kg); Normal Range: 275 - 295
NOTE: Points are jittered to reveal frequency

4 FINDINGS IN SPECIAL /SUBGROUP POPULATIONS

Given the small number of subjects in the subgroups and the small number of shifts in the overall population, it is difficult to draw meaningful conclusions from these shift data. P-values provided in the tables in the appendix are based on tests for interaction.

4.1 Gender, Race, Age and Geographic Region

4.1.1 Study 301

Age (< 65 years, ≥ 65 years)
There does not appear to be a differential treatment effect between treatment groups by age grouping (see Table 29).

Sex
Only eGFR calculated using the CKD-EPI formula suggested evidence of an interaction by gender (see Table 30). Among females, the proportion of subjects with an abnormal value was larger in the BLI-850 group (42.1%) compared to HalfLytely (24.0%). Conversely, among male subjects, the proportion was higher among subjects in the Halflytely (52.4%) group compared to BLI-850 (22.2%).

Race (non-White, White)
There is evidence of an interaction by race (Whites and non-Whites) for urea (BUN) and eGFR (see Table 31). For urea, among non-White subjects, the proportion with an abnormal values was higher in the HalfLytely group (38.7%) compared to control (19.4%). Among White subjects there were fewer subjects with an abnormal values with more in the HalfLytely group (8.6%)

compared to BLI-850 (4.3%). For eGFR calculated using either the CG or CKD-EPI formula, among non-White subjects, there were fewer in the BLI-850 group with an abnormal value compared to HalfLytely. Among White subjects, there were more abnormal values in the BLI-850 group compared to Halflytely.

4.1.2 Study 302

Age (< 65 years, ≥ 65 years)
There is evidence of an interaction by age grouping for direct and total bilirubin (see Table 34). For direct bilirubin among subjects <65 years of age, more subjects (11.4%) in the BLI-850 group had an abnormal value compared to MoviPrep (5.0%). Conversely, among subjects ≥ 65 years, fewer subjects in the BLI-850 group had an abnormal value (2.7%) compared to MoviPrep (9.1%). This trend was similar for total bilirubin.

Sex
There does not appear to be a differential treatment effect by sexes (see Table 35).

Race (non-White, White)
There does not appear to be a differential treatment effect by race groups (see Table 36).

4.2 Other Special/Subgroups Populations

4.2.1 Study 301

High Risk Patients
The only finding of an interaction by risk group was for eGFR calculated using the CG formula (see Table 32). This finding was driven by a larger proportion of subjects with an abnormal value in the BLI-850 group compared to (26.5% vs. 2.7%) in the high risk group. This large difference was not observed among the non-high risk subgroup.

4.2.2 Study 302

High Risk Patients
There does not appear to be a differential effect by treatment by risk group (see Table 37).

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The two trials evaluated in this review were randomized, assessor-blinded, active-controlled, non-inferiority, phase III, efficacy trials. Neither trial was designed nor powered to test hypotheses for specific laboratory parameters. Therefore, results from analyses presented in this review should not be considered confirmatory. In addition, given the large number of comparisons performed without any adjustments for multiplicity, confidence intervals that exclude the null value should not be taken as confirmatory evidence of statistical significance. However, because the two trials shared similar designs, differing with respect to the administration of BLI-850 (i.e., split-dose versus day before) and comparator treatment, trends in safety findings for BLI-850 from one trial can be viewed along with findings from the second

trial as supportive evidence. Comparison of the differences between treatment groups between studies is not appropriate as the comparator agents in the two studies are different.

It is not possible to establish the long-term safety of BLI-850 since the systematic follow-up of subjects ended on the day of the colonoscopy. While the trial protocols permitted follow-up of subjects based on the Investigator's discretion, the overall safety of BLI-850 beyond the day of the colonoscopy can not be inferred from these subset of subjects. The criteria for additional follow-up laboratory assessment based on clinically significant laboratory parameters at visit 2 were not prespecified, but were determined by the Investigator and therefore varied.

Twenty-eight (28) subjects randomized in trial 301 (BLI-850: 20; HalfLytely: 8) and 15 subjects randomized in trial 302 (BLI-850: 7; MoviPrep: 8) were removed from the all randomized population. While the majority of these subjects withdrew consent and none reportedly took any study medication, given the open-label (patient unblinded) design of these studies, there is a possibility that consent withdrawal could be related to knowledge of the treatment assignment, thus potentially resulting in a biased analysis population. This is of particular concern in study 301 where there were more than twice as many subjects in the BLI-850 arm withdrawn compared to control.
A moderate number of subjects in each study (~10%) that were randomized and took any amount of study treatment were excluded from the analysis of laboratory parameters since they did not have a valid laboratory value at one or both study visits. However, because the majority of missing values were related to laboratory issues (i.e. contaminated or hemolyzed samples) and therefore not resulting from a possible systematic bias, missing data sensitivity analyses were not performed.

5.2 Collective Evidence

In trial 301, 160 of 196 subjects randomized to BLI-850 (81.6%) and 173 of the 198 subjects randomized to HalfLytely (87.3%) were included in at least one of the statistical reviewer's laboratory analysis. This laboratory analysis set includes one less subject in the BLI-850 group than was included in the sponsor's analysis set. Specifically, subject 2004 was excluded from the reviewer's analyses since the original visit 2 sample was contaminated and the redraw was collected after the day of the colonoscopy. In trial 302, 174 of 193 subjects randomized to BLI-850 (90.2%) and 167 of the 193 subjects randomized to MoviPrep (86.5%) were included in at least one of the laboratory analysis.

For each of the laboratory parameters investigated at baseline for both studies, there was no evidence of statistically significant differences between BLI-850 and the respective comparator agent based on the mean laboratory value or the proportion of subjects with abnormal values.

In trial 301, BLI-850 had a greater percentage of values above the normal range at visit 2 for calcium compared to HalfLytely (8.6% vs. 3.6%) and total protein (4.5% vs. 0.6%). Based on the comparison of the change in means from baseline to visit 2, the only statistically significant difference between groups was for serum glucose, where mean increased slightly for the BLI-850 group (104.5 mg/dL to 105.4 mg/dL) and decreased in the HalfLytely group (105.9 mg/dL to 100.4 mg/dL).

In trial 301, three subjects in the BLI-850 group had CK values larger than 1000 U/L at visit 2 (normal range 24-170 U/L, Figure 2) and three subjects with serum glucose values greater than 1.5 times the upper limit of normal at visit 2 (normal range 70-141 mg/dL, Figure 1).

In trial 302, BLI-850 had a statistically significantly greater percentage of values above normal for total bilirubin compared to MoviPrep (11.2% vs. 3.7%). Laboratory parameters in which there was a greater non-significant percentage of abnormal values (all above normal) in the BLI-850 group compared to MoviPrep were albumin (7.3% vs. 3.8%) and ALT (6.2% vs. 3.3%). Statistically significant differences in the mean change from baseline between BLI-850 and MoviPrep were observed for the following laboratory parameters: bicarbonate, chloride, sodium, total bilirubin, urea (BUN), serum osmolality, and uric acid. However, the differences observed for bicarbonate, chloride, and sodium were driven by mean changes in the MoviPrep not the BLI-850 group. Conversely, for total bilirubin and urea (BUN) the difference between groups was driven by changes in the BLI-850 group.

5.3 Conclusions and Recommendations

Due in part to some potential safety concerns associated with bowel preparations for colonoscopy, laboratory parameters associated with the liver and renal function, and electrolytes balance at baseline and on the day of the colonoscopy were evaluated in this review. Findings from this review revealed that select laboratory parameters measured on the day of the colonoscopy differed between BLI-850 and the respective comparator bowel prep with respect to either a greater number of abnormal values or in the difference in mean change from baseline. Consistency in both directions and the magnitude of change in specific laboratory values were not observed between the trials nor did there appear to be a marked increase or decrease in any specific laboratory measure. This lack of a consistency should be interpreted cautiously as 1) neither trial was powered to show a difference in laboratory parameters, 2) the trials used different comparator agent and 3) 13-18% of subjects in study 301 and 10-13% of subjects in study 302 that were randomized to a study treatment were excluded from the safety analyses. The inability to evaluate the safety of BLI-850 beyond the day of the colonoscopy in both trials is considered a significant limitation. To fully evaluate the long-term safety of this product, the reviewer recommends a large randomized clinical trial with pre-specified safety and laboratory assessments out to 30-days post-treatment.

6 Supplemental Material

6.1 Miscellaneous Material (both studies)

Formulas

Anion gap:

Anion gap = [sodium (mEq/L)] – [chloride (mEq/L) + bicarbonate (mEq/L)]

eGFR Cockcroft-Gault:

$$\frac{(140 - \text{Age}) \times \text{Body Weight (in kg)} \times [0.85 \text{ if female}]}{72 \times \text{Serum Creatinine (in mg/dL)}}$$

eGFR Modification of Diet in Renal Disease (MDRD):

$$175 \times \text{Serum Creatinine (in mg/dL)}^{-1.154} \times \text{Age}^{-0.203} \times [1.212 \text{ if Black}] \times [0.742 \text{ if Female}]$$

eGFR Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI):

For women with serum creatinine ≤ 0.7:

$$(\text{Serum Creatinine}/0.7)^{-0.329} \times (0.993)^{\text{Age}} \times [166 \text{ if Black; x } 144 \text{ if White or other}]$$

For women with a serum creatinine > 0.7:

$$(\text{Serum Creatinine}/0.7)^{-1.209} \times (0.993)^{\text{Age}} \times [166 \text{ if Black; x } 144 \text{ if White or other}]$$

For men with serum creatinine ≤ 0.9:

$$(\text{Serum Creatinine}/0.9)^{-0.411} \times (0.993)^{\text{Age}} \times [163 \text{ if Black; x } 141 \text{ if White or other}]$$

For men with a serum creatinine > 0.9:

$$(\text{Serum Creatinine}/0.7)^{-1.209} \times (0.993)^{\text{Age}} \times [163 \text{ if Black; x } 141 \text{ if White or other}]$$

Note: The unit of serum creatinine is mg/dL for the CKD-EPI formula.

Normal Range

Table 26. Laboratory parameter normal range limits

Laboratory Parameter	units	Normal Range
Albumin	g/dL	3.7-4.9
ALP	U/L	40-135
ALT	U/L	0-47
Amylase	U/L	28-100
Anion Gap	mEq/L	8-16
AST	U/L	0-37
Bicarbonate	mEq/L	20-31
Calcium	mg/dL	8.4-10.2
Chloride	mEq/L	95-113
CK	U/L	F: 24-170; M: 24-195
Creatinine	mg/dL	F: 0.5-1; M: 0.6-1.4
eGFR CG		
eGFR CKD-EPI		
eGFR MDRD		
Direct Bilirubin	mg/dL	0-0.2
Gamma GT	U/L	F: 0-33; M: 0-51
Glucose, Serum	mg/dL	70-141
Magnesium	mEq/L	1.4-2.1
Osmolality, Serum	mOsm/kg	275-295
Phosphate	mg/dL	2.4-4.9
Potassium	mEq/L	3.6-5.2
Sodium	mEq/L	134-146
Total Bilirubin	mg/dL	0-1.1
Total Protein	g/dL	6.1-7.9
Urea (BUN)	mg/dL	9-24
Uric Acid	mg/dL	F: 2.2-6.4; M: 3.1-8.8

F—Females; M—Males

6.2 Supplemental Analyses

6.2.1 Baseline Comparisons (both studies)

Table 27. Summary of mean laboratory levels at baseline

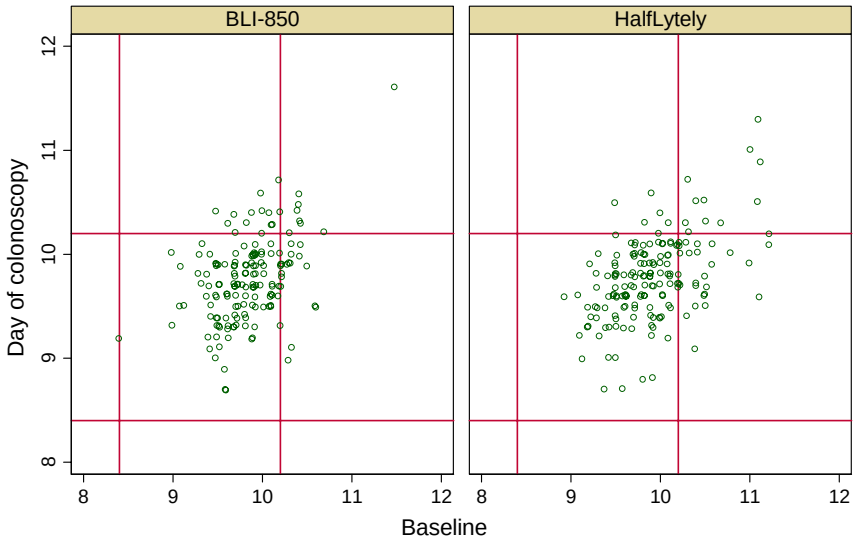
	Trial 301			Trial 302		
Laboratory Parameter	**BLI-850 mean (sd)**	**HalfLytely mean (sd)**	**p-value**	**BLI-850 mean (sd)**	**MoviPrep mean (sd)**	**p-value**
Albumin	4.5 (0.2)	4.5 (0.3)	0.54	4.5 (0.3)	4.5 (0.3)	0.32
ALP	71.4 (21.0)	71.8 (26.5)	0.88	71.7 (23.3)	73.3 (20.2)	0.51
ALT	26.8 (19.9)	26.9 (21.0)	0.98	25.9 (13.6)	26.7 (17.8)	0.64
Amylase	69.8 (26.6)	78.7 (96.7)	0.26	74.8 (109.4)	66.2 (27.1)	0.33
Anion Gap	11.7 (2.0)	12.0 (2.0)	0.27	13.0 (2.2)	12.8 (2.1)	0.35
AST	23.5 (9.0)	23.7 (10.1)	0.83	23.9 (8.0)	24.4 (11.9)	0.66
Bicarbonate	23.5 (9.0)	23.7 (10.1)	0.83	24.3 (2.4)	24.3 (2.4)	0.93
Calcium	9.8 (0.4)	9.9 (0.5)	0.2	9.9 (0.5)	9.8 (0.4)	0.1
Chloride	102.6 (2.6)	102.8 (2.4)	0.52	102.6 (2.3)	102.5 (2.5)	0.76
CK	122.1 (114.7)	118.2 (77.9)	0.72	129.5 (100.4)	120.3 (96.0)	0.39
Creatinine	1.0 (0.2)	1.0 (0.4)	0.96	1.0 (0.2)	0.9 (0.2)	0.4
eGFR CG	94.7 (34.0)	97.3 (36.4)	0.51	100.8 (31.5)	96.5 (31.3)	0.21
eGFR CKD-EPI	80.5 (19.8)	82.9 (21.4)	0.3	81.7 (17.4)	81.2 (17.7)	0.79
eGFR MDRD	75.1 (18.0)	77.3 (19.3)	0.28	76.5 (16.8)	75.4 (16.6)	0.55
Direct Bilirubin	0.1 (0.0)	0.1 (0.0)	0.68	0.1 (0.0)	0.1 (0.0)	0.19
Gamma GT	35.7 (41.5)	30.2 (26.2)	0.15	29.5 (30.2)	35.4 (48.2)	0.18
Glucose, Serum	104.5 (26.3)	105.9 (29.1)	0.65	102.2 (31.7)	102.0 (25.8)	0.94
Magnesium	1.8 (0.2)	1.8 (0.1)	0.83	1.8 (0.2)	1.8 (0.1)	0.99
Osmolality, Serum	288.2 (6.5)	288.0 (6.2)	0.74	288.7 (7.0)	287.5 (7.0)	0.12
Phosphate	3.5 (0.6)	3.6 (0.5)	0.18	3.6 (0.5)	3.5 (0.6)	0.61
Potassium	4.3 (0.5)	4.4 (0.5)	0.19	4.2 (0.4)	4.3 (0.4)	0.13
Sodium	139.5 (2.4)	139.7 (2.2)	0.46	139.9 (2.4)	139.5 (2.1)	0.19
Total Bilirubin	0.4 (0.2)	0.4 (0.2)	0.98	0.5 (0.3)	0.4 (0.2)	0.13
Total Protein	7.1 (0.4)	7.1 (0.4)	0.31	7.0 (0.4)	7.0 (0.4)	0.75
Urea (BUN)	16.4 (4.6)	16.7 (6.9)	0.64	16.7 (5.4)	16.0 (5.1)	0.23
Uric Acid	5.4 (1.5)	5.3 (1.4)	0.53	5.7 (1.4)	5.5 (1.5)	0.17

6.2.2 Trial BLI850-301

Table 28. Abnormal visit 2 values classified by being above or below normal range (Trial 301)

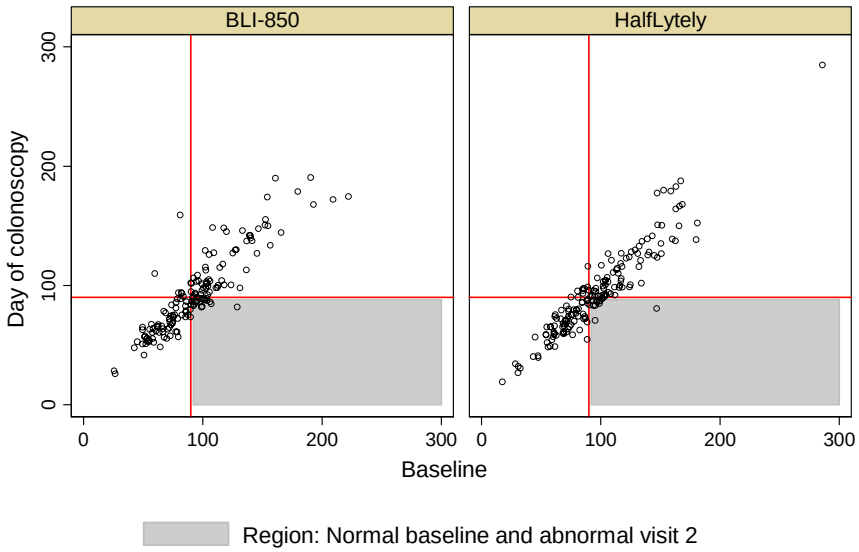
Laboratory Parameter	Below Normal Range		Above Normal Range	
	BLI-850 n/N (%)	HalfLytely n/N (%)	BLI-850 n/N (%)	HalfLytely n/N (%)
Albumin	0/152 (0.0)	0/164 (0.0)	7/152 (4.6)	9/164 (5.5)
ALP	0/153 (0.0)	3/162 (1.9)	0/153 (0.0)	2/162 (1.2)
ALT	0/148 (0.0)	0/161 (0.0)	8/148 (5.4)	5/161 (3.1)
Amylase	4/135 (3.0)	5/144 (3.5)	0/135 (0.0)	3/144 (2.1)
Anion Gap	0/155 (0.0)	2/170 (1.2)	5/155 (3.2)	8/170 (4.7)
AST	0/151 (0.0)	0/161 (0.0)	9/151 (6.0)	7/161 (4.3)
Bicarbonate	4/156 (2.6)	5/167 (3.0)	1/156 (0.6)	0/167 (0.0)
Calcium	0/139 (0.0)	0/139 (0.0)	12/139 (8.6)	5/139 (3.6)
Chloride	1/157 (0.6)	0/171 (0.0)	0/157 (0.0)	0/171 (0.0)
CK	0/138 (0.0)	1/151 (0.7)	10/138 (7.2)	6/151 (4.0)
Creatinine	0/145 (0.0)	0/155 (0.0)	3/145 (2.1)	4/155 (2.6)
eGFR CG	21/84 (25.0)	12/88 (13.6)	0/84 (0.0)	0/88 (0.0)
eGFR CKI-EPI	14/46 (30.4)	28/67 (41.8)	0/46 (0.0)	0/67 (0.0)
eGFR MDRD	9/29 (31.0)	18/40 (45.0)	0/29 (0.0)	0/40 (0.0)
Direct Bilirubin	0/157 (0.0)	0/167 (0.0)	14/157 (8.9)	18/167 (10.8)
Gamma GT	0/126 (0.0)	0/140 (0.0)	2/126 (1.6)	5/140 (3.6)
Glucose, Serum	0/146 (0.0)	1/156 (0.6)	10/146 (6.8)	4/156 (2.6)
Magnesium	1/158 (0.6)	1/169 (0.6)	0/158 (0.0)	0/169 (0.0)
Osmolality, Serum	2/139 (1.4)	1/153 (0.7)	3/139 (2.2)	8/153 (5.2)
Phosphate	0/155 (0.0)	0/168 (0.0)	2/155 (1.3)	2/168 (1.2)
Potassium	5/144 (3.5)	4/160 (2.5)	1/144 (0.7)	0/160 (0.0)
Sodium	0/157 (0.0)	0/169 (0.0)	1/157 (0.6)	0/169 (0.0)
Total Bilirubin	0/157 (0.0)	0/170 (0.0)	12/157 (7.6)	17/170 (10.0)
Total Protein	1/157 (0.6)	1/163 (0.6)	6/157 (3.8)	0/163 (0.0)
Urea (BUN)	17/147 (11.6)	17/152 (11.2)	0/147 (0.0)	0/152 (0.0)
Uric Acid	0/143 (0.0)	0/160 (0.0)	8/143 (5.6)	11/160 (6.9)

Figure 4. Scatterplot of visit 2 and baseline calcium values with normal range levels overlaid (301)



Lab: CALCIUM (mg/dL); Normal Range: 8.4 - 10.2
NOTE: points are jittered to reveal frequency

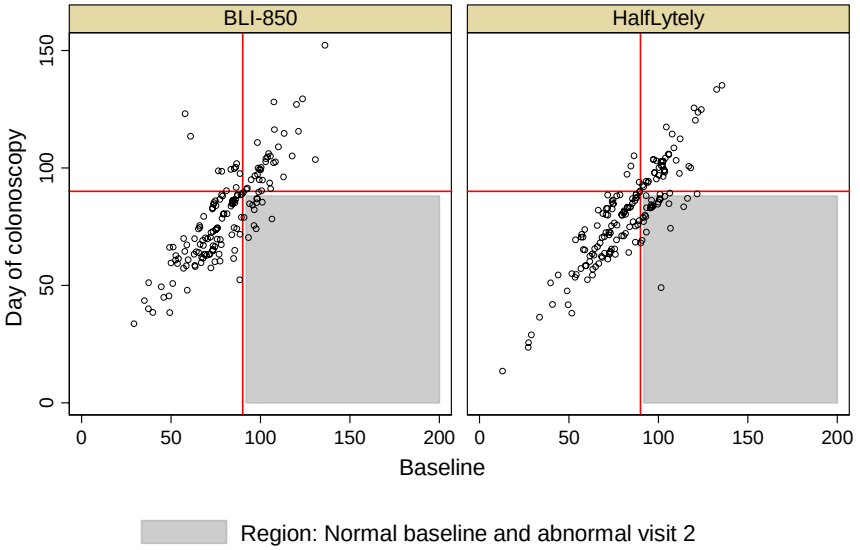
Figure 5. Scatterplot of visit 2 and baseline eGFR CG values with normal range levels overlaid (301)



Lab: eGFR CG; Normal Range: > 90
NOTE: points are jittered to reveal frequency

APPEARS THIS WAY ON ORIGINAL

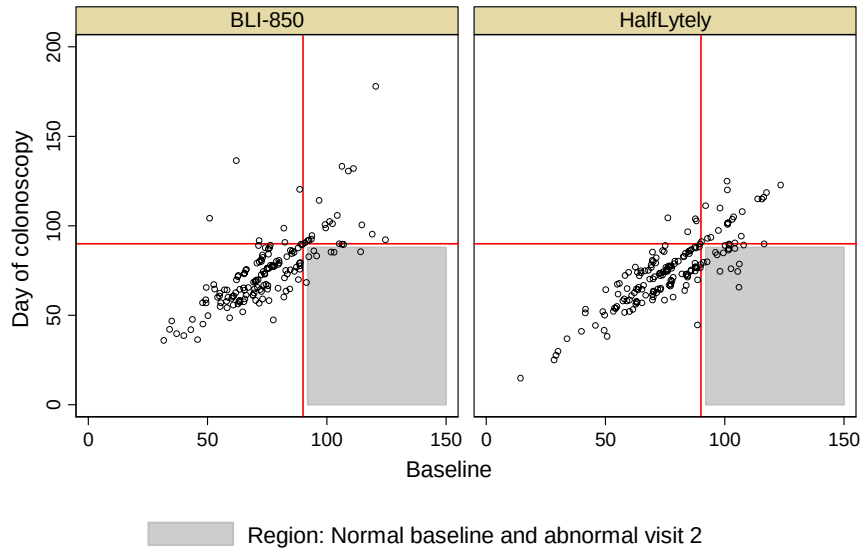
Figure 6. Scatterplot of visit 2 and baseline eGFR CKD-EPI values with normal range levels overlaid (301)



APPEARS THIS WAY ON ORIGINAL

Lab: eGFR CKD-EPI; Normal Range: > 90
NOTE: points are jittered to reveal frequency

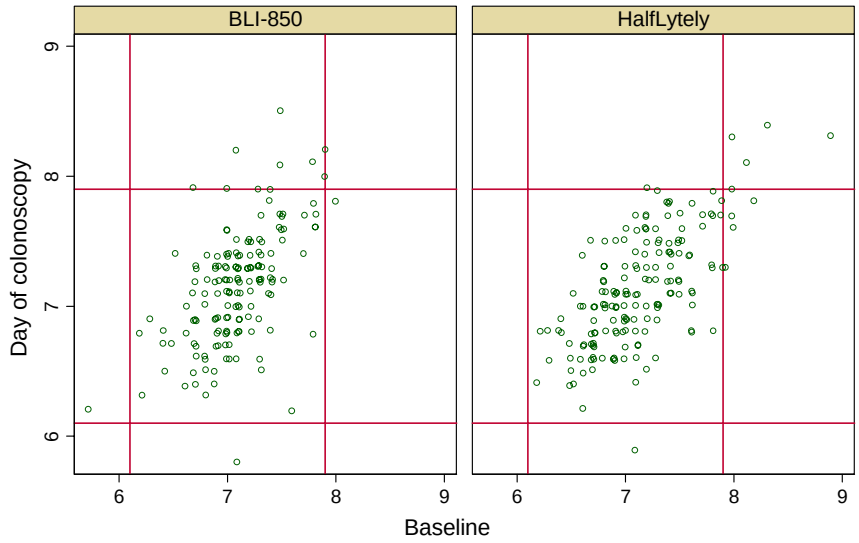
Figure 7. Scatterplot of visit 2 and baseline eGFR MDRD values with normal range levels overlaid (301)



APPEARS THIS WAY ON ORIGINAL

Lab: eGFR MDRD; Normal Range: > 90
NOTE: points are jittered to reveal frequency

Figure 8. Scatterplot of visit 2 and baseline total protein values with normal range levels overlaid (301)



Lab: TOTAL PROTEIN (g/dL); Normal Range: 6.1 - 7.9
NOTE: Points are jittered to reveal frequency

Table 29. Proportion of subjects with abnormal labs (normal baseline) by age (< 65, ≥ 65) (Trial 301)

	Age < 65 years		Age ≥ 65 years		
Laboratory Parameter	**BLI-850 n/N (%)**	**MoviPrep n/N (%)**	**BLI-850 n/N (%)**	**MoviPrep n/N (%)**	**p-value†**
ALBUMIN	5/111 (4.5)	8/124 (6.5)	2/41 (4.9)	1/40 (2.5)	0.44
ALP	0/115 (0.0)	4/122 (3.3)	0/38 (0.0)	1/40 (2.5)	-
ALT	8/109 (7.3)	4/120 (3.3)	0/39 (0.0)	1/41 (2.4)	-
AMYLASE	3/104 (2.9)	7/110 (6.4)	1/31 (3.2)	1/34 (2.9)	0.56
Anion Gap	5/117 (4.3)	9/129 (7.0)	0/38 (0.0)	1/41 (2.4)	-
AST	7/112 (6.3)	5/120 (4.2)	2/39 (5.1)	2/41 (4.9)	0.75
BICARBONATE	3/115 (2.6)	2/127 (1.6)	2/41 (4.9)	3/40 (7.5)	0.46
CALCIUM	11/108 (10.2)	3/103 (2.9)	1/31 (3.2)	2/36 (5.6)	0.18
CHLORIDE	1/118 (0.8)	0/129 (0.0)	0/39 (0.0)	0/42 (0.0)	-
CK	7/100 (7.0)	5/113 (4.4)	3/38 (7.9)	2/38 (5.3)	0.96
CREATININE	2/110 (1.8)	3/121 (2.5)	1/35 (2.9)	1/34 (2.9)	0.87
eGFR CG	17/78 (21.8)	10/82 (12.2)	4/6 (66.7)	2/6 (33.3)	0.60
eGFR CKD-EPI	14/46 (30.4)	24/62 (38.7)		4/5 (80.0)	-
eGFR MDRD	9/29 (31.0)	17/36 (47.2)		1/4 (25.0)	-
DIRECT BILIRUBIN	12/117 (10.3)	14/127 (11.0)	2/40 (5.0)	4/40 (10.0)	0.50
GLUCOSE, SERUM	8/110 (7.3)	3/117 (2.6)	2/36 (5.6)	2/39 (5.1)	0.42
Gamma GT	1/92 (1.1)	5/106 (4.7)	1/34 (2.9)	0/34 (0.0)	-
MAGNESIUM	0/117 (0.0)	1/129 (0.8)	1/41 (2.4)	0/40 (0.0)	-
OSMOLALITY,SERUM	3/108 (2.8)	7/119 (5.9)	2/31 (6.5)	2/34 (5.9)	0.48
PHOSPHATE	0/116 (0.0)	2/127 (1.6)	2/39 (5.1)	0/41 (0.0)	-
POTASSIUM	4/108 (3.7)	4/122 (3.3)	2/36 (5.6)	0/38 (0.0)	-
SODIUM	0/118 (0.0)	0/128 (0.0)	1/39 (2.6)	0/41 (0.0)	-
TOTAL BILIRUBIN	9/117 (7.7)	15/129 (11.6)	3/40 (7.5)	2/41 (4.9)	0.38
TOTAL PROTEIN	5/116 (4.3)	1/122 (0.8)	2/41 (4.9)	0/41 (0.0)	-
UREA (BUN)	15/112 (13.4)	14/119 (11.8)	2/35 (5.7)	3/33 (9.1)	0.53
URIC ACID	6/107 (5.6)	7/120 (5.8)	2/36 (5.6)	4/40 (10.0)	0.58

†- Test of treatment by subgroup interaction

Table 30. Proportion of subjects with abnormal labs (normal baseline) by sex (Trial 301)

	Females		Males		
Laboratory Parameter	**BLI-850 n/N (%)**	**MoviPrep n/N (%)**	**BLI-850 n/N (%)**	**MoviPrep n/N (%)**	**p-value†**
ALBUMIN	4/65 (6.2)	5/72 (6.9)	3/87 (3.4)	4/92 (4.3)	0.91
ALP	0/67 (0.0)	1/73 (1.4)	0/86 (0.0)	4/89 (4.5)	-
ALT	5/65 (7.7)	2/72 (2.8)	3/83 (3.6)	3/89 (3.4)	0.40
AMYLASE	2/60 (3.3)	3/59 (5.1)	2/75 (2.7)	5/85 (5.9)	0.76
Anion Gap	2/70 (2.9)	5/76 (6.6)	3/85 (3.5)	5/94 (5.3)	0.70
AST	4/69 (5.8)	3/73 (4.1)	5/82 (6.1)	4/88 (4.5)	0.96
BICARBONATE	1/71 (1.4)	3/75 (4.0)	4/85 (4.7)	2/92 (2.2)	0.20
CALCIUM	6/65 (9.2)	3/67 (4.5)	6/74 (8.1)	2/72 (2.8)	0.75
CHLORIDE	1/71 (1.4)	0/77 (0.0)	0/86 (0.0)	0/94 (0.0)	-
CK	6/62 (9.7)	3/63 (4.8)	4/76 (5.3)	4/88 (4.5)	0.55
CREATININE	1/66 (1.5)	2/68 (2.9)	2/79 (2.5)	2/87 (2.3)	0.63
eGFR CG	12/41 (29.3)	5/45 (11.1)	9/43 (20.9)	7/43 (16.3)	0.27
eGFR CKD-EPI	8/19 (42.1)	6/25 (24.0)	6/27 (22.2)	22/42 (52.4)	0.01
eGFR MDRD	3/9 (33.3)	6/19 (31.6)	6/20 (30.0)	12/21 (57.1)	0.26
DIRECT BILIRUBIN	10/70 (14.3)	12/75 (16.0)	4/87 (4.6)	6/92 (6.5)	0.77
GLUCOSE, SERUM	4/66 (6.1)	2/67 (3.0)	6/80 (7.5)	3/89 (3.4)	0.93
Gamma GT	0/60 (0.0)	1/69 (1.4)	2/66 (3.0)	4/71 (5.6)	-
MAGNESIUM	1/71 (1.4)	0/76 (0.0)	0/87 (0.0)	1/93 (1.1)	-
OSMOLALITY,SERUM	1/58 (1.7)	3/67 (4.5)	4/81 (4.9)	6/86 (7.0)	0.65
PHOSPHATE	2/68 (2.9)	1/74 (1.4)	0/87 (0.0)	1/94 (1.1)	-
POTASSIUM	2/66 (3.0)	1/72 (1.4)	4/78 (5.1)	3/88 (3.4)	0.80
SODIUM	1/71 (1.4)	0/76 (0.0)	0/86 (0.0)	0/93 (0.0)	-
TOTAL BILIRUBIN	8/70 (11.4)	10/76 (13.2)	4/87 (4.6)	7/94 (7.4)	0.67
TOTAL PROTEIN	4/70 (5.7)	1/75 (1.3)	3/87 (3.4)	0/88 (0.0)	-
UREA (BUN)	3/63 (4.8)	4/67 (6.0)	14/84 (16.7)	13/85 (15.3)	0.70
URIC ACID	2/68 (2.9)	1/76 (1.3)	6/75 (8.0)	10/84 (11.9)	0.35

†- Test of treatment by subgroup interaction

Table 31. Proportion of subjects with abnormal labs (normal baseline) by race (Non-White, White) (Trial 301)

	Non-White		White		
Laboratory Parameter	**BLI-850 n/N (%)**	**MoviPrep n/N (%)**	**BLI-850 n/N (%)**	**MoviPrep n/N (%)**	**p-value†**
ALBUMIN	1/31 (3.2)	0/41 (0.0)	6/121 (5.0)	9/123 (7.3)	-
ALP	0/31 (0.0)	0/40 (0.0)	0/122 (0.0)	5/122 (4.1)	-
ALT	3/30 (10.0)	1/39 (2.6)	5/118 (4.2)	4/122 (3.3)	0.39
AMYLASE	0/23 (0.0)	2/29 (6.9)	4/112 (3.6)	6/115 (5.2)	-
Anion Gap	1/31 (3.2)	1/42 (2.4)	4/124 (3.2)	9/128 (7.0)	0.47
AST	2/31 (6.5)	0/40 (0.0)	7/120 (5.8)	7/121 (5.8)	-
BICARBONATE	1/29 (3.4)	0/41 (0.0)	4/127 (3.1)	5/126 (4.0)	-
CALCIUM	1/27 (3.7)	2/34 (5.9)	11/112 (9.8)	3/105 (2.9)	0.21
CHLORIDE	0/31 (0.0)	0/42 (0.0)	1/126 (0.8)	0/129 (0.0)	-
CK	3/21 (14.3)	2/30 (6.7)	7/117 (6.0)	5/121 (4.1)	0.69
CREATININE	0/30 (0.0)	1/38 (2.6)	3/115 (2.6)	3/117 (2.6)	-
eGFR CG	1/24 (4.2)	3/28 (10.7)	20/60 (33.3)	9/60 (15.0)	0.11
eGFR CKD-EPI	1/15 (6.7)	12/25 (48.0)	13/31 (41.9)	16/42 (38.1)	0.02
eGFR MDRD	2/14 (14.3)	7/18 (38.9)	7/15 (46.7)	11/22 (50.0)	0.28
DIRECT BILIRUBIN	4/31 (12.9)	3/42 (7.1)	10/126 (7.9)	15/125 (12.0)	0.22
GLUCOSE, SERUM	2/28 (7.1)	0/35 (0.0)	8/118 (6.8)	5/121 (4.1)	-
Gamma GT	0/23 (0.0)	2/32 (6.3)	2/103 (1.9)	3/108 (2.8)	-
MAGNESIUM	0/31 (0.0)	1/41 (2.4)	1/127 (0.8)	0/128 (0.0)	-
OSMOLALITY,SERUM	2/24 (8.3)	2/40 (5.0)	3/115 (2.6)	7/113 (6.2)	0.25
PHOSPHATE	0/31 (0.0)	1/41 (2.4)	2/124 (1.6)	1/127 (0.8)	-
POTASSIUM	1/28 (3.6)	0/39 (0.0)	5/116 (4.3)	4/121 (3.3)	-
SODIUM	0/31 (0.0)	0/42 (0.0)	1/126 (0.8)	0/127 (0.0)	-
TOTAL BILIRUBIN	3/31 (9.7)	2/42 (4.8)	9/126 (7.1)	15/128 (11.7)	0.21
TOTAL PROTEIN	3/30 (10.0)	1/37 (2.7)	4/127 (3.1)	0/126 (0.0)	-
UREA (BUN)	12/31 (38.7)	7/36 (19.4)	5/116 (4.3)	10/116 (8.6)	0.03
URIC ACID	0/27 (0.0)	4/39 (10.3)	8/116 (6.9)	7/121 (5.8)	-

†- Test of treatment by subgroup interaction

Table 32. Proportion of subjects with abnormal labs (normal baseline) by High risk status (Trial 301)

	Non-high risk		High risk		
Laboratory Parameter	**BLI-850 n/N (%)**	**MoviPrep n/N (%)**	**BLI-850 n/N (%)**	**MoviPrep n/N (%)**	**p-value†**
ALBUMIN	4/87 (4.6)	6/91 (6.6)	3/65 (4.6)	3/73 (4.1)	0.64
ALP	0/88 (0.0)	3/90 (3.3)	0/65 (0.0)	2/72 (2.8)	-
ALT	3/87 (3.4)	3/90 (3.3)	5/61 (8.2)	2/71 (2.8)	0.36
AMYLASE	2/77 (2.6)	5/84 (6.0)	2/58 (3.4)	3/60 (5.0)	0.71
Anion Gap	4/88 (4.5)	9/96 (9.4)	1/67 (1.5)	1/74 (1.4)	0.57
AST	4/87 (4.6)	3/91 (3.3)	5/64 (7.8)	4/70 (5.7)	0.99
BICARBONATE	2/88 (2.3)	3/96 (3.1)	3/68 (4.4)	2/71 (2.8)	0.55
CALCIUM	5/80 (6.3)	2/80 (2.5)	7/59 (11.9)	3/59 (5.1)	0.98
CHLORIDE	1/91 (1.1)	0/96 (0.0)	0/66 (0.0)	0/75 (0.0)	-
CK	3/79 (3.8)	3/87 (3.4)	7/59 (11.9)	4/64 (6.3)	0.57
CREATININE	3/85 (3.5)	3/90 (3.3)	0/60 (0.0)	1/65 (1.5)	-
eGFR CG	12/50 (24.0)	11/51 (21.6)	9/34 (26.5)	1/37 (2.7)	0.04
eGFR CKD-EPI	8/28 (28.6)	18/41 (43.9)	6/18 (33.3)	10/26 (38.5)	0.59
eGFR MDRD	6/19 (31.6)	9/21 (42.9)	3/10 (30.0)	9/19 (47.4)	0.81
DIRECT BILIRUBIN	7/90 (7.8)	12/94 (12.8)	7/67 (10.4)	6/73 (8.2)	0.29
GLUCOSE, SERUM	5/87 (5.7)	2/95 (2.1)	5/59 (8.5)	3/61 (4.9)	0.69
Gamma GT	0/71 (0.0)	2/80 (2.5)	2/55 (3.6)	3/60 (5.0)	-
MAGNESIUM	0/90 (0.0)	1/96 (1.0)	1/68 (1.5)	0/73 (0.0)	-
OSMOLALITY,SERUM	3/81 (3.7)	6/91 (6.6)	2/58 (3.4)	3/62 (4.8)	0.83
PHOSPHATE	2/90 (2.2)	1/94 (1.1)	0/65 (0.0)	1/74 (1.4)	-
POTASSIUM	3/83 (3.6)	1/90 (1.1)	3/61 (4.9)	3/70 (4.3)	0.46
SODIUM	1/91 (1.1)	0/96 (0.0)	0/66 (0.0)	0/73 (0.0)	-
TOTAL BILIRUBIN	8/90 (8.9)	12/96 (12.5)	4/67 (6.0)	5/74 (6.8)	0.77
TOTAL PROTEIN	4/89 (4.5)	0/93 (0.0)	3/68 (4.4)	1/70 (1.4)	-
UREA (BUN)	11/88 (12.5)	10/87 (11.5)	6/59 (10.2)	7/65 (10.8)	0.83
URIC ACID	3/85 (3.5)	7/93 (7.5)	5/58 (8.6)	4/67 (6.0)	0.23

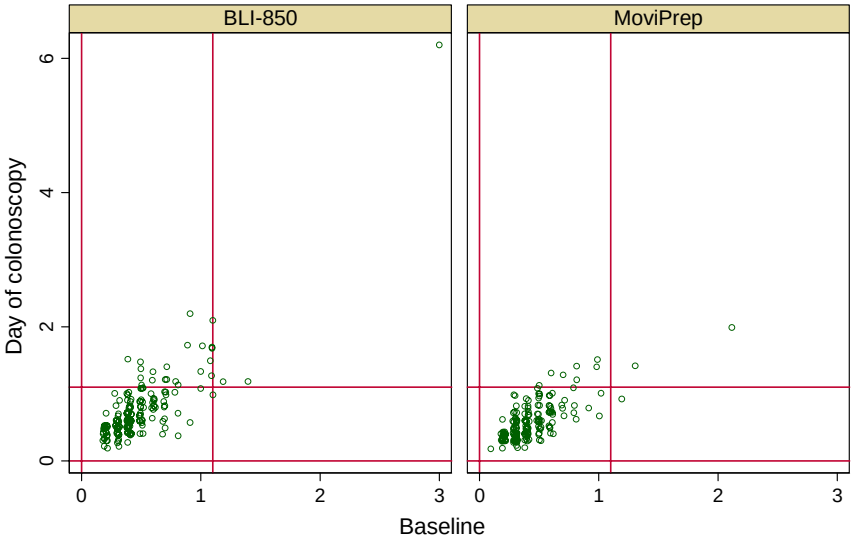
†- Test of treatment by subgroup interaction

6.2.3 Trial BLI850-302

Table 33. Abnormal visit 2 values classified by being above or below normal range (Trial 302)

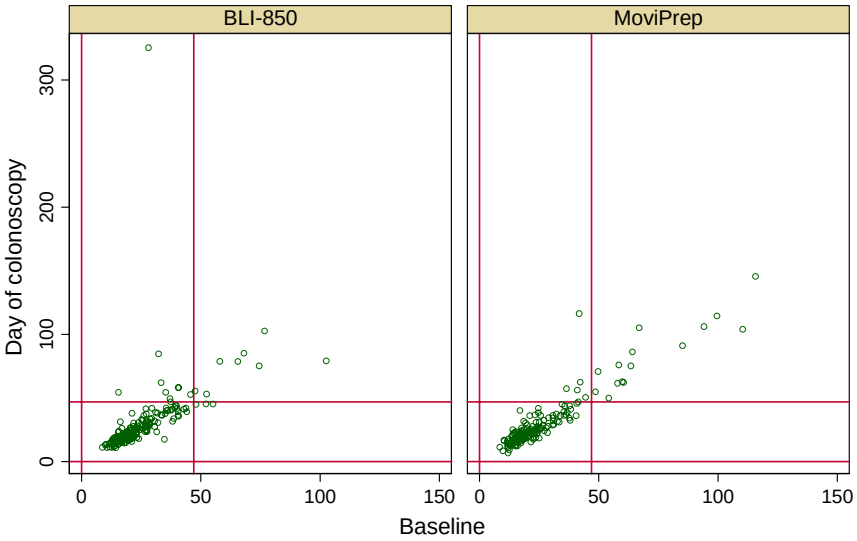
Laboratory Parameter	Below Normal Range		Above Normal Range	
	BLI-850 n/N (%)	MoviPrep n/N (%)	BLI-850 n/N (%)	MoviPrep n/N (%)
Albumin	0/164 (0.0)	0/159 (0.0)	12/164 (7.3)	6/159 (3.8)
ALP	0/166 (0.0)	0/162 (0.0)	1/166 (0.6)	1/162 (0.6)
ALT	0/162 (0.0)	0/150 (0.0)	10/162 (6.2)	5/150 (3.3)
Amylase	5/151 (3.3)	3/142 (2.1)	1/151 (0.7)	1/142 (0.7)
Anion Gap	2/166 (1.2)	0/155 (0.0)	17/166 (10.2)	12/155 (7.7)
AST	0/161 (0.0)	0/154 (0.0)	13/161 (8.1)	14/154 (9.1)
Bicarbonate	6/170 (3.5)	20/161 (12.4)	1/170 (0.6)	0/161 (0.0)
Calcium	0/141 (0.0)	0/144 (0.0)	6/141 (4.3)	7/144 (4.9)
Chloride	1/173 (0.6)	0/163 (0.0)	0/173 (0.0)	0/163 (0.0)
CK	0/147 (0.0)	0/143 (0.0)	10/147 (6.8)	7/143 (4.9)
Creatinine	0/167 (0.0)	0/153 (0.0)	2/167 (1.2)	1/153 (0.7)
eGFR CG	9/101 (8.9)	9/86 (10.5)	0/101 (0.0)	1/86 (1.2)
eGFR CKI-EPI	20/61 (32.8)	15/56 (26.8)	0/61 (0.0)	0/56 (0.0)
eGFR MDRD	16/32 (50.0)	10/28 (35.7)	0/32 (0.0)	0/28 (0.0)
Direct Bilirubin	0/169 (0.0)	0/163 (0.0)	16/169 (9.5)	10/163 (6.1)
Gamma GT	0/149 (0.0)	0/134 (0.0)	4/149 (2.7)	3/134 (2.2)
Glucose, Serum	3/160 (1.9)	3/150 (2.0)	3/160 (1.9)	5/150 (3.3)
Magnesium	0/169 (0.0)	1/163 (0.6)	0/169 (0.0)	1/163 (0.6)
Osmolality, Serum	3/151 (2.0)	3/145 (2.1)	6/151 (4.0)	12/145 (8.3)
Phosphate	5/171 (2.9)	2/160 (1.3)	1/171 (0.6)	2/160 (1.3)
Potassium	6/162 (3.7)	7/159 (4.4)	0/162 (0.0)	1/159 (0.6)
Sodium	1/169 (0.6)	1/163 (0.6)	0/169 (0.0)	0/163 (0.0)
Total Bilirubin	0/170 (0.0)	0/162 (0.0)	19/170 (11.2)	6/162 (3.7)
Total Protein	1/167 (0.6)	1/161 (0.6)	1/167 (0.6)	7/161 (4.3)
Urea (BUN)	21/162 (13.0)	14/153 (9.2)	1/162 (0.6)	1/153 (0.7)
Uric Acid	0/163 (0.0)	0/154 (0.0)	7/163 (4.3)	4/154 (2.6)

Figure 9. Scatterplot of visit 2 and baseline total bilirubin values with normal range levels overlaid (302)



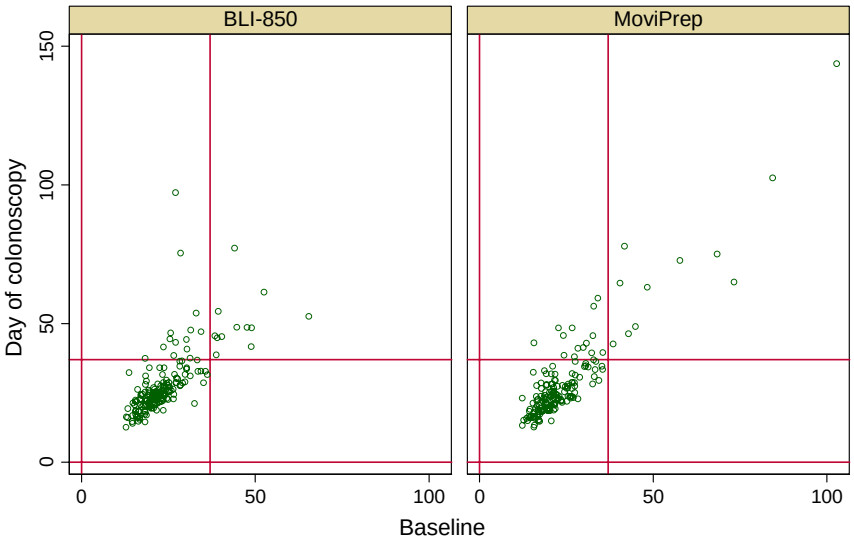
Lab: TOTAL BILIRUBIN (mg/dL); Normal Range: 0 - 1.1
NOTE: Points are jittered to reveal frequency

Figure 10. Scatterplot of visit 2 and baseline ALT values with normal range levels overlaid (302)



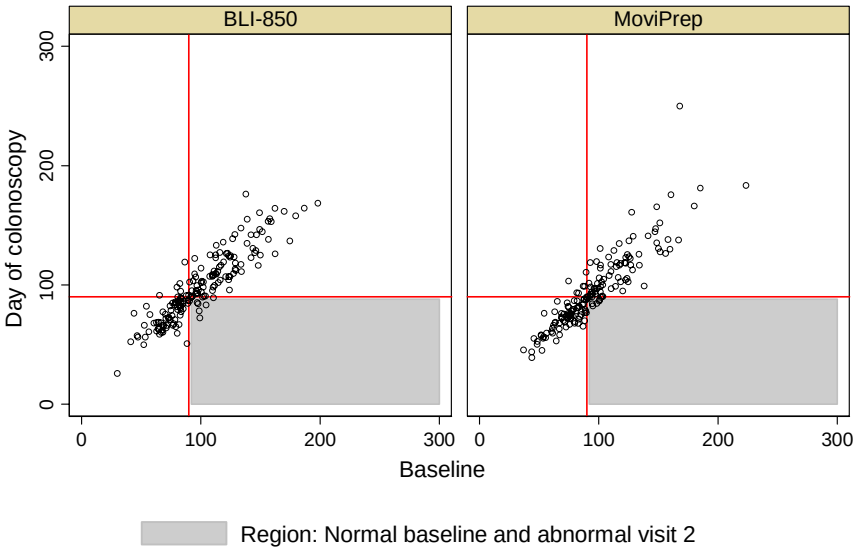
Lab: ALT (U/L); Normal Range: 0 - 47
NOTE: Points are jittered to reveal frequency

Figure 11. Scatterplot of visit 2 and baseline AST values with normal range levels overlaid (302)



Lab: AST (U/L); Normal Range: 0 - 37
NOTE: Points are jittered to reveal frequency

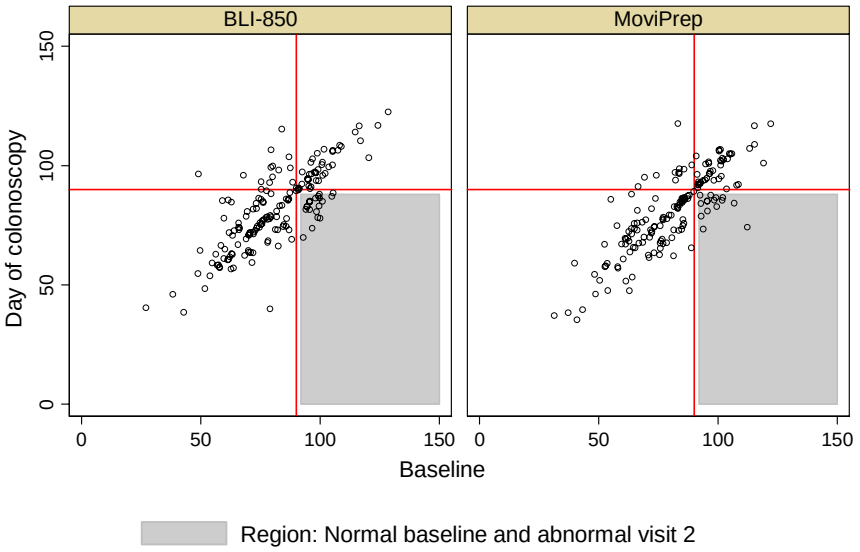
Figure 12. Scatterplot of visit 2 and baseline eGFR CG values with normal range levels overlaid (302)



APPEARS THIS WAY ON ORIGINAL

Lab: eGFR CG; Normal Range: > 90
NOTE: points are jittered to reveal frequency

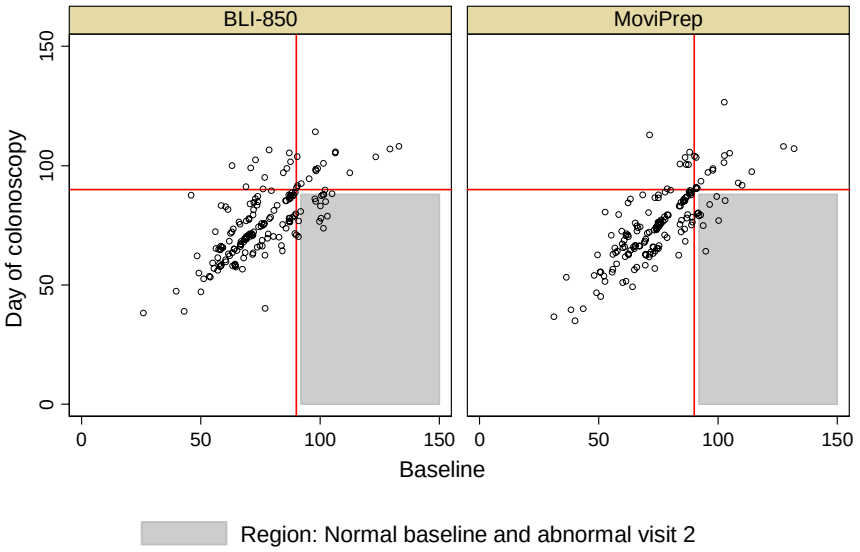
Figure 13. Scatterplot of visit 2 and baseline eGFR CKD-EPI values with normal range levels overlaid (302)



APPEARS THIS WAY ON ORIGINAL

Lab: eGFR CKD-EPI; Normal Range: > 90
NOTE: points are jittered to reveal frequency

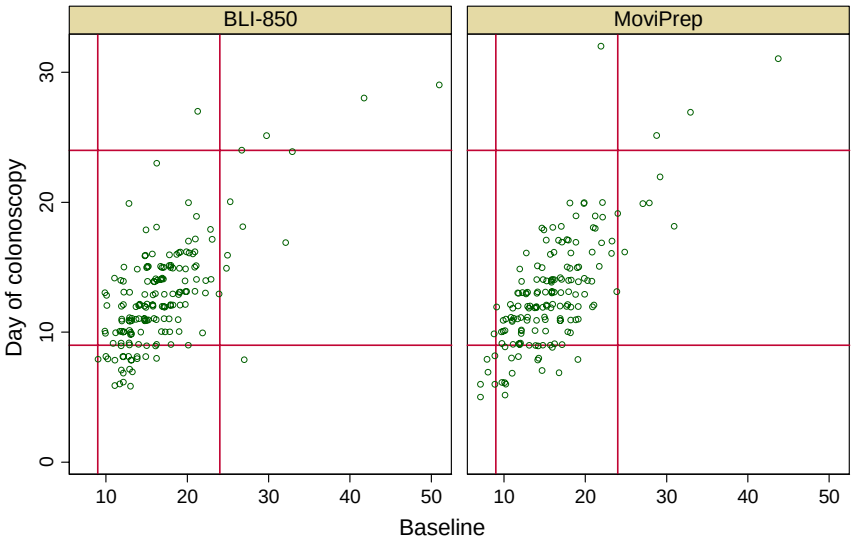
Figure 14. Scatterplot of visit 2 and baseline eGFR MDRD values with normal range levels overlaid (302)



APPEARS THIS WAY ON ORIGINAL

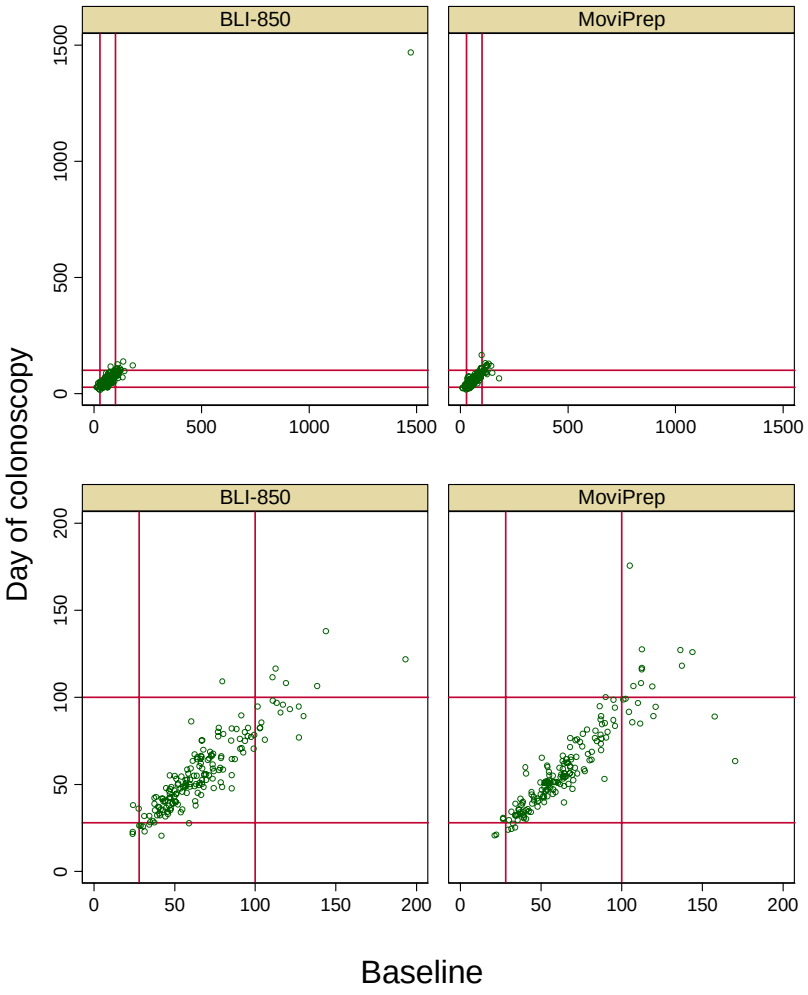
Lab: eGFR MDRD; Normal Range: > 90
NOTE: points are jittered to reveal frequency

Figure 15. Scatterplot of visit 2 and baseline urea (BUN) values with normal range levels overlaid (302)



Lab: UREA (BUN) (mg/dL); Normal Range: 9 - 24
NOTE: Points are jittered to reveal frequency

Figure 16. Scatterplot of visit 2 and baseline amylase values with normal range levels overlaid (302)



Lab: AMYLASE (U/L); Normal Range: 28 - 100
NOTE: points are jittered to reveal frequency

* Top panel-All subjects; Bottom panel-removed 1 subject in the BLI-850 with large value at baseline (and visit 2).

Table 34. Proportion of subjects with abnormal labs (normal baseline) by age (< 65, ≥ 65) (Trial 302)

	Age < 65 years		Age ≥ 65 years		
Laboratory Parameter	**BLI-850 n/N (%)**	**MoviPrep n/N (%)**	**BLI-850 n/N (%)**	**MoviPrep n/N (%)**	**p-value†**
ALBUMIN	10/127 (7.9)	5/118 (4.2)	2/37 (5.4)	1/41 (2.4)	0.90
ALP	1/130 (0.8)	1/117 (0.9)	0/36 (0.0)	0/45 (0.0)	-
ALT	9/125 (7.2)	4/105 (3.8)	1/37 (2.7)	1/45 (2.2)	0.76
AMYLASE	4/120 (3.3)	3/106 (2.8)	2/31 (6.5)	1/36 (2.8)	0.63
Anion Gap	13/129 (10.1)	7/115 (6.1)	6/37 (16.2)	5/40 (12.5)	0.76
AST	11/125 (8.8)	12/110 (10.9)	2/36 (5.6)	2/44 (4.5)	0.69
BICARBONATE	4/133 (3.0)	17/118 (14.4)	3/37 (8.1)	3/43 (7.0)	0.07
CALCIUM	6/114 (5.3)	5/111 (4.5)	0/27 (0.0)	2/33 (6.1)	-
CHLORIDE	1/136 (0.7)	0/119 (0.0)	0/37 (0.0)	0/44 (0.0)	-
CK	8/114 (7.0)	5/104 (4.8)	2/33 (6.1)	2/39 (5.1)	0.85
CREATININE	2/133 (1.5)	0/116 (0.0)	0/34 (0.0)	1/37 (2.7)	-
eGFR CG	8/94 (8.5)	10/78 (12.8)	1/7 (14.3)	0/8 (0.0)	-
eGFR CKD-EPI	20/57 (35.1)	14/52 (26.9)	0/4 (0.0)	1/4 (25.0)	-
eGFR MDRD	14/27 (51.9)	9/24 (37.5)	2/5 (40.0)	1/4 (25.0)	0.95
DIRECT BILIRUBIN	15/132 (11.4)	6/119 (5.0)	1/37 (2.7)	4/44 (9.1)	0.08
GLUCOSE, SERUM	3/127 (2.4)	6/110 (5.5)	3/33 (9.1)	2/40 (5.0)	0.20
Gamma GT	4/113 (3.5)	2/96 (2.1)	0/36 (0.0)	1/38 (2.6)	-
MAGNESIUM	0/132 (0.0)	0/119 (0.0)	0/37 (0.0)	2/44 (4.5)	-
OSMOLALITY,SERUM	7/123 (5.7)	10/111 (9.0)	2/28 (7.1)	5/34 (14.7)	0.76
PHOSPHATE	5/134 (3.7)	3/117 (2.6)	1/37 (2.7)	1/43 (2.3)	0.89
POTASSIUM	5/127 (3.9)	5/116 (4.3)	1/35 (2.9)	3/43 (7.0)	0.53
SODIUM	1/135 (0.7)	1/119 (0.8)	0/34 (0.0)	0/44 (0.0)	-
TOTAL BILIRUBIN	18/133 (13.5)	2/118 (1.7)	1/37 (2.7)	4/44 (9.1)	0.01
TOTAL PROTEIN	2/130 (1.5)	6/118 (5.1)	0/37 (0.0)	2/43 (4.7)	-
UREA (BUN)	20/130 (15.4)	14/114 (12.3)	2/32 (6.3)	1/39 (2.6)	0.61
URIC ACID	7/127 (5.5)	3/114 (2.6)	0/36 (0.0)	1/40 (2.5)	-

†- Test of treatment by subgroup interaction

Table 35. Proportion of subjects with abnormal labs (normal baseline) by sex (Trial 302)

	Females		Males		
Laboratory Parameter	**BLI-850 n/N (%)**	**MoviPrep n/N (%)**	**BLI-850 n/N (%)**	**MoviPrep n/N (%)**	**p-value†**
ALBUMIN	7/92 (7.6)	2/67 (3.0)	5/72 (6.9)	4/92 (4.3)	0.65
ALP	0/91 (0.0)	0/69 (0.0)	1/75 (1.3)	1/93 (1.1)	-
ALT	8/88 (9.1)	3/59 (5.1)	2/74 (2.7)	2/91 (2.2)	0.74
AMYLASE	4/83 (4.8)	1/58 (1.7)	2/68 (2.9)	3/84 (3.6)	0.39
Anion Gap	10/93 (10.8)	4/65 (6.2)	9/73 (12.3)	8/90 (8.9)	0.76
AST	8/89 (9.0)	7/63 (11.1)	5/72 (6.9)	7/91 (7.7)	0.88
BICARBONATE	3/95 (3.2)	8/67 (11.9)	4/75 (5.3)	12/94 (12.8)	0.61
CALCIUM	3/83 (3.6)	4/64 (6.3)	3/58 (5.2)	3/80 (3.8)	0.43
CHLORIDE	1/96 (1.0)	0/68 (0.0)	0/77 (0.0)	0/95 (0.0)	-
CK	5/80 (6.3)	2/54 (3.7)	5/67 (7.5)	5/89 (5.6)	0.82
CREATININE	2/95 (2.1)	1/67 (1.5)	0/72 (0.0)	0/86 (0.0)	-
eGFR CG	6/64 (9.4)	3/46 (6.5)	3/37 (8.1)	7/40 (17.5)	0.22
eGFR CKD-EPI	13/32 (40.6)	9/27 (33.3)	7/29 (24.1)	6/29 (20.7)	0.89
eGFR MDRD	9/13 (69.2)	5/14 (35.7)	7/19 (36.8)	5/14 (35.7)	0.22
DIRECT BILIRUBIN	12/93 (12.9)	8/67 (11.9)	4/76 (5.3)	2/96 (2.1)	0.39
GLUCOSE, SERUM	4/88 (4.5)	4/61 (6.6)	2/72 (2.8)	4/89 (4.5)	0.92
Gamma GT	0/82 (0.0)	1/58 (1.7)	4/67 (6.0)	2/76 (2.6)	-
MAGNESIUM	0/95 (0.0)	0/69 (0.0)	0/74 (0.0)	2/94 (2.1)	-
OSMOLALITY,SERUM	6/85 (7.1)	7/57 (12.3)	3/66 (4.5)	8/88 (9.1)	0.89
PHOSPHATE	3/95 (3.2)	3/65 (4.6)	3/76 (3.9)	1/95 (1.1)	0.22
POTASSIUM	1/89 (1.1)	0/67 (0.0)	5/73 (6.8)	8/92 (8.7)	0.00
SODIUM	1/95 (1.1)	0/68 (0.0)	0/74 (0.0)	1/95 (1.1)	-
TOTAL BILIRUBIN	15/94 (16.0)	5/66 (7.6)	4/76 (5.3)	1/96 (1.0)	0.51
TOTAL PROTEIN	1/94 (1.1)	3/68 (4.4)	1/73 (1.4)	5/93 (5.4)	0.98
UREA (BUN)	6/90 (6.7)	2/64 (3.1)	16/72 (22.2)	13/89 (14.6)	0.76
URIC ACID	2/92 (2.2)	3/68 (4.4)	5/71 (7.0)	1/86 (1.2)	0.07

†- Test of treatment by subgroup interaction

Table 36. Proportion of subjects with abnormal labs (normal baseline) by race (non-White, White) (Trial 302)

	Non-White		White		
Laboratory Parameter	**BLI-850 n/N (%)**	**MoviPrep n/N (%)**	**BLI-850 n/N (%)**	**MoviPrep n/N (%)**	**p-value†**
ALBUMIN	2/23 (8.7)	1/24 (4.2)	10/141 (7.1)	5/135 (3.7)	0.94
ALP	0/24 (0.0)	0/23 (0.0)	1/142 (0.7)	1/139 (0.7)	-
ALT	3/23 (13.0)	1/21 (4.8)	7/139 (5.0)	4/129 (3.1)	0.66
AMYLASE	0/16 (0.0)	0/20 (0.0)	6/135 (4.4)	4/122 (3.3)	-
Anion Gap	5/23 (21.7)	5/24 (20.8)	14/143 (9.8)	7/131 (5.3)	0.49
AST	1/22 (4.5)	3/24 (12.5)	12/139 (8.6)	11/130 (8.5)	0.38
BICARBONATE	1/24 (4.2)	5/24 (20.8)	6/146 (4.1)	15/137 (10.9)	0.55
CALCIUM	0/17 (0.0)	1/22 (4.5)	6/124 (4.8)	6/122 (4.9)	-
CHLORIDE	0/24 (0.0)	0/24 (0.0)	1/149 (0.7)	0/139 (0.0)	-
CK	2/18 (11.1)	0/18 (0.0)	8/129 (6.2)	7/125 (5.6)	-
CREATININE	1/24 (4.2)	0/22 (0.0)	1/143 (0.7)	1/131 (0.8)	-
eGFR CG	4/17 (23.5)	3/14 (21.4)	5/84 (6.0)	7/72 (9.7)	0.54
eGFR CKD-EPI	4/15 (26.7)	2/14 (14.3)	16/46 (34.8)	13/42 (31.0)	0.57
eGFR MDRD	4/10 (40.0)	2/8 (25.0)	12/22 (54.5)	8/20 (40.0)	0.93
DIRECT BILIRUBIN	2/23 (8.7)	1/24 (4.2)	14/146 (9.6)	9/139 (6.5)	0.79
GLUCOSE, SERUM	2/23 (8.7)	2/19 (10.5)	4/137 (2.9)	6/131 (4.6)	0.84
Gamma GT	2/17 (11.8)	0/18 (0.0)	2/132 (1.5)	3/116 (2.6)	-
MAGNESIUM	0/24 (0.0)	0/24 (0.0)	0/145 (0.0)	2/139 (1.4)	-
OSMOLALITY,SERUM	2/23 (8.7)	3/23 (13.0)	7/128 (5.5)	12/122 (9.8)	0.87
PHOSPHATE	0/23 (0.0)	1/24 (4.2)	6/148 (4.1)	3/136 (2.2)	-
POTASSIUM	1/21 (4.8)	1/23 (4.3)	5/141 (3.5)	7/136 (5.1)	0.76
SODIUM	0/24 (0.0)	0/24 (0.0)	1/145 (0.7)	1/139 (0.7)	-
TOTAL BILIRUBIN	2/24 (8.3)	1/24 (4.2)	17/146 (11.6)	5/138 (3.6)	0.71
TOTAL PROTEIN	0/22 (0.0)	3/22 (13.6)	2/145 (1.4)	5/139 (3.6)	-
UREA (BUN)	4/24 (16.7)	3/23 (13.0)	18/138 (13.0)	12/130 (9.2)	0.91
URIC ACID	1/22 (4.5)	1/23 (4.3)	6/141 (4.3)	3/131 (2.3)	0.71

†- Test of treatment by subgroup interaction

Table 37. Proportion of subjects with abnormal labs (normal baseline) by High risk status (Trial 302)

	Non-high risk		High risk		
Laboratory Parameter	**BLI-850 n/N (%)**	**MoviPrep n/N (%)**	**BLI-850 n/N (%)**	**MoviPrep n/N (%)**	**p-value†**
ALBUMIN	8/83 (9.6)	2/76 (2.6)	4/81 (4.9)	4/83 (4.8)	0.21
ALP	1/86 (1.2)	1/76 (1.3)	0/80 (0.0)	0/86 (0.0)	-
ALT	4/88 (4.5)	1/68 (1.5)	6/74 (8.1)	4/82 (4.9)	0.64
AMYLASE	3/80 (3.8)	2/68 (2.9)	3/71 (4.2)	2/74 (2.7)	0.87
Anion Gap	9/85 (10.6)	4/74 (5.4)	10/81 (12.3)	8/81 (9.9)	0.55
AST	3/85 (3.5)	6/73 (8.2)	10/76 (13.2)	8/81 (9.9)	0.17
BICARBONATE	3/88 (3.4)	12/76 (15.8)	4/82 (4.9)	8/85 (9.4)	0.29
CALCIUM	4/73 (5.5)	4/70 (5.7)	2/68 (2.9)	3/74 (4.1)	0.81
CHLORIDE	0/89 (0.0)	0/78 (0.0)	1/84 (1.2)	0/85 (0.0)	-
CK	6/83 (7.2)	4/68 (5.9)	4/64 (6.3)	3/75 (4.0)	0.81
CREATININE	0/88 (0.0)	1/78 (1.3)	2/79 (2.5)	0/75 (0.0)	-
eGFR CG	7/53 (13.2)	8/46 (17.4)	2/48 (4.2)	2/40 (5.0)	0.91
eGFR CKD-EPI	15/37 (40.5)	7/28 (25.0)	5/24 (20.8)	8/28 (28.6)	0.18
eGFR MDRD	8/18 (44.4)	4/16 (25.0)	8/14 (57.1)	6/12 (50.0)	0.59
DIRECT BILIRUBIN	8/87 (9.2)	3/77 (3.9)	8/82 (9.8)	7/86 (8.1)	0.42
GLUCOSE, SERUM	4/86 (4.7)	4/74 (5.4)	2/74 (2.7)	4/76 (5.3)	0.64
Gamma GT	4/82 (4.9)	1/63 (1.6)	0/67 (0.0)	2/71 (2.8)	-
MAGNESIUM	0/89 (0.0)	1/78 (1.3)	0/80 (0.0)	1/85 (1.2)	-
OSMOLALITY,SERUM	4/83 (4.8)	6/66 (9.1)	5/68 (7.4)	9/79 (11.4)	0.82
PHOSPHATE	3/88 (3.4)	3/75 (4.0)	3/83 (3.6)	1/85 (1.2)	0.36
POTASSIUM	3/85 (3.5)	3/77 (3.9)	3/77 (3.9)	5/82 (6.1)	0.74
SODIUM	0/87 (0.0)	0/78 (0.0)	1/82 (1.2)	1/85 (1.2)	-
TOTAL BILIRUBIN	10/86 (11.6)	1/77 (1.3)	9/84 (10.7)	5/85 (5.9)	0.17
TOTAL PROTEIN	2/85 (2.4)	2/77 (2.6)	0/82 (0.0)	6/84 (7.1)	-
UREA (BUN)	15/86 (17.4)	9/74 (12.2)	7/76 (9.2)	6/79 (7.6)	0.77
URIC ACID	5/86 (5.8)	1/77 (1.3)	2/77 (2.6)	3/77 (3.9)	0.17

†- Test of treatment by subgroup interaction

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/s/

BRADLEY W MCEVOY
09/12/2012

LAREE A TRACY
09/12/2012
I concur with this review.

ALOKA G CHAKRAVARTY
09/12/2012

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA/BLA Number: 203595 **Applicant:** BRAINTREE LABORATORIES, INC **Stamp Date:** December 16, 2011

Drug Name: (b) (4) (sodium sulfate, potassium sulfate and magnesium sulfate and PEG-3350 (b) (4) for oral solution) **NDA/BLA Type:** NDA Submission **Indication:** Cleansing of the colon as a preparation for colonoscopy in adults

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter for RTF	Yes	No	NA	Comments
1A	Paper Submission: Index is sufficient to locate necessary reports, tables, data, etc.	X			However, index for integrated statistical analysis results (ISS and ISE) are not correct.
1B	Electronic Submission: Indexing and reference links within the electronic submission are sufficient to permit navigation through the submission, including access to reports, tables, data, etc.			X	No Electronic Submission
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Efficacy was investigated for gender, racial, and geriatric subgroups investigated.	X			Sample size might be inadequate for subgroup analyses
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			However, define.pdf file did not provide enough information for this reviewer to really understand the variable meaning. In addition, No SAS programs for the primary and key secondary endpoints analyses were provided.

IS THE STATISTICAL SECTION OF THE APPLICATION IS FILEABLE ? Yes

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

Background

This New Drug Application is to support approval of (b) (4) a liquid and powder for oral administration intended for bowel cleansing prior to colonoscopy in adults.

(b) (4) is intended to provide an alternative to the Braintree product HalfLytely and Bisacodyl Tablet Bowel Prep Kit (HalfLytely). In particular the bisacodyl component of HalfLytely is replaced by a single dose of sulfate salts (about 22 grams). (b) (4) is intended as a colonic cleansing preparation for colonoscopy. Similar to HalfLytely, the preparation consists of two component steps: a 6 oz bottle of oral sulfate solution (OSS, containing about 22 grams sulfate salts) followed by 2L of a polyethylene glycol and electrolytes solution (PEGELS).

Review Issues

The two key issues identified are listed below:

- It is noted that the sponsor did not submit any justification to support the non-inferiority margin of 15%. Since the non-inferiority margin of 15% was not supported by the well-controlled historical studies conducted under conditions similar to those planned for the new trial as recommended by ICH E10, the non-inferiority margin of 15% is debatable and might not be acceptable.

- Since this is a single blinded study (one 5mg tablet versus two 5 mg tables), patients knew which drug was used for their bowel preparation. There was possibility for the investigators to be informed of the bowl preparation drug used by patients. Therefore, in reality, the single blinded trial had potential to be an open label trial.

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/s/

WEN JEN CHEN
02/17/2012

MICHAEL E WELCH
02/17/2012