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

CLINICAL STUDIES

NDA/BLA Serial Number:	202535
Drug Name:	PicoPrep (sodium picosulfate, magnesium oxide and citric acid) powder for oral solution
Indication(s):	Colon Cleansing in Preparation for Colonoscopy
Applicant:	Ferring Pharmaceuticals
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Table of Contents

1. EXECUTIVE SUMMARY

The Sponsor has submitted the results of two Phase 3, randomized, multicenter, assessor-blinded, active-control, non-inferiority studies to investigate the efficacy, safety and tolerability of PicoPrep split-dosing (Study FE2009-01) and PicoPrep day-before dosing (Study FE2009-02) in comparison to HalfLytely/Bisacodyl Tablets Bowel Prep Kit (10 mg, day-before dosing) for colon cleansing in preparation for colonoscopy in adult subjects.

From a statistical perspective, the data from the two phase 3 studies indicate that the PicoPrep split dose is superior to HalfLytely (10mg single dose) and that the PicoPrep single dose is non-inferior to HalfLytely (10 mg single dose) in colon cleansing in preparation for colonoscopy.

The primary analysis endpoint was the proportion of responders (rated excellent or good according to the Aronchick scale). For Study FE2009-01, the PicoPrep and HalfLytely responder rates were 84.2% and 74.9%, respectively and the 95% CI of the difference was (2.9%, 15.7%). For study FE2009-02, the PicoPrep and HalfLytely responder rates were 82.9% and 79.7%, respectively and the 95%CI of the difference was (-3.0%, 10.0%).

Several issues regarding subject disposition arose during the review of this submission. All the issues were conveyed to the Sponsor and were resolved. There were no major statistical review issues.

2. INTRODUCTION

A colonoscopy is a minimally invasive endoscopic examination of the colon. Colonoscopies may provide a visual diagnosis (e.g., ulceration, polyps) and allow the opportunity for biopsy and removal of suspected lesions. The success of a colonoscopy is dependent upon an empty bowel, which is essential for clear visualization of the colonic mucosa (including reaching the cecum) and completion of the colonoscopy. If a clear bowel is not achieved, the examination may need to be repeated; this creates a disruptive timing and rescheduling process for all: the patient, physician, and endoscopy staff. The Sponsor stated in their study report that prospective studies have reported that repeat colonoscopies due to the poor quality of bowel preparation are required in up to 6% of colonoscopy procedures. A more recent retrospective audit revealed a failure rate of 4.5%.

As identified in guidelines from the American Society of Colon and Rectal Surgeons (ASCRS), the American Society for Gastrointestinal Endoscopy (ASGE), and the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES), the measure of ideal or adequate preparation is defined as:

- Consistently and reliably emptying the colon of all fecal material rapidly with no gross or histological alteration of the colonic mucosa
- Not causing any subject discomfort or clinically relevant shifts in fluids or electrolytes
- Requiring a short period for ingestion and evacuation.

The Sponsor intends to establish efficacy, safety and tolerability of their drug, PicoPrep and to address all these needs.

The PicoPrep formulation contains the same 3 active ingredients (sodium picosulfate, magnesium oxide and citric acid) in the same milligram proportions as products sold for more than 3 decades under the trade names Picolax and Picosalax/Pico-Salax, also manufactured by Ferring. Picolax and Picosalax/Pico-Salax are currently approved for use and marketed in 10 countries including the United Kingdom (1980), Ireland (1983), Canada (2004), Malta (FE2009), Austria (2010), Czech Republic (2010), Denmark (2010), Germany (2010), Portugal (2010), and Norway (2010) and, although not yet marketed, has been approved in 23 additional countries.

2.1 Overview

The applicant has submitted two assessor-blind studies to demonstrate non-inferiority of PicoPrep to HalfLytely in overall colon cleansing in preparation for colonoscopy.

The study designs of the two trials were similar. The primary difference was that in Study FE2009-01 the subjects were to take the first pouch the day before and the second one the morning of the procedure (Split-Dose dosing). However, in Study FE2009-02 both pouches were to be used the day before the procedure.

Both trials were assessor-blinded and randomized. The applicant had planned for blinding of all persons involved in the conduct and evaluation of the studies, except the dispensing coordinator and subject, to mitigate possible bias. The HalfLytely/Bisacodyl Bowel Prep Kit (10 mg, day-before dosing) was selected as the active control. Placebo-controlled designs are neither practical nor ethical for these studies, as placebo subjects would potentially undergo a failed colonoscopy and need to repeat the procedure.

Table 1 shows a brief description of these two trials.

Table 1: Tabular Listing of Clinical Studies

Study ID	Study Design Overview	Objectives	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Treatment Duration
FE2009-01	Randomized, multicenter, assessor-blinded, parallel-group, active-control B/W "Split-Dose" PicoPrep versus HalfLytely for colon cleansing in preparation for colonoscopy	To demonstrate non-inferiority of PicoPrep to HalfLytely in overall colon cleansing in preparation for colonoscopy; to determine the efficacy of ascending colon cleansing in a non-inferiority fashion; and to evaluate the safety, tolerability, and satisfaction of the preparation	**PicoPrep:** **split-dose**, 1 dose over 2 days; Each dose = 2 pouches: the night before (first pouch) and between 5 and 9 hours prior to colonoscopy (second pouch) **HalfLytely/ Bisacodyl Tablets Bowel Prep Kit:** 1-day dosing; the day prior to colonoscopy two 5 mg bisacodyl tablets and 2 L HalfLytely	**PicoPrep:** Dosed: 305 Completed: 304 **HalfLytely:** Dosed: 298 Completed: 295	**PicoPrep:** 1 dose as 2 pouches over 2 days **HalfLytely:** 1-day dosing
FE2009-02	Randomized, multicenter, assessor-blinded, parallel-group, active-control B/W "Day-Before" PicoPrep versus HalfLytely for colon cleansing in preparation for colonoscopy	To demonstrate non-inferiority of PicoPrep to HalfLytely in overall colon cleansing in preparation for colonoscopy; to determine the efficacy of ascending colon cleansing in a non-inferiority fashion; and to evaluate the safety, tolerability, and satisfaction of the preparation	**PicoPrep:** **1-day dosing**; Each dose = 2 pouches: the day prior to colonoscopy in the afternoon (first pouch) and approximately 6 hours later (second pouch) **HalfLytely/Bisacodyl Tablets Bowel Prep Kit:** 1-day dosing; the day prior to colonoscopy two 5 mg bisacodyl tablets and 2 L HalfLytely	**PicoPrep:** Dosed: 296 Completed: 287 **HalfLytely:** Dosed: 302 Completed: 295	**PicoPrep:** 1-day dosing **HalfLytely:** 1-day dosing

2.2 Data Sources

This NDA was submitted in electronic format and is located at:
\\Cdsesub1\evsprod\NDA202535\202535.enx

Datasets used in both studies for the review purposes are labeled as: ADAE, ADDV, ADEX and ADFA under the Analysis Datasets subsection of the submission. These data sets were created in accordance with the CDISC ADAM data standards.

Material reviewed included the IND correspondence with the applicant during the IND stage, the study protocols and protocol amendments, statistical analysis plans, study reports, statistical methods, and protocol deviations.

3. STATISTICAL EVALUATION

Study FE2009-01 and Study FE2009-02 (hereafter referred to as Study 01 and Study 02) had the same objectives, same primary and secondary endpoints, same methods of randomization, and the same blinding and sample size calculations.

3.1 Evaluation of Efficacy

3.1.1 Study Design

Both trials had similar study design: PicoPrep (sodium picosulfate, magnesium oxide and citric acid) powder for oral solution consisted of 2 pouches of powder administered in a divided dose. PicoPrep was reconstituted by mixing the contents of a pouch in a cup with 5 ounces of cold water.

The only difference in study design was the PicoPrep dosing. In Study 01, the first pouch of PicoPrep was to be taken on day before colonoscopy procedure: between 5:00 PM and 9:00 PM; and the second pouch was to be used on the day of colonoscopy procedure, approximately 5 hours before but no more than 9 hours prior to the procedure.

However, in Study 02, both pouches were to be taken the day before procedure between 10:00 PM and 12:00 AM.

Both trials were phase 3 randomized, multicenter, assessor-blinded, active-control, non-inferiority (NI) studies investigating the efficacy, safety, and tolerability of PicoPrep versus HalfLytely for colon cleansing in preparation for colonoscopy in adult subjects. See study flow charts in Appendix.

Subjects who were candidates for participation in the study were screened for inclusion/exclusion criteria before enrollment into the study. The subject's eligibility was documented in the subject's CRF. Screening evaluations were to have been performed within 21 days prior to study enrollment and randomization.

Subjects requiring an elective complete colonoscopy were screened for inclusion in the study at Visit 1. Those subjects who fulfilled all inclusion and no exclusion criteria were randomized at Visit 2. Only the site's designated unblinded coordinator knew the subject's randomized treatment group. The unblinded coordinator instructed the subject on the use of the bowel preparation and gave the subject a diary card that provided dosing instructions and space to record whether the subject completed dosing requirements. All subjects were limited to a clear liquid diet only. All assessments were performed at Visit 3 (day of colonoscopy). Subjects returned to the investigative site for 3 follow-up visits: within 24 to 48 hours (Visit 4), in 7 days (Visit 5), and in 4 weeks (Visit 6) after the colonoscopy procedure.

Subjects were randomly assigned to 1 of the 2 preparations (PicoPrep or HalfLytely) at Visit 2. Following the administration of PicoPrep, subjects were to consume five (5) 8-ounce glasses of clear liquids of their choice over the next few hours. Subjects were to consume three (3) 8-ounce glasses of clear liquids before the colonoscopy.

Subjects randomized to the HalfLytely treatment group were instructed to begin their treatment (following the approved label instructions) by taking two 5 mg bisacodyl tablets in the afternoon on the day before colonoscopy, and then after the first bowel movement or after 6 hours, whichever occurred first, to drink the 2 L of HalfLytely solution at a rate of one 8-ounce glass every 10 minutes. The HalfLytely treatment group was required to complete treatment on the day before the colonoscopy.

It was planned that a sufficient number of subjects would be screened to ensure up to 600 randomized subjects (~300 subjects to each treatment group). Subjects were free to withdraw from the study at any time for any reason. Subjects could have been withdrawn from the study for the following reasons:

- The subject requested to discontinue participation in the study,
- The subject was unwilling or unable to comply with the protocol,
- The subject experienced an adverse event (AE) resulting in withdrawal,
- The Investigator or Sponsor requested the subject's withdrawal, or
- The subject developed a condition that, according to the exclusion criteria, would have prevented him/her from original entry to the study.

Subjects who discontinued from the study were not replaced.

Study 01 was conducted at 10 investigative sites in the United States (US). The first subject's first visit occurred on 10 May 2010 and the last subject completed the last visit on 12 October 2010.

Study 02 was conducted at 12 investigative sites in the United States (US). The first subject's first visit occurred on 10 May 2010 and the last subject completed the last visit on 18 October 2010.

Reviewer's Comment:
The statistical reviewer of the IND had brought up the weakness of choosing a 10 mg dosage for the active comparator and had recommended the sponsor to use the 20 mg dosage instead; nonetheless, the sponsor used the 10 mg dosage in the study.

3.1.2 Objectives

The primary objective of both studies was:

- To demonstrate non-inferiority or superiority of PicoPrep to HalfLytely in overall colon cleansing in preparation for colonoscopy

The secondary objectives of the study were:

- To demonstrate the efficacy of ascending colon cleansing in a non-inferiority fashion.
- To determine tolerability and satisfaction of the preparation, as assessed by a standardized subject questionnaire administered at the study site before colonoscopy.
- To evaluate safety and tolerability through the collection of adverse events, clinical laboratory tests, and physical examination.

3.1.3 Randomization

Randomization numbers were allocated sequentially to the subjects at each site by an Interactive Voice Response System (IVRS). Subjects were assigned numbers in the order in which they were enrolled. If a treatment kit to correspond with treatment assignment by IVRS was not available at the site for a subject, the unblinded coordinator provided an available kit (i.e., manually randomized the subject) and instructed the subject to administer the treatment according to the corresponding treatment instructions. Eight subjects were manually randomized in this study.

3.1.4 Blinding

Only the subject and the site's designated unblinded coordinator knew the treatment group to which that subject was randomized; the designated unblinded coordinator instructed the subject in use of the bowel preparation and maintained the drug accountability binder that recorded study drug assignments. Both the unblinded coordinator and the subject signed a non-disclosure affidavit form designed to prevent both from disclosing which bowel preparation treatment the subject used. Treatment was blinded to the colonoscopist who assessed the efficacy of the 2 tested preparations and all of their assistants.

In case of a serious, unexpected or other important adverse event, an individual subject's treatment could be unblinded by opening a decoding envelope for that subject. The reason for any blind break, the date, and by whom the blind was broken were to be recorded in the CRF.

3.1.5 Endpoints

The primary analysis variable was:
The proportion of subjects classified as responders (success) where a responder was a subject with a rating of "Excellent" or "Good" according to the Aronchick Scale at Visit 3 during colonoscopy.

The primary endpoint was assessed by a blinded colonoscopist, using the Aronchick Scale. Efficacy of ascending colon cleansing was measured by the blinded colonoscopist using the Ottawa Scale.

The blinded colonoscopist performed the primary efficacy assessment of overall colon cleansing, using the Aronchick Scale. Cleanliness was reported by describing the overall preparation of the colon, assigning a grade of excellent, good, fair, or inadequate, according to the definitions given in the table below.

Table 2: Aronchick Scale*

Grade	Description
Excellent	>90% of mucosa seen, mostly liquid stool, minimal suctioning needed for adequate visualization
Good	>90% of mucosa seen, mostly liquid stool, significant suctioning needed for adequate visualization
Fair	>90% of mucosa seen, mixture of liquid and semisolid stool, could be suctioned and/or washed
Inadequate	<90% of mucosa seen, mixture of semisolid and solid stool which could not be suctioned or washed

*The Aronchick Scale is universally accepted and has been used in pivotal trials that lead to new drug application (NDA) approvals, including the approval of HalfLytely.
Source: Sponsor's Submission

For the purpose of analysis, a subject was considered a responder following administration of the preparation if overall colon cleansing was rated as excellent or good on this 4-point scale.

The colonoscopist also recorded in the CRF whether the colonoscopy was completed. If the colonoscopy was not completed, the reason and whether a repeat was required were to be recorded. The Aronchick Scale is universally accepted and has been used in pivotal trials that lead to new drug application (NDA) approvals, including the approval of HalfLytely.

The two secondary variables were:

1. The proportion of subjects classified as responders (success) where a responder was a subject with a rating of Excellent, Good, or Fair according to the Ottawa Scale at Visit 3 during colonoscopy. (Key secondary endpoint)

2. Tolerability and satisfaction of the preparation, as measured by a standardized subject questionnaire administered on the day of colonoscopy and prior to the procedure.

The blinded colonoscopist performed the key secondary efficacy assessment of ascending colon cleansing, using the Ottawa Scale. Cleanliness was reported by assigning a score of 0, 1, 2, 3, or 4 according to the definitions in the table below. For the purpose of analysis, a subject was considered a clinical success following the preparation, if ascending colon cleansing was scored 0, 1, or 2 (excellent, good, or fair) on this 5-point scale. In addition, cleanliness of both the mid (transverse, descending) colon and the descending (recto-sigmoid) colon was evaluated using the Ottawa Scale.

Table 3: Ottawa Scale*

Grade	Description
0	**Excellent:** Mucosal detail clearly visible. If fluid is present, it is clear. Almost no stool residue
1	**Good:** Some turbid fluid or stool residue but mucosal detail still visible. Washing and suctioning not necessary
2	**Fair:** Turbid fluid or stool residue obscuring mucosal detail. However, mucosal detail becomes visible with suctioning. Washing not necessary.
3	**Poor:** Presence of stool obscuring mucosal detail and contour. However, with suctioning and washing, a reasonable view is obtained.
4	**Inadequate:** Solid stool obscuring mucosal detail and contour despite aggressive washing and suctioning.

*The Ottawa Scale is a validated scale for the assessment of bowel preparation quality and it demonstrated high inter-observer agreement and reliability.
Source: Sponsor's Submission

The key secondary endpoint will be the only secondary endpoint discussed in this review.

3.1.6 Populations (Analysis Sets)

The analysis sets for the studies included the following:

1. Intent-to-treat Analysis Set (Full Analysis Set, ITT): All randomized subjects who received any study treatment.

2. Modified Intent-to-treat Analysis Set (mITT): All randomized subjects who received any study treatment and produced an efficacy assessment based on the Aronchick or Ottawa scales. (Data set labeled ADFA submitted by the sponsor).

3. Per-Protocol Analysis Set (PP): Subjects who had major protocol violations, including not taking study drug in the prescribed time intervals, were excluded from the PP analysis set. Subjects to be excluded from the PP analysis set were identified prior to breaking the study blind. Treatment assignment for summary and analysis was according to randomization.

4. Safety Analysis Set: All subjects who received any study treatment were included in the Safety analysis data set. Treatment assignment for summary and analysis was based on actual treatment.

Reviewer's Comment:
Two subjects in the HalfLytely arm for Study 01 did not have recorded efficacy data and were imputed as treatment failures in the sponsor's efficacy (ITT) data set. The reviewer's principal analyses were based on a data set ADFA which did not have these two subjects. Regardless, there were no differences in the efficacy conclusions between the sponsors ITT or ADFA data sets.

The applicant has defined the Per Protocol Analysis Set as subjects who had major protocol violations, including not taking study drug in the prescribed time intervals, were excluded from the PP analysis set.

Subjects to be excluded from the PP analysis set were identified prior to breaking the study blind. Treatment assignment for summary and analysis was according to randomization.

3.1.7 Sample Size Calculations

In the Protocol, the applicant has stated that they have used the historical references to construct the anticipated responder rate of 85%. Based on the similarity of the current trial designs to that of historical studies, assuming that there is high likelihood that the current effect of the active control will be similar to the past (constancy assumption).

To determine the entire effect of the active control assumed to be present in this study (M1), the anticipated placebo response rate of 15% (range 0% - 15%) was utilized, based on the Statistical Review and Evaluation of the HalfLytely 20 mg/2L Tablets. This estimates the M1 component of this study to be 70% (85% – 15%).

Typically, the value of M2, the largest clinically acceptable difference of the test drug compared to the active control is computed by taking a fraction of M1. One common approach to determine M2 is to take one-half of the M1 interval, which, in this case, would be unacceptably high - 30% (0.5 x 70) because of high treatment effect and low placebo response. However, the NI margin (M2) of 9% will be used for this study, primarily based on clinical judgment, as well as historical precedent with recently conducted phase 3 program that led to the approval of OsmoPrep®, using 10% NI margin Statistical Review, NDA 21-892).

The sample size was determined assuming an estimated responder rate of 85% for both the PicoPrep and HalfLytely treated subjects, a 9.0% NI margin, 85% power, and a one-sided significance level of 0.025. Based on these assumptions, and using StatXact, Version 6.2 from Cytel Software Corp., the applicant determined that 287 subjects are required for each treatment group. To allow for departure in these assumptions a total of approximately 600 subjects (~300 for each treatment group) were recruited into this study.

The historical data the sponsor used to calculate the non-inferiority margin are listed in Table 4 below.

Table 4: Historical Data Sponsor Used To Calculate the Non-Inferiority Margin

Study	Study Design (Principal Trials)	Comparator	Primary Efficacy	Overall Response Rate	Non-Inferiority Margin
NDA 21-892 Review (OsmoPrep®)	Randomized, Investigator Blinded, non-inferiority n = 704	Visicol®	Overall colon cleansing (treatment success – cleansing response of excellent and good on 4-point scale)	94%	10%
NDA 21-551 Review (HalfLytely®) Published: J.A. DiPalma et al, Am J Gastroenterology 2003;98:2187-2191	Two Randomized Single-Blind, Investigator Unaware, Parallel, 2 arms studies n=200/study	NuLytely®	Overall colon cleansing successful vs. unsuccessful (successful = cleansing response of excellent and good on 4-point scale)	90% NuLytely® 86% HalfLytely®	16% as accessed by FDA Medical Reviewer
A. Navarro, P. T. Hession, Efficacy and Tolerability of Sodium Picosulphate/ Magnesium Citrate as a Bowel-cleansing Agent – Results from Literature Review, European Gastroenterology and Hepatol Review, Jul 2009	Review of 14 studies N= 792	Various Comparators	Overall Colon Cleansing, (Proportion of patients with at least adequate bowel cleansing)	Responder Rate for Colonoscopy 82%	N/A

Reviewer's Comment:
The statistical reviewer of the IND had suggested a NI margin of 4% based on allowing a 5% relative decrease from the control, if that was more acceptable from a clinical standpoint. Regardless, the sponsor still chose a 9% NI margin.

3.1.8 Statistical Methodologies

A non-inferiority analysis was performed by comparing the proportion of responders in the PicoPrep minus the proportion of responders in the HalfLytely preparation. The sponsor assessed the non-inferiority of PicoPrep to HalfLytely in the ITT population by constructing a 97.5% one-sided confidence interval (CI) for the difference in success rates (PicoPrep minus HalfLytely). If the lower confidence bound (LCB) exceeded -9.0%, PicoPrep was to be declared non-inferior to HalfLytely. If the non-inferiority criteria were satisfied, a test of superiority was to be performed within the same population. PicoPrep was to be declared superior to HalfLytely if the LCB exceeded 0.

The Sponsor and the reviewer used similar SAS code to obtain the 1-sided 97.5% CI (or 2-sided 95% CI):

Sponsor's code:

```
proc freq order=data;
tables treat*outcome /riskdiff alpha=.05;
weight count;
```

Reviewer's code:

proc freq data=efficacy dataset;
tables treat*primary endpoint variable/chisq riskdiff alpha=.05;

By default, the RISKDIFF option provides standard Wald asymptotic confidence limits for the risks (row 1, row 2 and overall) and the risk difference.

The SAS code provides the 95% 2-sided confidence interval for the difference in proportions. The lower limit of 95% 2-sided confidence interval produced by SAS is equivalent to the lower limit of the 97.5% 1-sided confidence interval of interest. The reviewer also used StatXact, V9.2 to produce the two-sided confidence intervals for the difference in proportions.

3.1.9 Changes to the Statistical Analysis Plan

The original protocol, dated 21 April 2010 was amended. Initially, an analysis on the primary variable using logistic regression with treatment, investigative site, and site-by-treatment in the model was planned to study the effect of site on the primary variable for the ITT data set. Instead, the Breslow-Day test was applied to test the homogeneity (or alikeness) of the chance of the observed positive treatment effect response of PicoPrep versus HalfLytely when compared across the investigative sites. No imputation of missing data was done.

Although major protocol deviations were to be summarized by category of violation and by frequency and percentage, only a listing of protocol deviations was provided. This information is provided in the Appendix

3.1.10 Patient Disposition

In Study 01, six hundred randomized subjects (300 subjects to each treatment group) were planned. A total of 608 subjects were randomized, 5 of whom (2 in PicoPrep and 3 in HalfLytely) were not treated. Of the 603 treated subjects; 305 subjects received PICOPREP and 298 subjects received HalfLytely. Of these, 304 (99.7%) PICOPREP subjects and 295 (99.0%) HalfLytely subjects completed the study.

Table 5: Study 01 – Subject Disposition

	Treatment Group		
	PICOPREP	HalfLytely	Total
Total randomized	307	301	608
Not treated	2	3	5
Withdrawal by subject	2	2	4
Lost to follow-up	0	1	1
Total treated	305	298	603
Total completed, n (%)	304 (99.7)	295 (99.0)	599 (99.3)
Total discontinuations, n (%)	1 (0.3)	3 (1.0)	4 (0.7)
Withdrawal by subject	1 (0.3)	0	1 (0.2)
Adverse event	0	1 (0.3)	1 (0.2)
Noncompliance with study drug	0	1 (0.3)	1 (0.2)
Other[a]	0	1 (0.3)	1 (0.2)

Note: Two subjects were identified for whom actual treatment received differed from randomized, planned treatment group assignment: PicoPrep Subject 110-021 and HalfLytely Subject 110-002; these 2 subjects were assessed under the planned group assignment in the ITT analysis set and were excluded from the PP analysis set.
a. Other: HalfLytely Subject 104-038: inadequate prep, unable to do procedure
Source: Sponsor's Table 7 -1, Page 41 of 80

In Study 02 a total of 598 subjects were enrolled and treated; 296 subjects were assigned to receive PICOPREP and 302 subjects were assigned to receive HalfLytely. Of these subjects, 287 of 296 (97.0%) PICOPREP subjects and 295 of 302 (97.7%) HalfLytely subjects completed the study. A total of 16 subjects discontinued the study; 5 subjects were randomized manually, 2 to PICOPREP and 3 to HalfLytely. Five randomized subjects (4 PICOPREP, 1 HalfLytely) were not treated and were excluded from all analyses.

Table 6: Study 02 – Subject Disposition

	Treatment Group		
	PICOPREP	HalfLytely	Total
Total randomized	300	303	603
Not treated (including incomplete preparation)	4	1	5
Withdrawal by subject	3	1	4
Other: could not tolerate prep	1	0	1
Total treated	296	302	598
Total completed, n (%)	287 (97.0)	295 (97.7)	582 (97.3)
Total discontinuations, n (%)	9 (3.0)	7 (2.3)	16 (2.7)
Withdrawal by subject	5 (1.7)	1 (0.3)	6 (1.0)
Protocol violation[a]	2 (0.7)	1 (0.3)	3 (0.5)
Adverse event	1 (0.3)	1 (0.3)	2 (0.3)
Lost to follow-up	0	2 (0.7)	2 (0.3)
Other[b]	1 (0.3)	2 (0.7)	3 (0.5)

a. Protocol violation: PicoPrep Subject 202-042: scope incomplete due to poor quality of the prep; PicoPrep Subject 212-048: patient could not return to site for Visits 4 and 5; HalfLytely Subject 211-039: prep did not work.
b. Other: PicoPrep Subject 202-039: Visit 3 colonoscopy could not be performed due to power outage at site; HalfLytely Subject 207-036: subject forgot; HalfLytely Subject 210-049: unable to return for Visit 6
Source: Sponsor's Table 7 -1, Page 41 of 81

In both Study 01 and Study 02, there were discrepancies in the number of subject-discontinuations between Table 7-1 (see above tables) in the study report and Table 14.1.1 under Subject Disposition of the "demographic" file.

Discrepancies are as follows:

Table 7: Study 01 – Discrepancies in Sponsor's Tables

	Table 7-1 Study Report			Table 14.1.1 Subject Disposition		
	PicoPrep	HalfLytely	Total	PicoPrep	HalfLytely	Total
Discontinuation or Withdrawal from the Study	2	3	5	6	8	14

Table 8: Study 02 - Discrepancies in Sponsor's Tables

	Table 7-1 Study Report			Table 14.1.1 Subject Disposition		
	PicoPrep	HalfLytely	Total	PicoPrep	HalfLytely	Total
Discontinuation or Withdrawal from the Study	14	8	22	21	10	31

Reviewer's Comment:
As it is shown in Tables 7 and 8 there was a total count of 9 subjects discrepant in each study. These discrepancies were communicated to the sponsor. The sponsor explained that the discrepancies are due to randomized subjects who never received study drug; and that these subjects were analyzed in the Integrated Summary of Efficacy and Safety (ISE and ISS).

In addition to the issues mentioned above, there were five untreated subjects in each of the studies whom the sponsor had not presented in the data listing; however, the sponsor classified these untreated subjects as treatment failures in the "All Randomized Subjects" analysis set.

3.1.11 Patient Demographic and Baseline Characteristics

The study population consisted of adults who were undergoing diagnostic or therapeutic colonoscopy in a natural endoscopic practice setting and met the inclusion/exclusion criteria. No statistically significant differences were observed between the treatment groups in any demographic characteristic in the Safety, ITT, and PP analysis sets in either of the two studies.

Study 01
In the Safety analysis set, the majority of the population was female (58.9%), White (88.4%), and <65 years of age (83.4%). Subjects ranged in age from 19 to 80 years, with an overall mean age of 55.2 years. Demographic characteristics of the ITT and PP analysis sets were similar to those of the Safety analysis set.

Study 02
In the Safety analysis set, the majority of the population was female (63.7%), White (90.6%), and <65 years of age (80.8%). Subjects ranged in age from 18 to 79 years, with an overall mean age of 56.5 years. Demographic characteristics of the ITT and PP analysis sets were similar to those of the Safety analysis set.

A summary Table for the demographic and baseline characteristics of subjects is presented in the Appendix.

3.1.12 Analysis Sets

Tables 9 and 10 below show the analysis sets for Study 01 and 02 respectively.

Table 9: Study 01 – Analysis Sets

	Treatment Group		
	PICOPREP	HalfLytely	Total
Total treated / Safety Analysis Set	305	298	603
Excluded from Intent-to-Treat Analysis Set	1	1	2
Did not have an efficacy assessment performed	1	1	2
Intent-to-Treat Analysis Set	304	297	601
Excluded from Per Protocol Analysis Set	27	23	50
Per Protocol Analysis Set	277	274	551

Note: Safety analysis set is summarized by actual treatment taken; ITT and PP analysis sets are summarized by randomized, planned treatment group.
Source: Table 7-2 of Sponsor's Study Report, Page 43 of 80
Reviewer's mITT analyses are based on 304 and 295 subjects in the Picoprep and HalfLytely groups, respectively.

Table 10: Study 02 – Analysis Sets

	Treatment Group		
	PICOPREP	HalfLytely	Total
Total treated / Safety Analysis Set	296	302	598
Excluded from Intent-to-Treat Analysis Set	2	2	4
Did not have an efficacy assessment performed	2	2	4
Intent-to-Treat Analysis Set	294	300	594
Excluded from Per Protocol Analysis Set	34	20	54
Per Protocol Analysis Set	260	280	540

Note: Safety analysis set is summarized by actual treatment taken; ITT and PP analysis sets are summarized by randomized, planned treatment group.
Source: Table 7-2 of Sponsor's Study Report, Page 43 of 81

3.1.13 Study 01 - Results and Findings

Primary Endpoint

Tables 11 and 12 show the response rates for each individual element of the Aronchick Scale for the ITT and PP populations, respectively. These tables were constructed by the reviewer.

Table 11: Study 01 - Percentages of Responders using the Aronchick Scale (ITT)

Aronchick Scale	PicoPrep (n=304)	HalfLytely (n=295)	Total (N=599)
Excellent	139 **(46%)**	100 **(34%)**	239
Good	117 (38.5%)	121 (41%)	238
Fair	47 (15%)	70 (24%)	117
Inadequate	1 **(0.3%)**	4 **(1%)**	5

Table 12: Study 01 – Percentages of Responders using the Aronchick Scale (PP)

Aronchick Scale	PicoPrep (n=277)	HalfLytely (n=274)	Total (N=551)
Excellent	127 **(46%)**	98 **(36%)**	225
Good	108 (39%)	109 (40%)	217
Fair	42 (15%)	64 (23%)	106
Inadequate	0 **(0%)**	3 **(1%)**	3

The results were similar in the two populations (ITT and PP); where 46% of the subjects in the PicoPrep arm had a response rate of "Excellent". For the HalfLytely group the response for the "Excellent" was 34% for ITT and 36% for PP populations.

Table 13 shows the results of the primary endpoint variable, the response rates as well as the difference in the two arms along with their associated 95% CI.

Table 13: Study 01 – Reviewer's Analysis* - Response Rates and Non-Inferiority Test for the Primary Endpoint (ITT) - (Combining Excellent with Good / Fair with (Inadequate)

Aronchick Scale	PicoPrep (n=304)	HalfLytely (n=295)	Difference 95% CI
Excellent + Good	**256/304 (84.2%)**	**221/295 (74.9%)**	**9.3% (2.9%, 15.7%)**
Fair + Inadequate	**48/304 (15.8%)**	**74/295 (25.1%)**	

*Reviewer's analyses were based on dataset "ADFA" which was submitted by the Sponsor

As shown in Table 13, PicoPrep demonstrated non-inferiority to HalfLytely since the lower confidence bound of the CI of the difference was greater than -9%. However, since the lower confidence bound was also above zero, superiority of PicoPrep to the comparator can be declared as the superiority test was pre-specified in the sponsor's analysis plan.

Table 14 was taken from the Sponsor's submission. It shows the response rates as well as the difference in the two arms along with their associated lower bound of a 1-sided 97.5% CI for both ITT and PP populations. For the sponsor's ITT analysis, it should be noted that two HalfLytely subjects with unknown responder status were assigned as treatment failures. In the reviewer's analysis, these two patients did not appear in the data set and were excluded.

Table 14: Study 01 –Non-inferiority Analysis for Percentage of Responders Using the Aronchick Scale at Visit 3 (ITT and PP Analysis Sets)

Analysis Set	Statistic	PICOPREP	HalfLytely	Treatment Difference: PICOPREP minus HalfLytely	1-Sided 97.5% CI
Intent-to-Treat	N	304	297		
	Responders[a], n (%)	256 (84.2)	221 (74.4)	9.8	3.4[b]
Per Protocol	N	277	274		
	Responders[a], n (%)	235 (84.8)	207 (75.5)	9.3	2.7[b]

Abbreviations: CI = confidence interval.
HalfLytely Subjects 104-038 and 105-021 with unknown responder status were classified as treatment failures in the ITT analysis set.
a. Excellent or good rating.
b. Non-inferior and superior.
Source: Table 9-1 of Sponsor's Study Report, Page 49 of 80

Based on Sponsor's results, the lower bound of the 1-sided 97.5% CI for the treatment difference was 3.4% in the ITT analysis set and 2.7% in the PP analysis set. Therefore non-inferiority of PicoPrep to HalfLytely was demonstrated in both analysis sets. The superiority objective was also met. For both analysis sets, the percentages of responders for PicoPrep were greater than those in the HalfLytely group.

The sponsor used the Breslow-Day statistic to test the homogeneity (or alikeness) of the chance of the observed positive treatment effect response of PicoPrep versus HalfLytely when compared across the investigative sites. There was no treatment by site interaction (p=0.4).

In addition, a reviewer's sensitivity analyses based on "Total treated" numbers where the additional few subjects were assigned treatment failure (See Tables 9 and 10) showed similar results and did not change the efficacy conclusions.

Secondary Endpoint

The protocol-defined, key secondary efficacy variable was the percentage of subjects classified as a clinical success (responder) for cleansing the ascending colon at Visit 3 during the colonoscopy, where success was defined as a rating of Excellent, Good, or Fair (0, 1, or 2, respectively) on the Ottawa Scale. Non-inferiority was to be demonstrated if the 1-sided 97.5% CI lower bound for the treatment difference (PicoPrep minus HalfLytely) was greater than -9% for the percentage of responders.

Based on Sponsor's results, the percentage of responders for PicoPrep was greater than for HalfLytely for cleansing the ascending colon in both the ITT analysis set (89.5% versus 78.8%) and the PP analysis set (90.3% versus 79.2%). The non-inferiority of PicoPrep to HalfLytely in cleansing the ascending colon was indicated in both analysis sets. Subsequently, the bound of the CI was determined to be greater than 0% and the superiority of PicoPrep was indicated in both the ITT and PP analysis sets. (b) (4)

Table 15 presents the response rates for the secondary endpoint variable for the ITT population.

Table 15: Study 01 - Percentages of Responders using Secondary Endpoint (OTTAWA Score Ascending) (ITT)

Ottawa Scale (Ascending)	PicoPrep (n=303)	HalfLytely (n=295)
Excellent	**51 (17%)**	**21 (7%)**
Good	**76 (25%)**	**58 (20%)**
Fair	**145 (48%)**	**155 (53%)**
Poor	**29 (10%)**	**56 (19%)**
Inadequate	**2 (1%)**	**5 (2%)**

– Reviewers Analysis - Based on dataset "ADFA" submitted by the Sponsor (ITT)

Table 15 shows the response rates for Ottawa Scale (ascending) by each score individually. PicoPrep has higher rates for scores of Excellent (17% vs. 7%) and Good (25% vs. 20%) than the HalfLytely arm.

Table 16 below shows the response rates for Ottawa Score=Ascending, where subjects with response of "Excellent", "Good" and "Fair" have been combined in one category and subjects with responses of "Poor" and "Inadequate" combined in the second category.

Table 16: Study 01 – Reviewer's Analysis* - Non-inferiority Analysis for Ascending Colon Cleansing Using the Ottawa Scale at Visit 3 (Day of Procedure), ITT Analysis Sets

Ottawa Scale (Ascending)	PicoPrep (n=303)	HalfLytely (n=295)	Difference 95% CI
Excellent + Good + Fair	**272/303 (90%)**	**234/295 (79%)**	**10% (5%, 16%)**
Fair + Poor	**31/303 (10.2%)**	**61/295 (20.7%)**	

*Reviewer's analyses were based on dataset "ADFA" which was submitted by the Sponsor

Again, as it can be seen from Table 16, PicoPrep had a higher response rate than that of HalfLytely (90% s.79%). The lower bound of the 95% CI was above zero (5%).

Table 17 was taken from the Sponsor's submission. It includes the response rates, the difference between the response rates along with the lower bound of the 1-sided 97.5% CI for both ITT and PP populations. As noted above, these secondary endpoint results should not be considered confirmatory.

Table 17: Study 01 – Sponsor's Study Report - Non-inferiority Analysis for Ascending Colon Cleansing Using the Ottawa Scale at Visit 3 (Day of Procedure), ITT and PP Analysis

Population	PICOPREP n/N (%)	HalfLytely n/N (%)	Treatment Difference: PICOPREP minus HalfLytely	1-Sided 97.5% CI
Intent-to-Treat Responders[a]	272/304 (89.5)	234/297 (78.8)	10.7	4.9[b]
Per Protocol Responders[a]	250/277 (90.3)	217/274 (79.2)	11.1	5.1[b]

Abbreviations: CI = confidence interval

PICOPREP Subject 103-019 and HalfLytely Subjects 104-038 and 105-021 with unknown responder status were classified as treatment failures.

a. Excellent, good, or fair rating.
b. Non-inferior and superior.

Source: Table 9-3 of Sponsor's Study Report, Page 51 of 80

3.1.14 Study 02 - Results and Findings

Primary Endpoint

Tables 18 and 19 show the response rates for each individual element of the Aronchick Scale for the ITT and PP populations, respectively. These tables were constructed by the reviewer.

Table 18: Study 02 – Percentages of Responders using the Aronchick Scale (ITT)

Aronchick Scale	PicoPrep (n=294)	HalfLytely (n=300)	Total (N=594)
Excellent	143 **(49%)**	121 **(40%)**	264
Good	101 (34%)	118 (39%)	219
Fair	46 (16%)	56 (19%)	102
Inadequate	4 **(1%)**	5 **(2%)**	9

Table 19: Study 02 – Percentages of Responders using the Aronchick Scale (PP)

Aronchick Scale	PicoPrep (n=260)	HalfLytely (n=280)	Total (N=540)
Excellent	126 (48%)	113 (40%)	239
Good	90 (35%)	109 (39%)	199
Fair	42 (16%)	53 (19%)	95
Inadequate	2 (1%)	5 (2%)	7

The results were similar in the two populations; in PicoPrep arm for ITT analysis set 49% and for PP 48% of subjects had a response of "Excellent". However, in the HalfLytely group both the ITT and PP populations had 40% "Excellent" response.

Table 20 shows the results of the primary endpoint variable, the response rates as well as the difference in the two arms along with their associated 95% CI.

Table 20: Study 02 – Reviewer's Analysis* - Response Rates and Non-Inferiority Test for the Primary Endpoint (ITT) - (Combining Excellent with Good – Fair with Inadequate)

Aronchick Scale	PicoPrep (n=294)	HalfLytely (n=300)	Difference 95% CI
Excellent + Good	**244/294 (82.9 %)**	**239/300 (79.7%)**	**3.3% (-3.0%, 10.0%)**
Fair + Inadequate	**50/294 (17.0%)**	**61/300 (20.3%)**	

*Reviewer's analyses were based on dataset "ADFA" which was submitted by the Sponsor

Subjects with an excellent or good rating on the scale at Visit 3 during colonoscopy were defined as responders. As shown in Table 20, non-inferiority of PicoPrep to HalfLytely was demonstrated as the lower confidence bound of the two-sided 95% CI for the treatment difference (PicoPrep minus HalfLytely) was greater than -9%. However, as remarked earlier, the 9% NI margin was not consistent with the reviewer's recommendations, and a more appropriate margin might have been 4%.

Table 21 was taken from the Sponsor's submission. It shows the response rates as well as the difference in the two arms along with their associated lower bound of the 1-sided 97.5% CI for both ITT and PP populations.

Table 21: Study 02 –Non-inferiority Analysis for Percentage of Responders Using the Aronchick Scale at Visit 3 (ITT and PP Analysis Sets)

Analysis Set	Statistic	PICOPREP	HalfLytely	Treatment Difference: PICOPREP minus HalfLytely	1-Sided 97.5% CI
Intent-to-Treat	N	294	300		
	Responders[a], n (%)	244 (83.0)	239 (79.7)	3.3	-2.9[b]
Per Protocol	N	260	280		
	Responders[a], n (%)	216 (83.1)	222 (79.3)	3.8	-2.8[b]

Abbreviation: CI = confidence interval.
a. Excellent or good rating.
b. Non-inferior.
Source: Table 9-1 of Sponsor's Study Report, Page 49 of 81

The sponsor-reported lower bound of the one-sided 97.5% CI for the treatment difference was -2.9% in the ITT analysis set and -2.8% in the PP analysis set; thus, non-inferiority of PicoPrep to HalfLytely was indicated in both analysis sets. For both analysis sets, the percentage of responders in the PicoPrep group was greater than in the HalfLytely group.

In addition, a reviewer's sensitivity analyses based on "Total treated" numbers where the additional few subjects were assigned treatment failure (See Tables 9 and 10) showed similar results and did not change the efficacy conclusions.

Secondary Endpoint

The protocol-defined, key secondary efficacy variable was the percentage of subjects classified as a clinical success (responder) for cleansing the ascending colon at Visit 3 during the colonoscopy, where success was defined as a rating of Excellent, Good, or Fair (0, 1, or 2, respectively) on the Ottawa Scale.

Table 22 presents the response rates for the secondary endpoint variable for the ITT population.

Table 22: Study 02 – Percentages of Responders using Secondary Endpoint (OTTAWA Score = Ascending) (ITT)

Ottawa Scale (Ascending)	PicoPrep (n=292)	HalfLytely (n=300)	Total (N=592)
Excellent	**43 (15%)**	**31 (10%)**	**74**
Good	**89 (30%)**	**99 (33%)**	**188**
Fair	**107 (37%)**	**122 (41%)**	**229**
Poor	**50 (17%)**	**48 (16%)**	**98**
Inadequate	**3 (1%)**	**0**	**3**

Table 22 shows the response rates for Ottawa Scale (ascending) by each score individually. PicoPrep has higher rates for scores of "Excellent" (15% vs. 10%).

Table 23 below shows the response rates for Ottawa Score=Ascending, where subjects with response of "Excellent", "Good" and "Fair" have been combined in one category and subjects with responses of "Poor" and "Inadequate" combined in the second category.

Table 23: Study 02 - Non-inferiority Analysis for Ascending Colon Cleansing Using the Ottawa Scale at Visit 3 (Day of Procedure), ITT and PP Analysis Sets

Population	PICOPREP N(%)	HalfLytely N(%)	Treatment Difference: PICOPREP-HalfLytely	1-Sided 97.5% CI
ITT Responders[a]	239/294 (81.3)	252/300 (84.0)	-2.7	-8.8[b]
PP Responders[a]	211/260 (81.2)	237/280 (84.6)	-3.5	-9.8

Abbreviations: CI = confidence interval, n=number of responders, N =number of subjects assessed, % = (n/N)*100 PICOPREP Subjects 202-042 and 204-044 with unknown responder status were classified as treatment failures.
a. Excellent, good, or fair rating.
b. Non-inferior.
Source: Table 9-3 of Sponsor's Study Report, Page 51 of 81

Based on Sponsor's results, the percentage of responders for HalfLytely was greater than PicoPrep for cleansing the ascending colon in both the ITT analysis set (81.3% versus 84%) and the PP analysis set (81.2% versus 84.6%). The non-inferiority of PicoPrep to HalfLytely in cleansing the ascending colon was indicated in ITT analysis set, only. (b) (4)

3.2 Evaluation of Safety

For information on safety, refer to the medical as well as the statistical safety review team.

4. FINDINGS IN SPECIAL SUBGROUP POPULATIONS

4.1 Gender, Race, Age and Geographic Region

Tables 24, 25 and 26 demonstrate the response rates by age category for study 01, 02 and combined studies.

Table 24: Study 01 - Primary Efficacy Endpoint - Response Rates (Aronchick Scale = Excellent + Good) by Age Category (ITT)

Age Category	PicoPrep	HalfLytely	Difference 95% CI
18 – 64	215/252 (85%)	188/248 (76%)	10% (3%, 16%)
65 - 80	41/52 (79%)	33/47(70%)	9% (-1%, 26%)

Table 25: Study 02 - Primary Efficacy Endpoint - Response Rates (Aronchick Scale = Excellent + Good) by Age Category (ITT)

Age Category	PicoPrep	HalfLytely	Difference 95% CI
18 – 64	194/234 (83%)	200/245 (82%)	1% (-6%, 8%)
65 - 80	50/60 (83%)	39/55 (71%)	12% (-3%, 38%)

Table 26: Both Studies Combined - Primary Efficacy Endpoint - Response Rates (Aronchick Scale = Excellent + Good) by Age Category - (ITT)

Age Category	PicoPrep (n=598)	HalfLytely (n=595)	Difference 95% CI
18 – 64	409/486 (84%)	388/493 (79%)	5% (1%, 10%)
65 - 80	91/112 (81%)	72/102 (71%)	11% (-1%, 22%)

Tables 27, 28 and 29 demonstrate the response rates by gender for study 01, 02 and both studies combined.

Table 27: Study 01 - Primary Efficacy Endpoint - Response Rates (Aronchick Scale = Excellent + Good) by Gender (ITT)

Gender	PicoPrep	HalfLytely	Difference 95% CI
Female	156/180 (87%)	138/171 (81%)	6% (-2%, 14%)
Male	100/124 (81%)	83/124 (67%)	14% (3%, 25%)

Table 28: Study 02 - Primary Efficacy Endpoint - Response Rates (Aronchick Scale = Excellent + Good) by Gender (ITT)

Gender	PicoPrep	HalfLytely	Difference 95% CI
Female	161/191 (84%)	155/188 (82%)	2% (-6%, 9%)
Male	83/103 (81%)	84/112 (75%)	6% (-5%, 17%)

Table 29: Both Studies Combined - Primary Efficacy Endpoint - Response Rates (Aronchick Scale = Excellent + Good) by Gender (ITT)

Gender	PicoPrep (n=598)	HalfLytely (n=595)	Difference 95% CI
Female	317/371 (85%)	293/359 (82%)	0.2 4% (-2%, 9%)
Male	183/227 (81%)	167/236 (71%)	0.1 10% (2%, 17%)

Table 30 shows the response rates by race for both studies combined.

Table 30: Both Studies Combined - Primary Efficacy Endpoint - Response Rates (Aronchick Scale = Excellent + Good) by Race (ITT)

Race	PicoPrep (n=598)	HalfLytely (n=595)	Difference 95% CI
White	446/536 (83%)	411/532 (77%)	6% (1%, 11%)
Blake or African American	50/58 (86%)	45/58 (76%)	9% (-5%, 23%)

The other racial groups had very small populations (between 1 to 5 subjects) and are insufficient to draw any conclusions. All studies were conducted in the US, so no regional analyses were needed.

Additional tables for subgroup analyses of the secondary endpoint are given in the Appendix.

5. SUMMARY AND CONCLUSIONS

5.1 Conclusions and Recommendations

From a statistical perspective, the data from Study FE2009-01 showed superiority PicoPrep (split dose) to HalfLytely/Bisacodyl Tablets, 10 mg. In addition, the results of Study FE2009-02 indicated that PicoPrep (single dose) is non-inferior to HalfLytely in colon cleansing in preparation for colonoscopy.

APPENDICES:

Figure 1: Study FE2009-01 - Study Flow Chart

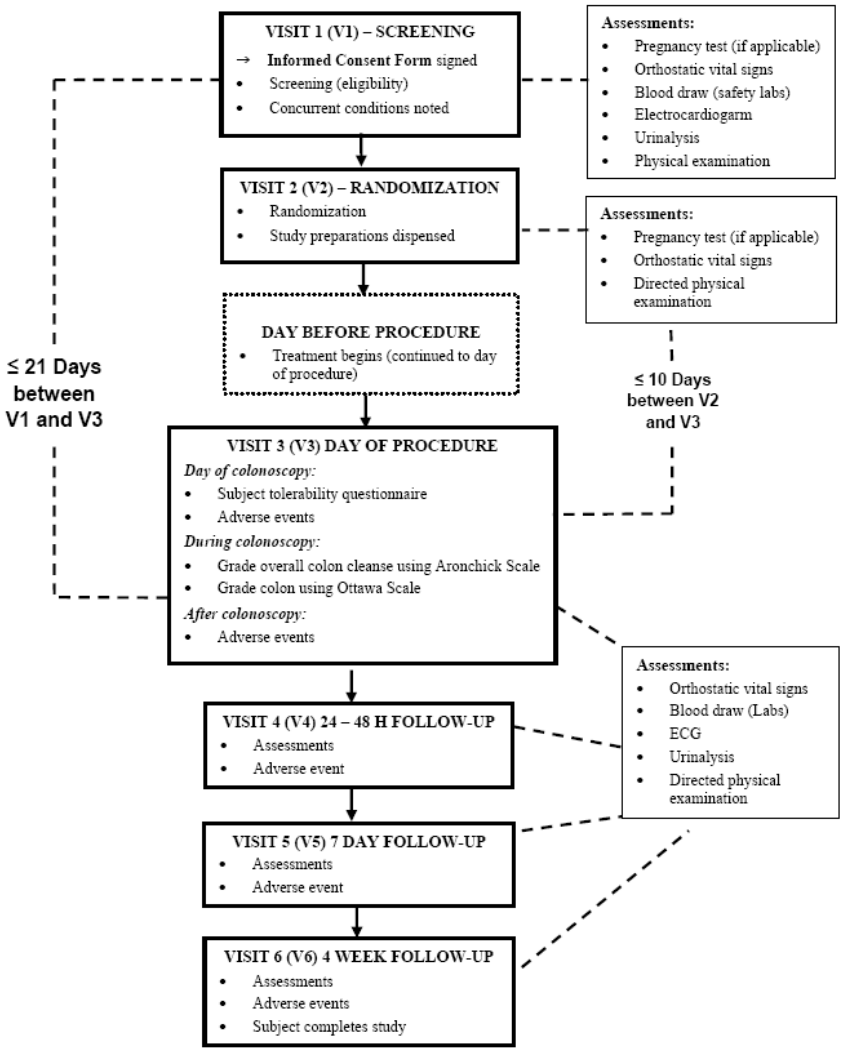
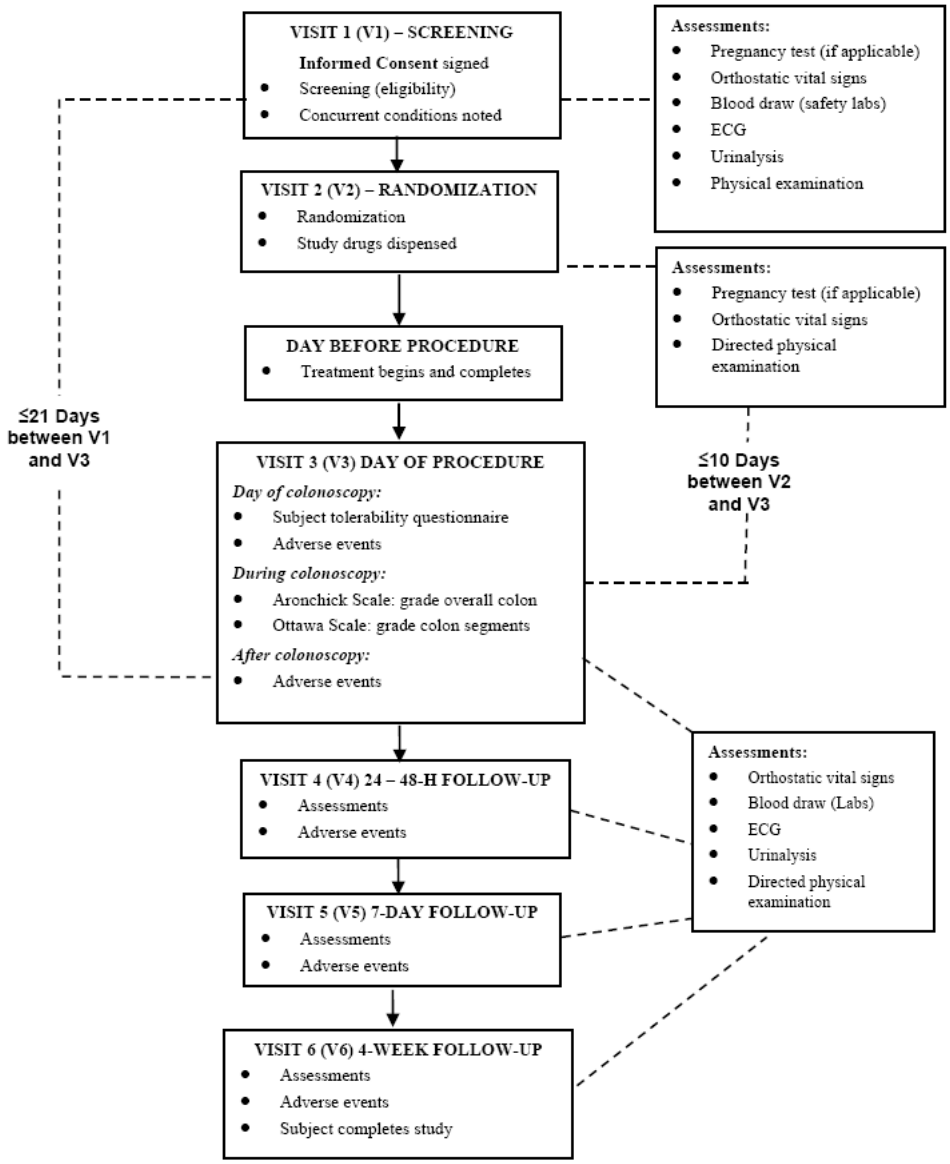


Figure 2: Study FE2009-02 - Study Flow Chart



Protocol Deviations:

A protocol deviation was defined as any variance from the criteria for the enrollment and conduct of the study, as specified in the protocol. Prior to study unblinding, a blinded review of all subjects with protocol deviations was conducted to determine which, if any, subjects had deviations that met criteria specified in the SAP for exclusion from the PP analysis set.

- Violation of any of the protocol inclusion or exclusion criteria.
- Violation of the dosing regimen, as recorded on the CRF, including the amount and time of study drug administration.
- Receiving incorrectly randomized study drug.
- Taking exclusionary medications during the study and/or prior to the procedure.

Study 01 – Protocol Deviations:

Of the 601 subjects who received study drug and had a colonoscopy performed, 27 subjects in the PicoPrep treatment group and 23 subjects in the HalfLytely treatment group met the protocol-defined criteria for exclusion from the PP analysis set. Violations of inclusion/exclusion criteria were primarily screening laboratory values outside of normal range for which the Sponsor gave a waiver.

Major protocol deviations that led to exclusion from the PP analysis set in the PicoPrep treatment group included:

- Inclusion/exclusion violation (primarily laboratory value outside normal range): Subjects 101-003, 101-010, 101-012, 101-029, 101-046, 101-073, 101-100, 101-125, 103-009, 103-010, 103-036, 103-041, 103-055, 105-014, 105-039, 106-113, 110-014, 110-016 (18 subjects).
- Exclusionary medication taken: Subjects 101-081, 101-095, 102-024, 102-058, 107-075, 109-021, 110-001, and 110-016 (8 Subjects).
- Incomplete efficacy assessments: Subjects 101-095, 103-019.
- Incorrectly randomized: Subject 110-021 (randomized to Kit #100553 and inadvertently dispensed Kit #100533).

Major protocol deviations that led to exclusion from the PP analysis set in the HalfLytely treatment group included:

- Inclusion/exclusion violation: Subjects 101-025, 101-027, 101-123, 101-126, 103-008, 103-024, 103-027, 103-049, 105-022, 105-024, 105-026, 105-045, and 110-009.
- Exclusionary medication taken: Subjects 101-042, 104-016, 107-005, 107-029, 107-082, 109-005, and 110-015.
- Incomplete efficacy assessments: Subjects 104-038, 105-021.
- Incorrectly randomized: Subject 110-002 (randomized to Kit #100533 and inadvertently dispensed Kit #100553).
- A total of eight subjects were manually randomized in this study.

Minor deviations included study visit outside of the visit window, missed visit, and missed study procedure, noncompliance with preparation, and addition to medical history after randomization.

No investigators were prematurely unblinded. For a summarized Table of the violations, refer to Appendix.

Study 02 – Protocol Deviations:

Major protocol deviations that led to exclusion from the PP analysis set in the PicoPrep treatment group included:

- Inclusion/exclusion criteria violation: Subjects 202-045, 202-047, 203-051, 203-057, 204-010, 204-014, 204-024, 204-033, 204-045, 204-052, 205-023, 205-030, 206-001, 208-004, 208-053, 208-057, 210-030, 210-055
- Exclusionary medication taken: Subjects 203-020, 203-063, 204-043, 205-025, 205-045, 207-010, 207-028, 207-032, 207-033, 208-034, 212-076, 212-086
- Incomplete efficacy assessments: Subjects 202-042, 204-044, 209-028
- Violation of dosing regimen: Subjects 210-053 and 210-055

Major protocol deviations that led to exclusion from the PP analysis set in the HalfLytely treatment group included:

- Inclusion/exclusion criteria violation: Subjects 202-017, 203-041, 205-027, 205-036, 208-010, 208-011, 208-025, 208-049, 210-014, 210-031, 210-045, 210-049
- Exclusionary medication taken: Subjects 201-004, 203-005, 204-054, 206-004, 208-006, 208-008, 208-016, 211-033

Three subjects were discontinued due to protocol deviations (PicoPrep Subject 202-042: scope incomplete due to poor quality of the prep; PicoPrep Subject 212-048: patient could not return to site for Visits 4 and 5; HalfLytely Subject 211-039: prep did not work).

No subject was incorrectly randomized in Study 02.

Study 01 (The Split Dose Study):
Deviations during Treatment Phase (one subject might have multiple records)

Protocol Deviation Category	Treatment Arm Subject ID		Analysis Term
	PicoPrep	HalfLytely	
Exclusion Violation		108015	Platelets Cancelled, Not Repeated
		110009	Creatinine Out Of Range. Ncs Per Investigator. Enrolled Per Sponsor Directive
	106113		The Subject Had An Ileo-Transverse Colostomy. (Discovered During Visit 3)
Inclusion Violation		106092	Pt Didn't Finish Prep, Therefore No Colonoscopy Was Preformed. (Non Compliance)
Major: Exclusionary Medication (s)		101042 104016 107005 107029 107082 109005 110015	Exclusionary Medications Were Taken
	101081 101095 102024 102058 107075 109021 110001 110016		
Major: Incorrectly Randomized Study Med		110021	Received Incorrectly Randomized Study Medication
	110002		
Major: Visit(s)/Assessment(s) Incomplete		104038 105021	Did Not Complete Efficacy Assessments
	101095 103019		
Missed Procedure		101041 101053	Potassium, Alkaline Phosphatase, And Ast Not Processed Secondary To Hemolysis
		101097	Colonoscopy Incomplete Due To Poor Prep
		101107 101109	Potassium, Alkaline Phosphatase And Ast Not Processed Secondary To Hemolysis
		101123	Platlets Clumped Per Icon Labs
		102041 102043	Potassium, Alkaline Phosphate And Ast Cancelled To Amount Of Hemolysis In Sample
		102068 103011	Platelets Cancelled Due To Clumping
		103028	Platelet Evaluation Invalid Due To Clumping
		103066	Patient Could Not Provide Urine Specimen
		104041	Physical Not Done
		104053	Pe Not Done
		105008	Urine Sample Not Collected
		105016	Pt/Ptt Not Processed Due To Insufficient Volume
		105021	Unable To Complete Colonoscopy Due To Redundant Colon
		105024	Hematology/Urinalysis Not Performed Due To Age Of Specimen Which Exceeds Stability Data. Specimens Collect
		106092	Colonoscopy Not Performed Due To Incomplete Preparation

		110003	Pt/Ptt Not Done Due To Insufficient Volume Of Blood
		110010	Potassium, Total Bilirubin, Alkaline Phosphate, Ast, Ait, And Magnesium Not Processed Due To Hemolyzatio
		110015	Kt, T Billi, Alk Phos, Ast, Alt, Creatinine Not Processed Due To Hemolysis
		110015	Platelets Not Processed Due To Clumping
	101019		Potassium, Alkaline Phosphatase Hemolysis And Ast Not Processed By Icon Labs
	101024		Potassium, Total Protein, Alkaline Phosphatase Ast. Alt Gamma Gt Magnesium Creatine Not Processed Secondar
	101031		Potassium, Alkaline Phosphatase And Ast Not Processed Secondary To Hemolysis
	101105		Cbc Clotted Not Processed By Icon Lab
	101114 101122		Potassium, Alkaline Phosphatase And Ast Not Processed Secondary To Hemolysis
	101125		Platelets Not Processed Secondary To Clumping
	101125		Potassium, Alkaline Phosphatase, Ast Not Processed Secondary To Hemolysis
	103010		Urine Not Collected. Patient Unable To Obtain
	103019		Unable To Complete Ascending Colon/Ottowa Scale Due To Structural Abnormality
	103055		No Urine Specimen Provided By Pt
	104008		Subject Did Not Leave A Urine Sample
	104045		Labs Not Collected
	104052		Bowel Prep-Subject Questonair Not Completed
	105002		Pt/Ptt Not Processed Due To Insufficient Quantity
	105018		Subject Took Prep But Did Not Undergo Colonoscopy
	105023		Urine Not Collected Bladder Empty
	106115		The Subject Was Unable To Provide A Urine Sample At V3
	107076		Potassium, Alkaline Phosphate And Ast Cancelled Due To Hemolysis. But Was Drawn The Next Day For Visit 4 T
	107077		Potassium, Ast And Alkaline Phosphate Cancelled Due To Hemolysis Not Redrawn Since It Was Done Again The N
	107090		Platelets To Clumping Not Redraw Due To Cancelled
	108012		Labs (Potassium, Alkaline Phosphate, Ast) Cancelled Due To Hemolysed Sample-Not Repeated
	110013		Potassium, Alkaline Phosphate, Ast Not Processed Due To Hemolyzation
	110014		K, Thilli, Alk Phos Not Processed D/T Hemolyzation
Other		101008	Patient Took Medication Out Of Window, Started Late And Did Not Take All Of It
		101049	Study Drug Partially Taken
		101072	Patient Took Prep Early Despite Directions That Were Administered
		101079	Patient Took Prep 2 Hours 15 Minutes Early-Per Subject Decision
		101086	Patient Did Not Finish Prep Completely. And Did Not Bring Back Unused Drug
		101112	Patient Had Incomplete Prep-Unable To Perform Colonoscopy-Pt Did Not Finish Prep
		101116	Subject Finished Prep The Day Of Procedure In The Morning.
		102021	Cancelled Labs Due To Hemolyzation
		102054	Pt Did Not Finish All Of Prep
		102060	Subject Did Not Complete Entire Prep
		103003	Pt/Ptt Not Tested By Lab Due To Insufficient Volume
		103060	Unable To Calculate Platelets Due To Clumping Per Lab
		104009	Study Drug Partially Used
		104024	Patient Took Study Medication 1.5 Hrs After Scheduled Time
		104038	Subjet Now-Compliance With Prep-Vomited
		104039	Patient Vomited During Prep Consumption
		104042 106024 106064	Subject Did Not Complete Prep

		106106 107065	
		104054	Vomitted Prep
		106002 106007 106015 106046 106049 106080	Potassium, Alkaline Phophate, And Ast Values Were Cancelled By The Lab Due To Hemolysis
		106009	Ip Taken Outside Specified Time Period
		106029 106048 106064 106077 106092 106107	Drug Packaging: Part Of Drug Packaging Inadvertently Discarded By Subject
		106046	Subject Dosed 2p Incorrectly. The Subject Dosed Outside The Time Parameters
	101004 101020		Study Drug Volume Not Fully Taken
	101007		Study Drug Taken Out Of Window
	101045		Potassium, Alkaline Phosphatase, Ast Not Processed Secondary To Hemolysis
	101062		Potassium, Alkaline Phosphatase, Ast Not Processed Secondary To Hemolysis
	101095		Subject With Poor Colon Prep-Colonscopy Re-Done
	101105		Prep Taken Early Based On 730 Start Time-Md Ran Late
	102014		Subject Dosed Outside Of Specified Time Period
	102026		Some Labs Cancelled Due To Hemolysis
	102027		Subject Dosed Outside Of Specified Time Period
	102048		Platelets Cancelled Due To Clumping
	102048		Potassium, Alkaline Phosphate, And Ast Cancelled Due To Hemolysis In Sample
	104044		Time Of Dose Not Recorded.
	105019		Study Drug Taken Out Of Window
	105023		Subject Did Not Adhere To Diet Restrictions During Prep
	106005		Potassium, Alkaline Phosphate, Ast Labs Cancelled Due To The Amount Of Hemolysis In The Sample
	106013		Potassium, Alkaline Phosphate, & Ast Valves Were Cancelled By Lab Due To Hemolysis
	106017		Potassium, Alkaline Phosphate & Ast Values Cancelled By Lab Due To Hemolysis
	106033		Part Of Drug Packaging Inadvertently Discarded By Subject
	106034		Part Of Drug Packaging Inadvertently Discarded By Subject.
	106035		Potassium, Alkaline Phosphate & Ast Values Cancelled By Lab Due To Hemolysis
	106035		Subject Dosed Out Of Window.
	106037		Drug Packaging. Part Inadvertently Discarded.
	106037		Potassium, Alkaline Phosphate, And Ast Values Cancelled By Lab Due To Hemolysis
	106041		Colon Prep Dosing Out Of Window
	106054		Drug Packaging: Part Of Packaging Inadvertently Discarded
	106055		Alkaline Phosphatase, Ast, And Potassium All Hemolyzed
	106058		Serum Slightly Hemolyzed: Alkaline Phosphatase, Ast, Potassium
	106061		Serum Slightly Hemolyzed Alkaline Phosphatase, Ast, Potassium
	106065		Serum Slightly Hemolyzed: Alkaline Phosphatase, Ast, Alt, Total Bilirubin, Potassium, Creatinine, Enzymati
	106073		Serum Slightly Hemolyzed: Alkaline Phosphate, Ast, Potassium
	106078		Test Result Invalid Due To Clumping (Platelets)
	106093		Part Of Drug Packaging Inadvertently Discarded
	106095		Drug Packaging: Part Of Packaging Inadvertently Discarded

	106098		Noncompliance: Vomitted Prep
	106098		Subject Used 2 Enemas For Scope.
	106113		Ileo-Transverse Colostomy Added To Medical History After Randomization.
	107040		Invalid Chemistry Results.
	107046		Alt, Ast, Sodium Cancelled Due To Amout Of Hemolysis In Sample
	107058		Pt Took Second Dose @ Midnight Instead Of 5 Am
	108012		Did Not Complete Entire Prep
	108020		Platelets Cancelled Due To Clumping-Not Repeated
	109021		Subject Did Not Stop Taking Iron Pills 7 Days Prior To Colonoscopy Since Subject Was Screened 6 Days Prior
Out of Visit Window (Early/Late Visits)			
		101001	Visit 3 Out Of Window
		101101	Potassium, Alkaline Phosphatase, Ast And Cbc Not Processed By Icon Secondary To Hemolysis
		106009	One Day Out Of Window
		106101	V3 Out Of Window
	101003		Study Prep Taken Out Of Window
	101004		Study Prep Taken Out Of Window
	101021		Study Prep Taken Out Of Window
	101093		Study Prep Taken Out Of Window
	102038		Patient Was Out Of Window For V3
	103036		Patient Scheduled Out Of Window Due To Inability To Randomize Via Ivrs
	106043		1 Day Outside Of The Study Allowed Window
	106058		Visit 3 Occured >10 Days After Visit 2

Study 01 (The Split Dose Study):
Subjects who Did not Complete Efficacy

PicoPrep	HalfLytely	Reason for Not Completing
	106092	Pt Didn't Finish Prep, Therefore No Colonoscopy Was Preformed. (Non Compliance)
	104038	Did Not Complete Efficacy Assessments
	105021	Did Not Complete Efficacy Assessments
101095		Did Not Complete Efficacy Assessments
103019		Did Not Complete Efficacy Assessments
	101097	Colonoscopy Incomplete Due To Poor Prep
	105021	Unable To Complete Colonoscopy Due To Redundant Colon
	106092	Colonoscopy Not Performed Due To Incomplete Preparation
104052		Bowel Prep-Subject Questioner Not Completed
105018		Subject Took Prep But Did Not Undergo Colonoscopy
	101008	Patient Took Medication Out Of Window, Started Late And Did Not Take All Of It
	101049	Study Drug Partially Taken
	101086	Patient Did Not Finish Prep Completely. And Did Not Bring Back Unused Drug
	101112	Patient Had Incomplete Prep-Unable To Perform Colonoscopy-Pt Did Not Finish Prep
	102054	Pt Did Not Finish All Of Prep
	102060	Subject Did Not Complete Entire Prep
	104009	Study Drug Partially Used
	104042	Subject Did Not Complete Prep
	106024	Subject Did Not Complete Prep

	106064	Subject Did Not Complete Prep
	106106	Subject Did Not Complete Prep
	107065	Subject Did Not Complete Prep
	106029	Part Of Drug Packaging Inadvertently Discarded By Subject
	106048	Part Of Drug Packaging Inadvertently Discarded By Subject
	106064	Part Of Drug Packaging Inadvertently Discarded By Subject
	106077	Part Of Drug Packaging Inadvertently Discarded By Subject
	106092	Part Of Drug Packaging Inadvertently Discarded By Subject
	106107	Part Of Drug Packaging Inadvertently Discarded By Subject
106033		Part Of Drug Packaging Inadvertently Discarded By Subject
106034		Part Of Drug Packaging Inadvertently Discarded By Subject
106037		Part Of Drug Packaging Inadvertently Discarded By Subject
106054		Part Of Drug Packaging Inadvertently Discarded By Subject
106093		Part Of Drug Packaging Inadvertently Discarded By Subject
106095		Part Of Drug Packaging Inadvertently Discarded By Subject
101004		Study Drug Volume Not Fully Taken
101020		Study Drug Volume Not Fully Taken
105023		Subject Did Not Adhere To Diet Restrictions During Prep
108012		Did Not Complete Entire Prep

Study 01 - Demographic and Baseline Characteristics (Safety Analysis Set)

Demographic Characteristic	Treatment Group: PICOPREP N = 305	Treatment Group: HalfLytely N = 298	Total N = 603	p-value[a]
Age (years)				0.3115
Mean (SD)	54.8 (10.04)	55.7 (10.00)	55.2 (10.02)	
Median	55.0	56.0	55.0	
Range	22 – 77	19 – 80	19 – 80	
Age range, n (%)				
16[b]-64	253 (83.0)	250 (83.9)	503 (83.4)	
≥65	52 (17.0)	48 (16.1)	100 (16.6)	
Sex, n (%)				0.8686
Male	124 (40.7)	124 (41.6)	248 (41.1)	
Female	181 (59.3)	174 (58.4)	355 (58.9)	
Race, n (%)				0.2409
White	265 (86.9)	268 (89.9)	533 (88.4)	
Black/African American	36 (11.8)	27 (9.1)	63 (10.4)	
American Indian/Alaska Native	1 (0.3)	1 (0.3)	2 (0.3)	
Asian	0	1 (0.3)	1 (0.2)	
Native Hawaiian/Other Pacific Islander	0	1 (0.3)	1 (0.2)	
Other	3 (1.0)	0	3 (0.5)	
Ethnicity, n (%)				0.7723
Hispanic or Latino	7 (2.3)	5 (1.7)	12 (2.0)	
Not Hispanic or Latino	298 (97.7)	293 (98.3)	591 (98.0)	
Height (cm)				0.8487
Mean (SD)	169.8 (10.80)	169.7 (9.50)	169.7 (10.17)	
Median	167.6	167.6	167.6	
Range	139.7 – 198.1	147.3 – 198.1	139.7 - 198.1	
Weight (kg)				0.8007
Mean (SD)	85.1 (19.81)	85.5 (20.64)	85.3 (20.21)	
Median	83.2	83.6	83.4	
Range	48.6 – 154.9	46.6 – 163.6	46.6 – 163.6	
Body Mass Index (kg/m^2)				0.8021
Mean (SD)	29.4 (5.68)	29.6 (6.34)	29.5 (6.01)	
Median	28.6	29.2	28.8	
Range	18.3 – 49.8	16.6 – 54.4	16.6 – 54.4	

Source: Sponsor's Table 7-4, Study Report, Page 45 of 80.

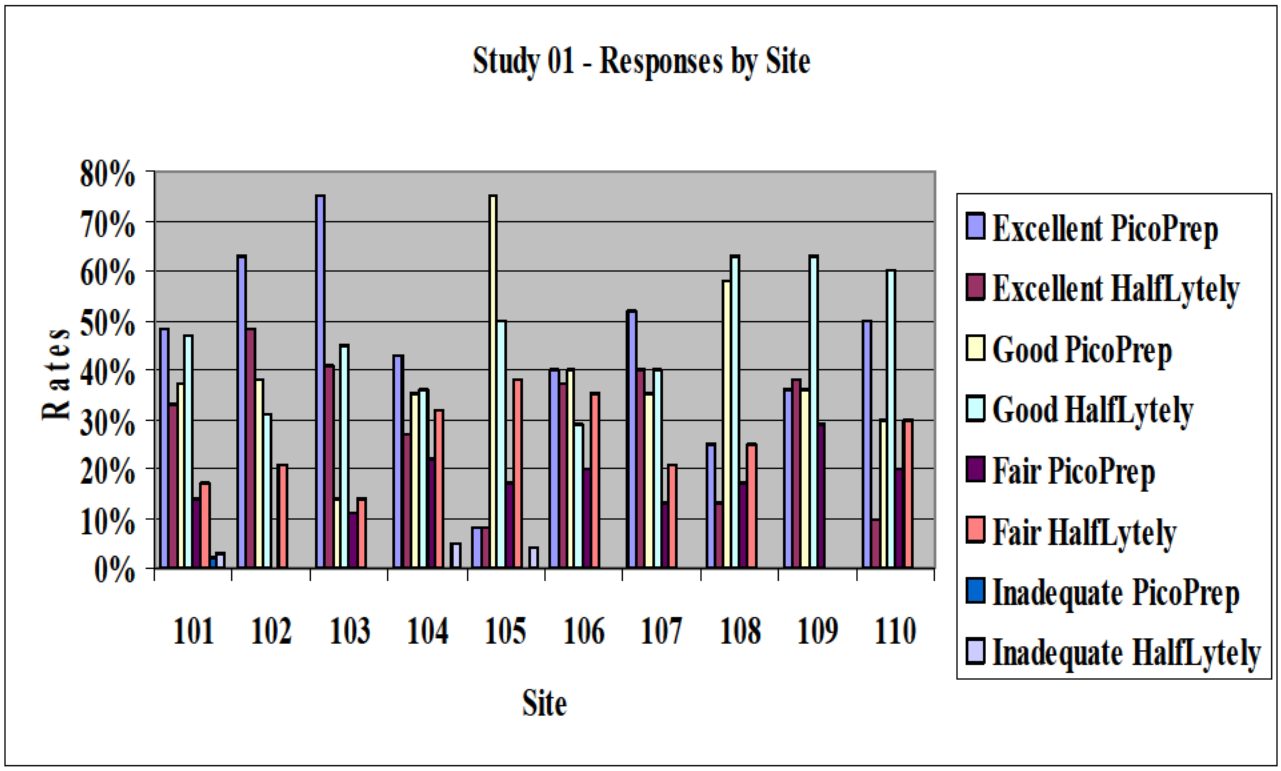
Study 02 - Demographic and Baseline Characteristics (Safety Analysis Set)

Demographic Characteristic	PICOPREP N=296	HalfLytely N=302	Total N=598	p-value
Age (years)				0.5486
Mean (SD)	56.8 (9.66)	56.2 (10.11)	56.5 (9.89)	
Median	57.0	56.0	56.0	
Range	21 -78	18-79	18-79	
Age range, n (%)				
16b-64	236 (79.7)	247 (81.8)	483 (80.8)	
:> 65	60 (20.3)	55 (18.2)	115 (19.2)	
Sex, n (%)				0.6099
Male	104 (35.1)	113 (37.4)	217 (36.3)	
Female	192 (64.9)	189 (62.6)	381 (63.7)	
Race, n(%)				0.1653
White	274 (92.6)	268 (88.7)	542 (90.6)	
Black/African American	22 (7.4)	32 (10.6)	54 (9.0)	
American Indian/Alaska Native	0	1 (0.3)	1 (0.2)	
Asian	0	1 (0.3)	1 (0.2)	
Native Hawaiian/Other Pacific Islander	0	0	0	
Other	0	0	0	
Ethnicity, n (%)				0.2017

Abbreviation: SD standard deviation.
a. Based on Wilcoxon rank sum test for treatment comparisons of means and Fisher's exact test for treatment comparisons of incidence rates.
b. Although the summary table lists the age category as 16 -64, subjects were to be at least 18 years of age for entry in the study and no subject was younger than 18.
Source: Sponsor's Table 7-4, Study Report, Page 45 of 81.

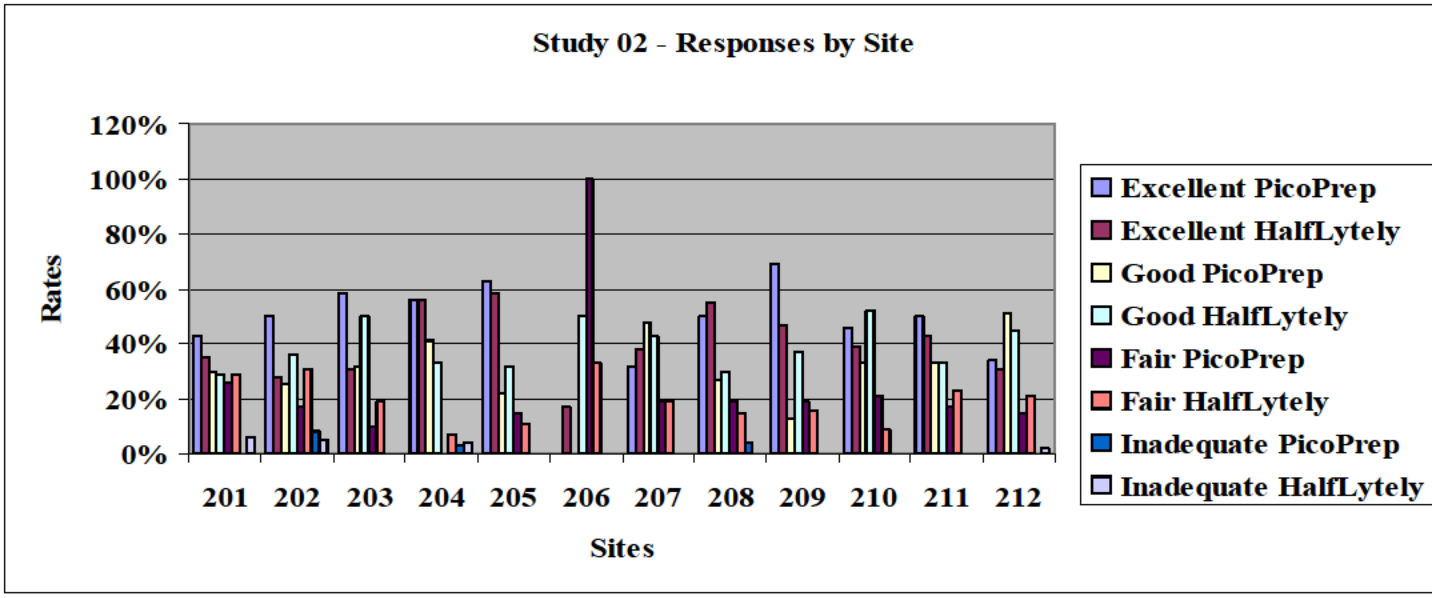
Study 01 – Treatment Outcome by Site

Site ID	Treatment/Outcome Status								Totals	
	Excellent		Good		Fair		Inadequate			
	PicoPrep	HalfLytely	PicoPrep	HalfLytely	PicoPrep	HalfLytely	PicoPrep	HalfLytely	PicoPrep	HalfLytely
101	48%	33%	37%	47%	14%	17%	2%	3%	63	60
102	63%	48%	38%	31%	0	21%	0	0	24	42
103	75%	41%	14%	45%	11%	14%	0	0	28	29
104	43%	27%	35%	36%	22%	32%	0	5%	23	22
105	8%	8%	75%	50%	17%	38%	0	4%	24	24
106	40%	37%	40%	29%	20%	35%	0	0	60	49
107	52%	40%	35%	40%	13%	21%	0	0	46	43
108	25%	13%	58%	63%	17%	25%	0	0	12	8
109	36%	38%	36%	63%	29%	0	0	0	14	8
110	50%	10%	30%	60%	20%	30%	0	0	10	10
Total	139	100	117	121	47	70	1	4	304	295



Study 02 – Treatment Outcome by Site

Site ID	Treatment Outcome								Totals		
	Excellent		Good		Fair		Inadequate				
	PicoPrep	HalfLytely	PicoPrep	HalfLytely	PicoPrep	HalfLytely	PicoPrep	HalfLytely	PicoPrep	HalfLytely	Total
201	43%	35%	30%	29%	26%	29%	0	6%	23	17	40
202	50%	28%	25%	36%	17%	31%	8%	5%	24	36	60
203	58%	31%	32%	50%	10%	19%	0	0	31	26	57
204	56%	56%	41%	33%	0	7%	3%	4%	32	27	59
205	63%	58%	22%	32%	15%	11%	0	0	27	19	46
206	0%	17%	0%	50%	100%	33%	0	0	1	6	7
207	32%	38%	48%	43%	19%	19%	0	0	31	21	52
208	50%	55%	27%	30%	19%	15%	4%	0	26	33	59
209	69%	47%	13%	37%	19%	16%	0	0	16	19	35
210	46%	39%	33%	52%	21%	9%	0	0	24	33	57
211	50%	43%	33%	33%	17%	23%	0	0	18	21	39
212	34%	31%	51%	45%	15%	21%	0	2%	41	42	83
Total	143	121	101	118	46	56	4	5	294	300	594



Secondary Efficacy Endpoint - (Ottawa Scale = Ascending = Excellent + Good + Fair)
Both Studies Combined (ITT)

Ottawa Scale	PicoPrep (n=598)	HalfLytely (n=595)	Difference 95% CI
Excellent + Good + Fair	511/595 (86%)	486/595 (82%)	4% (0%, 8%)
Poor + Inadequate	84/595 (14%)	109/595 (18%)	

Secondary Efficacy Endpoint - (Ottawa Scale = Ascending = Excellent + Good + Fair)
by Age Category - Both Studies Combined (ITT)

Age Category	PicoPrep (n=598)	HalfLytely (n=595)	Difference 95% CI
18 – 64	416/484 (86%)	402/493 (82%)	4% (-0%, 9%)
65 - 80	95/111 (86%)	84/102 (82%)	3% (-7%, 13%)

Secondary Efficacy Endpoint - (Ottawa Scale = Ascending = Excellent + Good + Fair)
by Gender - Both Studies Combined (ITT)

Gender	PicoPrep (n=598)	HalfLytely (n=595)	Difference 95% CI
Female	317/368 (86%)	302/359 (84%)	2% (-3%, 7%)
Male	194/227 (85%)	184/236 (78%)	8% (1%, 15%)

Secondary Efficacy Endpoint- (Ottawa Scale = Ascending = Excellent + Good + Fair)
by Race - Both Studies Combined (ITT)

Race	PicoPrep (n=598)	HalfLytely (n=595)	Difference 95% CI
White	457/533 (86%)	439/532 (83%)	3% (-1%, 8%)
Blake or African American	50/58 (86%)	42/58 (72%)	14% (-1%, 28%)

The other racial groups had very small populations (between 1 to 3 subjects) to draw any conclusions.

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/s/

SHAHLA S FARR
06/27/2012

MICHAEL E WELCH
06/27/2012
Concur with review.

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:	202535/000
Drug Name:	Picoprep (sodium picosulfate, magnesium oxide and citric acid) powder for oral solution
Applicant:	Ferring International Inc.
Date(s):	Submission: 9/16/2011; Consult request: 12/13/2011; PDUFA: 7/16/2012
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: Zana Marks, MD; Medical Team Lead: Robert Fiorentino, MD
Project Manager:	Maureen Dewey

Keywords: Safety analyses, Laboratory parameters, shift analysis, AE under-reporting

Table of Contents

List of Tables

List of Figures

1 EXECUTIVE SUMMARY

The Division of Gastroenterology and Inborn Error Products (DGIEP) consulted the Division of Biometrics VII to provide a statistical safety review for Picoprep (sodium picosulfate, magnesium oxide and citric acid) powder for oral solution as purgative agent of the colon in preparation for a colonoscopy (NDA# 202535). The consult requested a targeted review focusing on potential safety issues associated with bowel preps including changes in laboratory parameters related to the liver, electrolytes and kidney. This review is in response to the consult and has a primary focus to assess whether differences between the study treatments in laboratory parameters exist following administration of study drug, and whether the differences persist through the study follow-up. In addition, this review provides a detailed examination of the specific reported adverse events including: cardiac arrhythmia, seizure and ischemic colitis.

The statistical safety review was performed using data from two phase III, assessor-blinded (patient unblinded), multi-center, randomized, active-controlled, non-inferiority clinical trials designed to investigate the efficacy, safety and tolerability of Picoprep compared to the marketed bowel prep HalfLytely (PEG-3350, sodium chloride, sodium bicarbonate, and potassium chloride for oral soluation and bisacodyl delayed-release tablet). Both trials share a similar study design differing only with respect to the administration of PicoPrep. Specifically, in trial 2009-01, PicoPrep was administered as a split-dose (over two days); in trial 2009-02 PicoPrep was administered the day before the colonoscopy. Both trials were conducted in generally healthy male and female patients ages 18 to 80 undergoing an elective colonoscopy.

Both trials collected laboratory and limited adverse event information on the day of the colonoscopy and on three additional post-treatment follow-up visits over one month. Laboratory parameters were also assessed at baseline.

In trial 2009-01 the safety analysis population, defined as all patients that received at least one dose of study medication, where treatment assignment is based on treatment received, included 603 patients (305 PicoPrep and 298 Halflytely); the safety analysis population for trial 2009-02 included 598 patients (296 Picoprep and 302 Halflytely).

Neither clinical trial was powered nor designed to test safety-related hypotheses concerning specific adverse events or laboratory parameters. Therefore, results from analyses of safety events and abnormal parameters 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 replication of results where feasible.

Findings from this review revealed that select laboratory parameters collected on the day of the colonoscopy (visit 3) differed between groups with respect to either a greater number of abnormal values (in the PicoPrep arm compared to HalfLytely) or the difference in mean change from baseline, which disfavored the PicoPrep arm. Laboratory parameters that differed between groups in both trials include albumin, AST, chloride and magnesium, while the following parameters differed in trial 2009-01 but not 2009-02: urea, potassium and sodium. At the

completion of both trials the initial imbalances that were observed resolved, as presented in Table 1.

Table 1. Incidence of abnormal values for laboratory parameters at the day of the colonoscopy (visit 3) and at the last follow-up visit (visit 6) among patients with normal baseline values

		2009-01		2009-02	
Laboratory Parameters	**Visit**	**PicoPrep n/N (%)**	**HalfLytely n/N (%)**	**PicoPrep n/N (%)**	**HalfLytely n/N (%)**
Potassium	*3*	26/260 (10.0)	16/268 (6.0)	13/274 (4.7)	14/271 (5.2)
	6	13/284 (4.6)	10/278 (3.6)	8/275 (2.9)	11/284 (3.9)
Sodium	*3*	11/298 (3.7)	5/295 (1.7)	3/286 (1.0)	3/295 (1.0)
	6	3/299 (1.0)	5/291 (1.7)	1/284 (0.4)	1/296 (0.3)
Chloride†	*3*	11/301 (3.7)	1/298 (0.3)	3/287 (1.0)	0/297 (0.0)
	6	2/302 (0.7)	3/294 (1.0)	0/285 (0.0)	0/298 (0.0)
Magnesium†‡	*3*	34/294 (11.6)	0/294 (0.0)	25/288 (8.7)	4/289 (1.4)
	6	8/296 (2.7)	3/290 (1.0)	5/286 (1.7)	5/290 (1.7)
Urea†	*3*	60/287 (20.9)	33/276 (12.0)	46/267 (17.2)	39/274 (14.2)
	6	17/287 (5.9)	12/272 (4.4)	15/264 (5.7)	16/274 (5.8)
Albumin†	3	28/294 (9.5)	13/289 (4.5)	16/277 (5.8)	8/283 (2.8)
	6	6/295 (2.0)	3/285 (1.1)	1/275 (0.4)	3/284 (1.1)
AST	3	15/255 (5.9)	9/265 (3.4)	19/272 (7.0)	10/265 (3.8)
	6	6/277 (2.2)	5/275 (1.8)	5/271 (1.8)	10/277 (3.6)

†-95% CI for risk difference at visit 3 excludes 0 in trial 2009-01;
‡-95% CI for risk difference at visit 3 excludes 0 in trial 2009-02.
Visit 3—day of the colonoscopy; Visit 6—28 days after follow-up.

Commonly occurring adverse events of abdominal bloating, distension, pain/cramping, and watery diarrhea were collected in both trials if the events required changes in study drug or study discontinuation, resulted in therapeutic or diagnostic procedures, met the criteria for a serious adverse event, or showed clinically significant worsening during study. There were few of these events reported (<1%) in either trial arm in both trials.

In trial 2009-01 the most commonly reported adverse event was nausea (PicoPrep 4.9%, HalfLytely 4.7%), followed by headache (PicoPrep 4.3%, HalfLytely 2.3%) and vomiting (PicoPrep 1.6%, HalfLytely 3.7%). In trial 2009-02 the most commonly reported adverse event was nausea (PicoPrep 3.7%, HalfLytely 5.3%), followed by headache (PicoPrep 3.4%, HalfLytely 3.3%) and vomiting (PicoPrep 2.0%, HalfLytely 2.6%). The frequency of the events nausea and vomiting in the HalfLytely treatment arms are well below the incidence rates reported in the HalfLytely product label, suggesting possible under-reporting. The difference is most pronounced for nausea, with estimates of 4.7% and 5.3% in the two RCTs compared to 34% and 42% that appear in the HalfLytely product label.

In the both trials there were no reported adverse events for cardiac arrhythmia, seizure, or ischemic colitis, and no patient deaths.

In conclusion, while there were differences between PicoPrep and HalfLytely in selected laboratory parameters collected on the day on the colonoscopy, these differences corrected prior to the completion of follow-up, indicating that imbalances were not present for a prolonged period. Based on review of collected adverse event data, there were no notable imbalances between PicoPrep and HalfLytely. However, the quality of the safety data is of concern given the possibility of under-reporting and selected reporting of commonly occurring adverse events. Therefore, the product label should state that the true risks of the commonly occurring adverse events (those associated with these products) are likely to be larger than what was reported in the two pivotal trials. In addition, the product label should explicitly detail the adverse event collection strategy used in both trials and caution against comparing reported rates of commonly reported adverse in the PicoPrep label against those in other bowel preparation product labels.

2 INTRODUCTION

2.1 Overview

On 16 September 2011 Ferring International Inc. submitted to FDA a New Drug Application (NDA 202535) for Picoprep (sodium picosulfate, magnesium oxide and citric acid) powder for oral solution as purgative agent of the colon in preparation for a colonoscopy. On 13 December 2011, 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 safety issues that are investigated in this review are adverse events and laboratory parameters related to electrolytes, liver chemistries, creatinine and cardiac status. Of primary interest is to assess whether differences in laboratory parameters exist between treatment groups following administration of the study drug, and whether the differences persist through the study follow-up.

This statistical review is supported by the following two confirmatory efficacy clinical trials conducted by the sponsor:

- Trial FE2009-01: "A Randomized, Assessor-Blinded, Multi-Center Study Investigating the Efficacy, Safety and Tolerability of "Split-Dose" PICOPREP^{TM} for Oral Administration versus HalfLytely® for Colon Cleansing in Preparation for Colonoscopy"
- Trial FE2009-02: "A Randomized, Assessor-Blinded, Multi-Center Study Investigating the Efficacy, Safety and Tolerability of "Day Before" PICOPREP^{TM} for Oral Administration versus HalfLytely ® for Colon Cleansing in Preparation for Colonoscopy".

Findings from the statistical safety review are also intended to provide DGIEP supportive material to address a citizen petition for drug applications containing sodium picosulfate. The citizen petition, submitted to FDA on 29 September 2011 by the law firm Cooley, LLP, requests

that FDA i) refrain from approving any NDA containing as active ingredients sodium piosulfate 10mg, magnesium oxide 3.5g, and citric acid 12g for bowel cleansing, or ii) if approval of any such sodium picosulfate NDA is granted, that the product labeling be required to carry a boxed warning describing the heightened risks of electrolyte imbalance and ischemic colitis. Details of the FDA response to this citizen petition are not contained in this review. Refer to the clinical review.

For the statistical review of the clinical efficacy data refer to the statistical review by Dr. Shahla Farr.

2.2 Data Sources

On 16 September 2011 the sponsor submitted the NDA application to FDA in the electronic common technical document (eCTD) format. The submission, including study protocols, analysis plans, study data, and study reports are located at:

\\CDSESUB1\EVSPROD\NDA202535\202535.enx.

Also referenced in this review is the HalfLytely product label (label approval date: 07/16/1980; accessed from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021551s013lbl.pdf)

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Missing Laboratory Tests

In both trials the majority of laboratory parameters examined had one or fewer missing values, as shown in Table 20Table 21 in Section 6. Exceptions to this trend are data from visit 3 for the laboratory parameters ALP, AST and potassium. In trial 2009-01, each of these parameters had 27 (8.9%) and 16 (5.4%) missing values in the PicoPrep and HalfLytely treatment arms, respectively. In trial 2009-02, these three parameters each had 5 (1.7%) missing values in the PicoPrep arm and 12 (4.0%) for HalfLytely. The most commonly reported reason for a missing laboratory value was hemolyzed serum (see Table 21 in Section 6).

Reporting of Commonly Occurring Adverse Events

The incidence of the adverse events vomiting and nausea appear to be smaller than one may expect given the known association of bowel preps with these events. It is possible these adverse events were systematically under-reported, which would make the incidence estimates biased. Additional discussion and details of this concern are provided in Section 3.3.4.3.

3.2 Evaluation of Efficacy

This review does not include an assessment of efficacy.

3.3 Evaluation of Safety

3.3.1 Study Design and Endpoints

Study Design
FE2009-01 and FE2009-02 are phase III, assessor-blinded, multi-center, randomized, active-controlled non-inferiority trials designed to investigate the efficacy, safety and tolerability of PicoPrep for bowel preparation for colonoscopy. Both trials share similar designs differing only with respect to the administration of PicoPrep. In FE2009-01 PicoPrep is administered as a split-dose (over two days); in FE2009-02 PicoPrep is administered the day before the colonoscopy.

Each trial planned to randomize 600 patients over a 6-month enrollment period from investigative sites across the US.

Patients requiring an elective colonoscopy were screened for trial inclusion at visit 1. At visit 2, patients in trial FE2009-01 that satisfied the trial inclusion/exclusion criteria were randomized using 1:1 randomization within site to one of the following products:

- PicoPrep: 2-sachets for oral solution in two divided doses given a night before (first dose) and approximately 5 hours prior to colonoscopy (second dose). Each sachet contains 10mg sodium picosulfate, 3.5g magnesium oxide and 12g citric acid.
- HalfLytely for oral solution and two 5mg Bisacodyl tablets given according to the subject product instruction from the manufacturer, given the day before the procedure. HalfLytely powder contains the following active ingredients: 210g PEG-EL 3350, 5.6g sodium chloride, 2.86g sodium carbonate, and 0.74g potassium chloride.

Patients in trial FE2009-02 that were randomized to PicoPrep were instructed to take the two sachets the day before the colonoscopy, with the first sachet to be taken between 4:00 and 6:00PM, and the second sachet taken at least 6 hours later.

At each site, a designated unblinded coordinator instructed each patient as to the proper administration and the timing of the randomized treatment. In an attempt to ensure blinding of the assessor of the colonoscopy, each patient and unblinded coordinator signed a nondisclosure affidavit form.

Following the colonoscopy (visit 3), patients were instructed to return to the investigational site for 3 additional follow-up visits: within 24-48 hours (+1 day, visit 4), in 7 days (+3 days, visit 5) and in 4 weeks (±5 days, visit 6).

Patients 18 to 80 years of age scheduled to undergo elective colonoscopy were included in the study if they had at least 3 spontaneous bowel movements per week for 1 month prior to the colonoscopy, willing and competent to complete the trial, and signed the informed consent. Females 1) must either be postmenopausal, surgically sterile, or using a medically approved contraception; and 2) that are of childbearing potential have a negative pregnancy test.

Patients were excluded from the study if they had acute surgical abdominal conditions, active inflammatory bowel disease, any prior colorectal surgery, colon disease, ascites, gastrointestinal (GI) disorders, upper GI surgery, renal insufficiency, recent participation in a investigational study, any clinical significant laboratory values at screening, and hypersensitivity to active ingredients.

At visit 1 each patient's demographic, medical history, weight and height was assessed. At each visit except visit 2 the following assessments were made: laboratory, urinalysis, 12-lead electrocardiogram and concomitant medications. All laboratory measurements were performed by a central laboratory.

Adverse event data was collected at visits 3 through visit 6. **The protocol specified that the adverse events abdominal bloating, distension, pain/cramping, and watery diarrhea, which are known to occur in response to colon cleansing, were only to be documented as an adverse event if the findings induced an action, such as 1) changes in study drug or study discontinuation, 2) resulted in therapeutic or diagnostic procedures, 3) met the criteria for a serious adverse event, or 4) showed clinically significant worsening during study.** Adverse events were coded using MedDRA version 13.0.

Reviewer comment: The above strategy for reporting select adverse events except under exceptional circumstances is problematic as it will result in an underestimate of the true incidences. This unconventional reporting strategy will pose limitations in safety labeling specific to these adverse events.

An information request was submitted to the sponsor on 27 January 2012 requesting that the sponsor submit a revised adverse event data set including all adverse event occurrences since the case report form did not explicitly specify the modified collection strategy for select adverse events. In March 2012 the sponsor notified FDA that all available safety data were included in the original 9/16/2011 submission. Despite this discrepancy between the case report form and the protocol, the sponsor stated "the Investigators were instructed to report these AEs if there was action taken or there were seriousness criteria" and that "study sites were trained … on identification and proper documentation of adverse events".

Study Endpoints
All analyses were performed on the safety analysis set, defined as all patients that received at least one dose of study medication, where treatment assignment is based on treatment received.

Adverse events assessed in this review are those occurring at least 2% of the patients and those that are described in the product label for SUPREP, which is a bowel preparation product that is similar to PicoPrep. The focus on SUPREP is motivated by efforts to standardized bowel preparation product labels, which began with the SUPREP label. Adverse events appearing in the SUPREP label include cardiac arrhythmias, seizures, and ischemic colitis.

Laboratory parameters related to liver function evaluated in this review include: albumin (ALB), alkaline phosphatase (ALP), alanine transaminase (ALT), aspirate transaminase (AST), bilirubin, and gamma glutamly transpeptidase (GGT).

Laboratory parameters related to electrolytes or renal function evaluated in this review include: calcium (CA), chloride (CL), potassium (K), magnesium (MG), creatinine (CREATENZ), creatinine clearance (EGFR, defined by Cockcroft-Gault equation) and urea.

3.3.2 Patient Disposition, Demographics & Baseline Characteristics

Trial 2009-01 randomized 608 patients in 10 investigational sites. After excluding 5 patients that did not receive a treatment (PicoPrep 2, HalfLytely 3), the safety analysis set includes 603 patients; 305 that received Picoprep and 298 Halflytely.

Trial 2009-02 randomized 603 patients in 12 investigational sites. After excluding 5 patients that did not receive a treatment (PicoPrep 4, HalfLytely 1), the safety analysis set includes 598 patients; 296 that received Picoprep and 302 Halflytely.

Table 2 displays patient baseline characteristics by trial showing overall balance between treatment groups. Both trials had a greater percentage of females and patients greater than 55 years of age. The majority (>=87%) of patients in both trials were white. Most patients have a medical history that includes cardiovascular, gastrointestinal and renal/genitourological issues.

Table 2. Baseline demographics by study

	Split-dose (Trial 2009-01)			Day before (Trial 2009-02)		
Demographic	**PicoPrep (N=305) n (%)**	**HalfLytely (N=298) n (%)**	**p-value**	**PicoPrep (N=296) n (%)**	**HalfLytely (N=302) n (%)**	**p-value**
Sex						
Male	124 (41)	124 (42)	0.869	104 (35)	113 (37)	0.610
Age						
Age >= 55	154 (51)	161 (54)	0.415	181 (61)	178 (59)	0.617
mean (sd)	54.8 (10)	55.7 (10)	0.276	56.8 (10)	56.2 (10)	0.467
Race			0.869			0.610
White	265 (87)	268 (90)		274 (93)	268 (89)	
Black	36 (12)	27 (9)		22 (7)	32 (11)	
Other	4 (1)	3 (1)		0 (0)	2 (1)	
Medical History						
Cardiovascular	173 (57)	167 (56)	0.870	175 (59)	172 (57)	0.510
Gastrointestinal	236 (77)	218 (73)	0.257	221 (75)	221 (73)	0.579
Metabolic/Endocrine	86 (28)	80 (27)	0.716	115 (39)	108 (36)	0.399
Neurological	78 (26)	80 (27)	0.781	86 (29)	71 (24)	0.115
Renal/Genitourological	197 (65)	183 (61)	0.448	184 (62)	178 (59)	0.360

3.3.3 Statistical Methodologies

To evaluate whether differences in laboratory parameters exist between treatment arms after administration of the study treatment, the following analyses were performed using laboratory values collected at visit 3 (day of colonoscopy):

- *Shift analysis*: Compare the incidence of laboratory values outside the normal range among patients that were normal at baseline. For comparative purposes, risk differences

(RD) for PicoPrep compared to HalfLytely and 95% confidence intervals (CI) are included. Refer to Table 22 in the Appendix for normal range reference values.

- *Mean Analysis:*
  - Calculated mean laboratory value and 95% CI.
  - Calculated the difference in mean change (DMC) from baseline for PicoPrep compared to HalfLytely and 95% CI.

To assess whether imbalances between treatment arms persist at subsequent follow-up visits, the above analyses were repeated using laboratory values collected at visits 4, 5 and 6.

To supplement results from the shift analysis, *modified* scatter plots of laboratory values against visit were constructed to identify trends in the post-treatment laboratory values and to identify potential outliers. This plot is similar to the so-called violin plot (J.L. Hintze, et al.; The American Statistician, Vol 52 (2):181-84, 1998) and is intended to illustrate the frequency of patients with the same laboratory value by horizontally shifting their values, where the degree of shifting is proportional to the number of patients that share the value. Potential outliers are identified from visual inspection. Overlaid on the plots are the normal range limits.

Adverse event data is summarized by frequency tabulation by trial and treatment arm.

3.3.4 Results and Conclusion

3.3.4.1 Liver Function Tests

Baseline Values

In trial 2009-01, for each of the 6 liver function tests assessed, there were no statistically significant differences at baseline between PicoPrep and HalfLytely with regard to either the mean laboratory value (Table 3) or the number of abnormal laboratory values (Table 4). A moderately large proportion of patients had a baseline GGT value outside the normal range (PicoPrep 16.7%, HalfLytely 14.4%), and are therefore excluded from the shift analysis. For the other tests there are fewer patients excluded from the shift analysis. These findings and general trends were observed for trial 2009-02.

Table 3. Summary of baseline liver function laboratory parameters by trial

	2009-01			2009-02		
Laboratory Parameter	**PicoPrep (N=305) Mean (sd)**	**HalfLytely (N=298) Mean (sd)**	**p-value**	**PicoPrep (N=296) Mean (sd)**	**HalfLytely (N=302) Mean (sd)**	**p-value**
Albumin (g/L)	44.7 (2.7)	44.7 (2.5)	0.75	45.0 (2.5)	45.3 (2.5)	0.24
ALP (IU/L)	72.8 (25.1)	74.1 (36.6)	0.61	71.3 (19.4)	71.3 (19.4)	0.98
ALT (IU/L)	26.0 (14.9)	24.2 (13.4)	0.11	25.0 (18.3)	25.6 (17.2)	0.65
AST (IU/L)	25.6 (10.7)	24.7 (10.8)	0.30	23.4 (8.8)	25.0 (11.9)	0.07
Bilirubin (umol/L)	7.8 (4.3)	7.4 (3.6)	0.24	7.8 (4.4)	7.7 (4.0)	0.85
GGT (IU/L)	31.2 (36.6)	30.0 (48.9)	0.73	30.7 (35.7)	33.5 (49.3)	0.43

Table 4. Number of baseline liver function laboratory values outside normal range by trial

	2009-01			2009-02		
Laboratory Parameter	**PicoPrep (N=305) n (%)**	**HalfLytely (N=298) n (%)**	**Fisher p-value**	**PicoPrep (N=296) n (%)**	**HalfLytely (N=302) n (%)**	**Fisher p-value**
Albumin	8 (2.6)	9 (3.0)	0.81	13 (4.4)	14 (4.6)	1
ALP	17 (5.6)	14 (4.7)	0.71	10 (3.4)	9 (3.0)	0.82
ALT	25 (8.2)	15 (5.0)	0.14	19 (6.4)	18 (6.0)	0.87
AST	26 (8.5)	18 (6.0)	0.27	14 (4.7)	21 (7.0)	0.3
Bilirubin	5 (1.6)	3 (1.0)	0.72	9 (3.0)	6 (2.0)	0.44
GGT	51 (16.7)	43 (14.4)	0.5	47 (15.9)	55 (18.2)	0.51

Post-Treatment Values

Study FE2009-01

Shift Analysis

Table 5 displays the percent of patients by liver function test and post-treatment visit that are outside the normal range given they had a normal baseline value. As a supplement to this Table, Table 23 in Section 6.1.1 classifies the abnormal laboratory values according to whether they are below or above the normal range.

Albumin: At visit 3 a statistically significantly greater percentage of patients that received PicoPrep had an albumin value outside the normal range (9.5% versus 4.5%; RD =5.0%; 95% CI= 0.9, 9.1). At visit 4 there are considerably fewer abnormal values, with the number being similar between treatment arms (PicoPrep 2.0% and HalfLytely 0.3%).

AST: At visit 3 there is a non-statistically significant increase in number of patients that received PicoPrep with an abnormal value compared to HalfLytely (5.9% versus 3.4%; RD=2.5%; 95% CI=-1.1, 6.1). This result should be interpreted cautiously as 1) a notable percentage had a missing laboratory value at visit 3 (8.9% PicoPrep and 5.4% HalfLytely), and 2) there is significantly more abnormal values for PicoPrep at visit 4 (3.6% versus 0.7%; RD per 100 pts=2.9; 95% CI=0.5, 5.3). Note: at visit 3 patient 107051 in the PicoPrep group had notably large albumin value at visit 3 (142 IU/L, baseline = 23 IU/L) (see Figure 4). Defer to the clinical review for discussion of any clinical relevance this may suggest.

ALT: There are more abnormal values among patients that received PicoPrep at visit 3 and 4, with the increase at visit 4 being statistically significant (3.2% versus 0.7%; RD =2.5%; 95% CI=0.2, 4.8) compared to the HalfLytely group. No differences exist between treatment groups at visit 6.

Bilirubin: At visit 3, the percentage of abnormal values is similar between treatment groups (PicoPrep 12.2%, HalfLytely 14.0%). The percentages in both groups decreases with visits; by visit 6 there are no abnormal values for HalfLytely compared to 4 for PicoPrep.

ALP and GGT: At each post-treatment visit there is a similar percentage of patients in both treatment groups with an abnormal ALP value with no discernable trend by study visit. The same trend is observed for GGT.

Table 5. Liver function values outside normal range given normal at baseline (trial 2009-01)

Laboratory Parameter	Visit	PicoPrep n/N (%)	HalfLytely n/N (%)	RD (95% CI)
Albumin	3	28/294 (9.5)	13/289 (4.5)	5.0 (0.9, 9.1)
	4	6/295 (2.0)	1/286 (0.3)	1.7 (-0.1, 3.4)
	5	5/296 (1.7)	4/286 (1.4)	0.3 (-1.7, 2.3)
	6	6/295 (2.0)	3/285 (1.1)	1.0 (-1.0, 3.0)
ALP	3	4/263 (1.5)	5/268 (1.9)	-0.3 (-2.5, 1.8)
	4	2/285 (0.7)	4/281 (1.4)	-0.7 (-2.4, 1.0)
	5	1/287 (0.3)	5/281 (1.8)	-1.4 (-3.1, 0.3)
	6	4/286 (1.4)	3/280 (1.1)	0.3 (-1.5, 2.1)
ALT	3	9/275 (3.3)	5/281 (1.8)	1.5 (-1.1, 4.1)
	4	9/278 (3.2)	2/279 (0.7)	2.5 (0.2, 4.8)
	5	9/279 (3.2)	5/280 (1.8)	1.4 (-1.1, 4.0)
	6	6/278 (2.2)	3/279 (1.1)	1.1 (-1.0, 3.2)
AST	3	15/255 (5.9)	9/265 (3.4)	2.5 (-1.1, 6.1)
	4	10/276 (3.6)	2/276 (0.7)	2.9 (0.5, 5.3)
	5	7/278 (2.5)	6/276 (2.2)	0.3 (-2.2, 2.9)
	6	6/277 (2.2)	5/275 (1.8)	0.3 (-2.0, 2.7)
Bilirubin	3	36/296 (12.2)	41/293 (14.0)	-1.8 (-7.3, 3.6)
	4	7/298 (2.3)	2/292 (0.7)	1.7 (-0.3, 3.6)
	5	4/299 (1.3)	0/292 (0.0)	1.3 (0.0, 2.6)
	6	4/298 (1.3)	0/291 (0.0)	1.3 (0.0, 2.6)
GGT	3	6/251 (2.4)	5/255 (2.0)	0.4 (-2.1, 3.0)
	4	6/252 (2.4)	1/252 (0.4)	2.0 (-0.1, 4.0)
	5	7/253 (2.8)	2/253 (0.8)	2.0 (-0.3, 4.3)
	6	6/252 (2.4)	8/252 (3.2)	-0.8 (-3.7, 2.1)

Mean Analysis

Table 6 below presents the mean laboratory value and the difference in mean change from baseline for PicoPrep compared to HalfLytely. As a supplement to this Table, Figure 5 in Section 6.1.1 displays the mean change from baseline for each treatment group.

Albumin: At visit 3 there was a greater increase in the mean change from baseline in the PicoPrep group compared to HalfLytely that approached statistical significance (DMC=0.4 g/L; 95% CI=-0.02, 0.76). At the subsequent follow-up visits both treatments had statistically significantly lower mean values compared to baseline (see Figure 5), which are of a similar magnitude between treatment groups.

GGT: At each post-treatment visit there are no notable differences between groups in the change in mean from baseline

Bilirubin, AST, ALT and ALP: While the mean bilirubin levels significantly increased from baseline to visit 3 in both treatment groups (see Figure 5), the difference in the changes between groups is not statistically significant (DMC=-0.0 umol/L; 95% CI = -0.8, 0.8). Values returned to baseline after visit 3. The same general trend is observed for AST, ALT and ALP.

Table 6. Mean liver function values and difference in mean change from baseline (trial 2009-01)

Laboratory Parameter	Visit	PicoPrep mean (95% CI)	HalfLytely mean (95% CI)	DMC from baseline (95% CI)
Albumin (g/L)	BL	44.7 (44.4, 45.0)	44.7 (44.4, 44.9)	
	3	45.7 (45.4, 46.1)	45.3 (45.0, 45.6)	0.4 (-0.0, 0.8)
	4	43.8 (43.5, 44.1)	43.9 (43.6, 44.2)	-0.1 (-0.5, 0.2)
	5	43.9 (43.6, 44.2)	44.1 (43.8, 44.4)	-0.2 (-0.6, 0.1)
	6	44.1 (43.8, 44.4)	44.2 (43.9, 44.5)	-0.1 (-0.5, 0.3)
ALP (IU/L)	BL	72.8 (70.0, 75.7)	74.1 (70.0, 78.3)	
	3	74.2 (71.5, 76.8)	74.5 (70.6, 78.5)	1.2 (-0.2, 2.7)
	4	72.4 (69.4, 75.5)	73.0 (69.0, 77.0)	0.6 (-0.7, 1.9)
	5	71.6 (68.7, 74.6)	72.3 (68.6, 76.1)	0.1 (-1.3, 1.4)
	6	72.1 (68.9, 75.2)	72.8 (68.8, 76.7)	0.4 (-1.2, 2.0)
ALT (IU/L)	BL	26.0 (24.4, 27.7)	24.2 (22.7, 25.7)	
	3	28.0 (25.8, 30.2)	26.6 (23.5, 29.7)	-0.6 (-3.1, 1.9)
	4	26.3 (24.4, 28.2)	24.2 (21.6, 26.8)	0.2 (-1.8, 2.2)
	5	25.5 (23.6, 27.4)	24.0 (21.8, 26.2)	-0.3 (-2.2, 1.6)
	6	25.4 (23.5, 27.3)	23.3 (21.7, 24.9)	0.4 (-1.1, 1.8)
AST (IU/L)	BL	25.6 (24.4, 26.8)	24.7 (23.5, 25.9)	
	3	28.3 (26.3, 30.4)	27.6 (25.3, 29.9)	0.0 (-2.3, 2.3)
	4	25.4 (23.9, 26.8)	23.8 (22.4, 25.3)	0.6 (-0.7, 1.9)
	5	24.5 (23.3, 25.7)	23.5 (22.1, 24.9)	0.1 (-1.2, 1.4)
	6	25.1 (23.7, 26.5)	23.5 (22.2, 24.9)	0.7 (-0.5, 1.8)
Bilirubin (umol/L)	BL	7.8 (7.3, 8.3)	7.4 (7.0, 7.8)	
	3	13.3 (12.4, 14.1)	12.9 (12.1, 13.8)	-0.0 (-0.8, 0.8)
	4	7.4 (6.9, 7.9)	7.2 (6.7, 7.7)	-0.2 (-0.7, 0.3)
	5	7.3 (6.9, 7.8)	7.2 (6.7, 7.6)	-0.2 (-0.7, 0.2)
	6	7.8 (7.3, 8.3)	7.3 (6.8, 7.7)	0.1 (-0.3, 0.6)
GGT (IU/L)	BL	31.2 (27.1, 35.3)	30.0 (24.4, 35.5)	
	3	32.6 (27.8, 37.4)	29.8 (24.2, 35.4)	1.5 (-0.7, 3.8)
	4	30.3 (26.0, 34.7)	28.7 (23.0, 34.3)	0.5 (-1.0, 2.1)
	5	30.2 (26.1, 34.3)	28.8 (23.6, 34.0)	0.2 (-2.0, 2.4)
	6	31.7 (26.9, 36.6)	29.9 (24.3, 35.5)	0.6 (-2.4, 3.6)

DMC—Difference in mean change, BL=baseline assessment

Study FE2009-02

Shift Analysis

Table 7 shows the percent of patients by liver function test and post-treatment visit that are outside the normal range given they had a normal baseline measurement. As a supplement to this Table, Table 24 in Section 6.1.2 classifies the abnormal laboratory values according to whether they are below or above the normal range.

Albumin: At visit 3 there is a non-statistically significant increase in the proportion of PicoPrep patients with an abnormal value compared to HalfLytely (5.8% versus 2.8%). Compared to visit 3, the percentage of abnormal values at visit 4 is smaller for both treatment groups and is similar between them (PicoPrep 0.7%, HalfLytely 1.1%).

AST: At visit 3 there are more abnormal values in the PicoPrep group compared to HalfLytely (7.0% versus 3.8%) though not statistically significant (RD=3.2%; 95% CI=-0.6, 7.0). At visit 4 the percentage of abnormal values for PicoPrep decreases to 2.9%, which is slightly below the percentage for HalfLytely (4.1%).

Bilirubin: At visit 3, both treatment arms have a similar percentage of patients with an abnormal laboratory value (PicoPrep 8.5%, HalfLytely 8.0%); by visit 4 the percentages are considerably decreased from those seen at visit 3 and similar between groups.

GGT: Compared to HalfLytely, there is a greater number of abnormal values for PicoPrep at visit 3 (4.5% versus 1.6%) and visit 4 (4.1% versus 1.3%); neither of these differences are statistically different. By visit 6 the percentages are similar percentage between treatment arms.

ALT and ALP: At each follow-up visit the percentage of abnormal ALT values in the two treatment groups is small and similar between groups. This trend is similar for ALP, except the percentages tended to be smaller. Note: There are a few outlier values observed for ALP at visit 5 and 6 in the PicoPrep group (see Figure 7). The importance of these outliers is unclear.

Table 7. Liver function values outside normal range given normal at baseline (trial 2009-02)

Laboratory Parameter	Visit	PicoPrep n/N (%)	HalfLytely n/N (%)	RD (95% CI)
Albumin	3	16/277 (5.8)	8/283 (2.8)	2.9 (-0.4, 6.3)
	4	2/275 (0.7)	3/279 (1.1)	-0.3 (-1.9, 1.2)
	5	2/275 (0.7)	7/279 (2.5)	-1.8 (-3.9, 0.3)
	6	1/275 (0.4)	3/284 (1.1)	-0.7 (-2.1, 0.7)
ALP	3	2/276 (0.7)	3/276 (1.1)	-0.4 (-1.9, 1.2)
	4	2/278 (0.7)	2/283 (0.7)	0.0 (-1.4, 1.4)
	5	3/277 (1.1)	4/283 (1.4)	-0.3 (-2.2, 1.5)
	6	1/275 (0.4)	2/289 (0.7)	-0.3 (-1.5, 0.9)
ALT	3	10/271 (3.7)	9/277 (3.2)	0.4 (-2.6, 3.5)
	4	10/269 (3.7)	7/275 (2.5)	1.2 (-1.8, 4.1)
	5	3/269 (1.1)	10/276 (3.6)	-2.5 (-5.0, 0.0)
	6	5/269 (1.9)	12/280 (4.3)	-2.4 (-5.3, 0.4)
AST	3	19/272 (7.0)	10/265 (3.8)	3.2 (-0.6, 7.0)
	4	8/273 (2.9)	11/271 (4.1)	-1.1 (-4.2, 2.0)
	5	2/273 (0.7)	4/271 (1.5)	-0.7 (-2.5, 1.0)
	6	5/271 (1.8)	10/277 (3.6)	-1.8 (-4.5, 1.0)
Bilirubin	3	24/281 (8.5)	23/289 (8.0)	0.6 (-3.9, 5.1)
	4	2/280 (0.7)	1/287 (0.3)	0.4 (-0.8, 1.6)
	5	1/279 (0.4)	0/288 (0.0)	0.4 (-0.3, 1.1)
	6	3/279 (1.1)	3/292 (1.0)	0.0 (-1.6, 1.7)
GGT	3	11/245 (4.5)	4/244 (1.6)	2.9 (-0.2, 5.9)
	4	10/242 (4.1)	3/239 (1.3)	2.9 (-0.0, 5.8)
	5	7/241 (2.9)	4/240 (1.7)	1.2 (-1.4, 3.9)
	6	12/241 (5.0)	9/244 (3.7)	1.3 (-2.3, 4.9)

Mean Analysis

Table 8 below presents the mean laboratory value and the difference in mean change from baseline for PicoPrep compared to HalfLytely. As a supplement to this Table, Figure 8 in Section 6.1.2 displays the mean change from baseline for each treatment group.

Albumin: Compared to baseline, the visit 3 mean albumin level significantly increased in the PicoPrep group (see Figure 8), while decreasing slightly for HalfLytely, with the difference in mean change between treatment groups being statistically significant (DMC=0.9 g/L; 95% CI = 0.5, 1.3). These findings are not changed after excluding a possible outlier in the HalfLytely group with a visit 3 albumin value slightly above 25 g/L (see Figure 6). At visit 5 there is no difference between groups.

Bilirubin and AST: While PicoPrep and HalfLytely both have a statistically significant increases in mean bilirubin levels from baseline (see Figure 8), no differences are noted between treatment groups in mean change from baseline. Mean values are similar to baseline at subsequent visits in both treatment groups. The same general trend is observed for AST.

ALP, ALT and GGT: The mean ALP levels are of a similar magnitude between treatment groups at each post-treatment visit. The same general trend is observed for the laboratory parameters ALT and GGT.

Table 8. Mean liver function values and difference in mean change from baseline (trial 2009-02)

Laboratory Parameter	Visit	PicoPrep mean (95% CI)	HalfLytely mean (95% CI)	DMC from baseline (95% CI)
Albumin (g/L)	BL	45.0 (44.8, 45.3)	45.3 (45.0, 45.6)	-
	3	45.7 (45.4, 46.0)	45.1 (44.7, 45.4)	0.9 (0.5, 1.3)
	4	44.5 (44.2, 44.7)	44.3 (44.0, 44.6)	0.4 (0.1, 0.7)
	5	44.4 (44.1, 44.7)	44.5 (44.2, 44.7)	0.2 (-0.1, 0.6)
	6	44.4 (44.1, 44.7)	44.4 (44.2, 44.7)	0.2 (-0.1, 0.6)
ALP (IU/L)	BL	71.3 (69.1, 73.5)	71.3 (69.1, 73.5)	-
	3	72.1 (69.9, 74.3)	71.2 (68.9, 73.5)	0.8 (-0.5, 2.0)
	4	70.1 (68.1, 72.1)	70.6 (68.5, 72.8)	0.2 (-1.1, 1.4)
	5	70.1 (67.8, 72.4)	70.9 (68.8, 73.0)	-0.7 (-2.2, 0.8)
	6	70.7 (68.4, 73.0)	70.9 (68.7, 73.0)	-0.2 (-1.8, 1.3)
ALT (IU/L)	BL	25.0 (22.9, 27.1)	25.6 (23.7, 27.6)	-
	3	26.2 (24.5, 27.9)	26.8 (24.7, 28.8)	-0.1 (-1.9, 1.8)
	4	25.1 (23.6, 26.7)	26.0 (24.0, 28.1)	-0.3 (-2.4, 1.8)
	5	23.4 (21.6, 25.2)	24.9 (23.0, 26.7)	-1.0 (-3.1, 1.1)
	6	24.6 (23.1, 26.0)	26.0 (24.0, 28.0)	-1.0 (-3.2, 1.2)
AST (IU/L)	BL	23.4 (22.4, 24.4)	25.0 (23.6, 26.3)	-
	3	26.2 (24.9, 27.6)	27.2 (25.5, 28.9)	0.6 (-0.7, 1.9)
	4	24.0 (22.9, 25.2)	25.2 (23.7, 26.7)	0.4 (-0.9, 1.8)
	5	22.5 (21.5, 23.6)	24.5 (23.0, 26.0)	-0.4 (-1.8, 1.0)
	6	23.3 (22.3, 24.2)	24.6 (23.1, 26.0)	0.2 (-0.9, 1.4)
Bilirubin (umol/L)	BL	7.8 (7.3, 8.3)	7.7 (7.2, 8.1)	-
	3	12.7 (11.9, 13.4)	12.6 (11.9, 13.3)	0.0 (-0.6, 0.6)
	4	7.5 (7.0, 7.9)	7.2 (6.8, 7.7)	0.2 (-0.2, 0.6)
	5	7.3 (6.8, 7.8)	7.2 (6.8, 7.7)	-0.1 (-0.5, 0.4)
	6	7.6 (7.1, 8.1)	7.5 (7.0, 8.0)	0.0 (-0.4, 0.5)
GGT (IU/L)	BL	30.7 (26.7, 34.8)	33.5 (28.0, 39.1)	-
	3	29.9 (26.1, 33.6)	34.1 (28.2, 40.0)	-0.8 (-3.0, 1.3)
	4	28.8 (25.5, 32.0)	33.0 (27.2, 38.8)	-1.3 (-3.8, 1.2)
	5	29.1 (25.7, 32.5)	32.3 (27.0, 37.7)	-1.3 (-4.2, 1.7)
	6	32.1 (27.7, 36.6)	33.6 (27.8, 39.4)	0.7 (-2.3, 3.7)

DMC—difference in mean change, BL=baseline assessment

3.3.4.2 Electrolyte Values and Renal Function Tests

Baseline Values

In both trials for each of the electrolyte and renal laboratory parameters listed in Table 9, there are no statistically significant differences at baseline between PicoPrep and HalfLytely for either the mean laboratory value (Table 9) or the number of abnormal values (Table 10).

In trial 2009-01, 26.6% and 28.2% of patients in the PicoPrep and HalfLytely groups, respectively, had a creatinine value outside the normal range, and are therefore excluded from the shift analysis. The laboratory test creatinine also had a sizable number of patients with baseline values outside the normal range (PicoPrep 13.1%, HalfLytely 9.7%). The same general trends are observed in trial 2009-02.

Table 9. Summary of baseline electrolyte and renal laboratory values by trial

	2009-01			2009-02		
Laboratory Parameter	**PicoPrep (N=305) Mean (sd)**	**HalfLytely (N=298) Mean (sd)**	**p-value**	**PicoPrep (N=296) Mean (sd)**	**HalfLytely (N=302) Mean (sd)**	**p-value**
Potassium (mmol/L)	4.2 (0.4)	4.3 (0.5)	0.18	4.2 (0.4)	4.2 (0.4)	0.98
Sodium (mmol/L)	139.6 (2.1)	139.7 (2.1)	0.49	139.4 (2.0)	139.3 (2.0)	0.62
Chloride (mmol/L)	102.7 (2.5)	102.7 (2.3)	0.84	102.6 (2.4)	102.4 (2.4)	0.29
Magnesium (mmol/L)	0.9 (0.1)	0.9 (0.1)	0.64	0.9 (0.1)	0.9 (0.1)	0.67
Calcium (mmol/L)	2.4 (0.1)	2.4 (0.1)	0.30	2.4 (0.1)	2.4 (0.1)	0.47
Creatinine (umol/L)	74.0 (17.8)	74.0 (15.1)	0.99	73.5 (16.2)	72.8 (15.9)	0.56
EGFR	114.6 (37.7)	112.9 (38.2)	0.58	108.3 (31.5)	111.8 (34.0)	0.20
Urea (mmol/L)	5.5 (1.6)	5.6 (1.7)	0.60	5.5 (1.6)	5.7 (1.6)	0.16

Table 10. Number of baseline electrolyte and renal laboratory values outside normal range by trial

	2009-01			2009-02		
Laboratory Parameter	**PicoPrep (N=305) n (%)**	**HalfLytely (N=298) n (%)**	**Fisher p-value**	**PicoPrep (N=296) n (%)**	**HalfLytely (N=302) n (%)**	**Fisher p-value**
Potassium	20 (6.6)	15 (5.0)	0.49	11 (3.7)	15 (5.0)	0.55
Sodium	4 (1.3)	3 (1.0)	1	4 (1.4)	2 (0.7)	0.45
Chloride	1 (0.3)	0 (0.0)	1	3 (1.0)	0 (0.0)	0.12
Magnesium	7 (2.3)	4 (1.3)	0.55	2 (0.7)	8 (2.6)	0.11
Calcium	11 (3.6)	12 (4.0)	0.83	14 (4.7)	15 (5.0)	1
Creatinine	40 (13.1)	29 (9.7)	0.2	25 (8.4)	27 (8.9)	0.89
EGFR	81 (26.6)	84 (28.2)	0.71	93 (31.4)	74 (24.5)	0.07
Urea	16 (5.2)	22 (7.4)	0.32	25 (8.4)	24 (7.9)	0.88

Post-Treatment Values

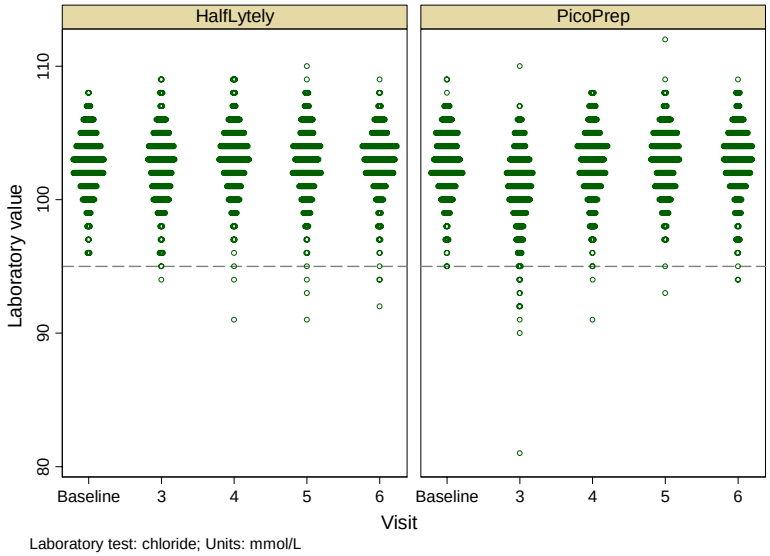
Study FE2009-01

The number of patients with an abnormal laboratory value for the electrolyte or renal parameters is presented in Table 11. As a supplement to this Table, Table 25 in Section 6.2.1 classifies the abnormal values according to whether they are below or above the normal range.

Shift Analysis

Chloride: At visit 3 the percentage of patients with an abnormal chloride value is statistically significantly greater in the PicoPrep group (3.7%) compared to HalfLytely (0.3%) resulting in a RD of 3.3% and 95% CI=1.1, 5.5. At this visit, there are several patients in the PicoPrep group with a chloride level below normal (see Figure 1), with patient 108012 having a notably small value near 80 mmol/L. At visit 4 there is a decrease in the percentage of abnormal values for PicoPrep, to 0.7%, which is similar to the percentage for HalfLytely (0.7%).

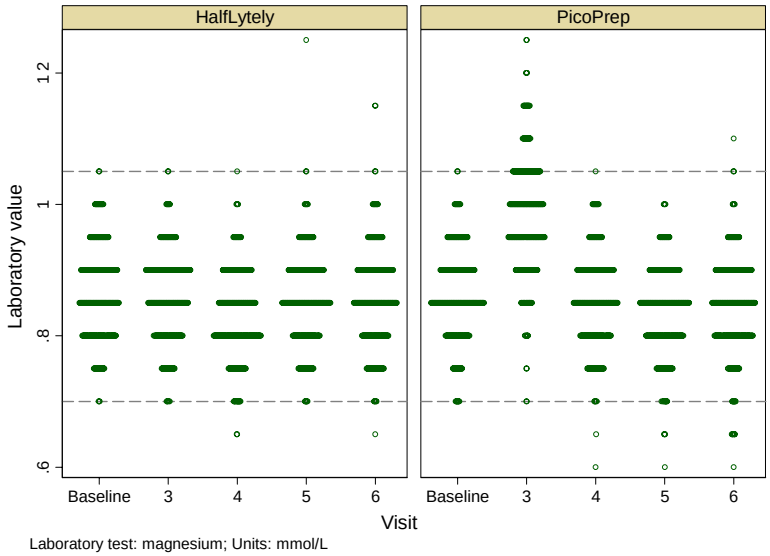
Figure 1. Modified scatterplot of chloride values by visits among patients with normal baseline (trial 2009-01)



Dotted line represents lower bound of normal

Magnesium: PicoPrep has significantly more patients with a magnesium laboratory value outside the normal range at visit 3 (11.6% versus 0%, RD =11.6%; 95% CI=7.9, 15.2). This is likely associated with PicoPrep containing magnesium as an active ingredient. After visit 3, magnesium levels returned to normal as shown in Figure 2.

Figure 2. Modified scatterplot of MG values by visits among patients with normal baseline (trial 2009-01)



Dotted line represents upper and lower bounds of normal

Urea: At visit 3, both treatment arms had a large percentage of abnormal values, with statistically significantly more for PicoPrep (20.9% versus 12.0%; RD of 8.9%, 95% CI=2.9, 15.0). At visit 4 there is a decrease in the number of patients with an abnormal value, with the PicoPrep group continuing to have a greater proportion of patients with abnormal values (5.6% versus 3.3%, difference not statistically significant). This trend continued until visit 6.

Sodium: At visit 3 a greater number of patients in the PicoPrep group had an abnormal sodium (3.7% versus 1.7%, RD=2.0%; 95% CI=-0.6, 4.6); all of abnormal PicoPrep values were below the lower limit of normal, with patient 108012 having a notably small value (see Figure 9). Note: This patient also had a notably abnormal value for chloride at visit 3. At the next follow-up visit the number of abnormal values dropped for PicoPrep to a level that is similar to HalfLytely (1.3% versus 1.7%).

Potassium: At visit 3 a greater number of patients in the PicoPrep group had an abnormal value compared to HalfLytely (10.0% versus 6.0%, RD=4.0%; 95% CI=-0.6, 8.6). This non-significant difference should be interpreted cautiously given 15 and 24 patients in the HalfLytely and PicoPrep group, respectively, were excluded from this analysis because of missing values. At visit 4 the percentages are smaller for both treatment groups, with the percentage remaining greater for PicoPrep (6.7% versus 3.9%). By visit 6 the percentages are similar in the two groups.

Calcium, Creatinine, and Creatinine Clearance: The percentage of abnormal calcium values is similar for PicoPrep and HalfLytely at each post-treatment visit. The same general trend is observed for creatinine and creatinine clearance.

Table 11. Electrolyte and renal values outside normal range given normal at baseline (trial 2009-02)

Outside normal range	Visit	PicoPrep n/N (%)	HalfLytely n/N (%)	RD (95% CI)
Potassium	3	26/260 (10.0)	16/268 (6.0)	4.0 (-0.6, 8.6)
	4	19/282 (6.7)	11/279 (3.9)	2.8 (-0.9, 6.5)
	5	16/285 (5.6)	16/279 (5.7)	-0.1 (-3.9, 3.7)
	6	13/284 (4.6)	10/278 (3.6)	1.0 (-2.3, 4.3)
Sodium	3	11/298 (3.7)	5/295 (1.7)	2.0 (-0.6, 4.6)
	4	4/299 (1.3)	5/292 (1.7)	-0.4 (-2.4, 1.6)
	5	3/300 (1.0)	2/292 (0.7)	0.3 (-1.2, 1.8)
	6	3/299 (1.0)	5/291 (1.7)	-0.7 (-2.6, 1.2)
Chloride	3	11/301 (3.7)	1/298 (0.3)	3.3 (1.1, 5.5)
	4	2/302 (0.7)	2/295 (0.7)	-0.0 (-1.3, 1.3)
	5	1/303 (0.3)	3/295 (1.0)	-0.7 (-2.0, 0.6)
	6	2/302 (0.7)	3/294 (1.0)	-0.4 (-1.8, 1.1)
Magnesium	3	34/294 (11.6)	0/294 (0.0)	11.6 (7.9, 15.2)
	4	2/296 (0.7)	2/291 (0.7)	-0.0 (-1.3, 1.3)
	5	4/297 (1.3)	1/291 (0.3)	1.0 (-0.5, 2.5)
	6	8/296 (2.7)	3/290 (1.0)	1.7 (-0.5, 3.9)
Calcium	3	6/292 (2.1)	7/286 (2.4)	-0.4 (-2.8, 2.0)
	4	2/292 (0.7)	6/283 (2.1)	-1.4 (-3.4, 0.5)
	5	5/293 (1.7)	4/283 (1.4)	0.3 (-1.7, 2.3)
	6	7/292 (2.4)	5/282 (1.8)	0.6 (-1.7, 3.0)
Creatinine	3	7/260 (2.7)	15/268 (5.6)	-2.9 (-6.3, 0.5)
	4	20/264 (7.6)	12/267 (4.5)	3.1 (-1.0, 7.1)
	5	11/264 (4.2)	13/267 (4.9)	-0.7 (-4.2, 2.8)
	6	12/264 (4.5)	15/265 (5.7)	-1.1 (-4.9, 2.6)
eGFR	3	22/221 (10.0)	17/214 (7.9)	2.0 (-3.3, 7.4)
	4	32/223 (14.3)	22/212 (10.4)	4.0 (-2.2, 10.1)
	5	22/223 (9.9)	17/213 (8.0)	1.9 (-3.5, 7.2)
	6	24/223 (10.8)	21/211 (10.0)	0.8 (-4.9, 6.5)
Urea	3	60/287 (20.9)	33/276 (12.0)	8.9 (2.9, 15.0)
	4	16/287 (5.6)	9/274 (3.3)	2.3 (-1.1, 5.7)
	5	17/288 (5.9)	11/274 (4.0)	1.9 (-1.7, 5.5)
	6	17/287 (5.9)	12/272 (4.4)	1.5 (-2.2, 5.2)

Mean Analysis

Table 12 below presents the mean laboratory value and the difference in mean change from baseline for PicoPrep compared to HalfLytely.

Sodium: At visit 3, compared to HalfLytely, there was a significantly greater decrease in mean sodium levels from baseline (DMC=-0.6 mmol/L; 95% CI=-0.9, -0.2) in the PicoPrep arm. These findings are not sensitive to excluding patient 108012, which is a possible outlier in the PicoPrep group; this patient had a sodium value just above 120 mmol/L at visit 3 (see Figure 9). By visit 4, there was no difference between treatment groups.

Chloride: At visit 3, compared to HalfLytely, there was a significantly greater decrease in mean levels from the baseline (DMC=-1.6 mmol/L; 95% CI=-2.0, -1.2) in the PicoPrep arm. These findings are not sensitive to excluding a possible outlier in the PicoPrep group with a chloride value near 80 mmol/L at visit 3 (see Figure 1). After visit 3, no differences between groups are noted.

Magnesium: Compared to HalfLytely, patients that received PicoPrep had a significantly greater increase in the mean change from baseline at visit 3 (DMC=0.12 mmol/L; 95% CI=0.11, 0.14). Among patients that received PicoPrep, the significantly elevated mean magnesium levels at visit 3 were below the mean baseline levels at subsequent visits (see Figure 10).

Potassium and Urea: Despite PicoPrep and HalfLytely each having a significantly lower mean potassium values at visit 3 compared to baseline (see Figure 10), the difference between treatment groups is not statistically significant (DMC=-0.03; 95% CI = -0.10, 0.04). At visit 5 there is no difference between groups compared to baseline. This same general trend is observed for urea.

Calcium: At each post-treatment visit there is no difference between groups.

Creatinine Clearance: Despite PicoPrep and HalfLytely each having statistically significant decreases in their mean values from baseline at each of the post-treatment visits (see Figure 10), there is no statistical difference between treatment groups.

Creatinine: At visits 3, 5 and 6 there is no statistical difference in the mean change between treatment groups.

Table 12. Mean laboratory value and difference in mean change from baseline (trial 2009-01)

Laboratory Parameter	Visit	PicoPrep Mean (95% CI)	HalfLytely mean (95% CI)	DMC from baseline (95% CI)
Potassium (mmol/L)	BL	4.21 (4.17, 4.26)	4.26 (4.21, 4.31)	
	3	4.11 (4.05, 4.16)	4.18 (4.12, 4.23)	-0.03 (-0.10, 0.04)
	4	4.15 (4.10, 4.20)	4.12 (4.08, 4.17)	0.07 (0.01, 0.14)
	5	4.18 (4.13, 4.23)	4.24 (4.18, 4.29)	-0.01 (-0.08, 0.06)
	6	4.15 (4.11, 4.20)	4.23 (4.18, 4.27)	-0.03 (-0.09, 0.04)
Sodium (mmol/L)	BL	139.6 (139.4, 139.9)	139.7 (139.5, 140.0)	
	3	138.9 (138.6, 139.2)	139.6 (139.3, 139.9)	-0.6 (-0.9, -0.2)
	4	139.3 (139.0, 139.5)	139.4 (139.2, 139.7)	-0.0 (-0.4, 0.3)
	5	139.5 (139.3, 139.8)	139.5 (139.2, 139.7)	0.2 (-0.1, 0.5)
	6	139.5 (139.2, 139.7)	139.5 (139.2, 139.8)	0.1 (-0.3, 0.4)
Chloride (mmol/L)	BL	102.7 (102.4, 102.9)	102.7 (102.4, 103.0)	
	3	100.9 (100.5, 101.2)	102.5 (102.2, 102.8)	-1.6 (-2.0, -1.2)
	4	102.6 (102.3, 102.9)	103.0 (102.7, 103.3)	-0.3 (-0.7, 0.0)
	5	102.9 (102.6, 103.2)	102.7 (102.4, 103.0)	0.3 (-0.1, 0.6)
	6	102.8 (102.5, 103.1)	102.8 (102.5, 103.1)	0.0 (-0.3, 0.4)
Magnesium (mmol/L)	BL	0.86 (0.85, 0.87)	0.86 (0.85, 0.87)	
	3	0.98 (0.97, 0.99)	0.86 (0.85, 0.87)	0.12 (0.11, 0.14)
	4	0.85 (0.84, 0.86)	0.83 (0.82, 0.84)	0.02 (0.01, 0.03)
	5	0.83 (0.83, 0.84)	0.85 (0.84, 0.86)	-0.02 (-0.03, -0.01)
	6	0.84 (0.83, 0.85)	0.85 (0.84, 0.86)	-0.01 (-0.02, 0.00)
Calcium (mmol/L)	BL	2.37 (2.36, 2.38)	2.36 (2.35, 2.37)	
	3	2.37 (2.35, 2.38)	2.37 (2.36, 2.38)	-0.01 (-0.03, 0.00)
	4	2.33 (2.32, 2.35)	2.33 (2.32, 2.34)	-0.01 (-0.02, 0.01)
	5	2.35 (2.34, 2.36)	2.34 (2.33, 2.35)	0.00 (-0.01, 0.02)
	6	2.35 (2.34, 2.37)	2.36 (2.35, 2.37)	-0.01 (-0.03, 0.00)
Creatinine (umol/L)	BL	74.0 (72.0, 76.0)	74.0 (72.3, 75.7)	
	3	74.9 (73.0, 76.9)	75.4 (73.8, 77.0)	-0.9 (-2.1, 0.3)
	4	77.4 (75.2, 79.7)	75.9 (74.2, 77.6)	1.4 (0.1, 2.8)
	5	76.1 (74.0, 78.2)	76.0 (74.3, 77.7)	-0.2 (-1.5, 1.1)
	6	76.5 (74.5, 78.5)	76.1 (74.4, 77.8)	0.4 (-1.0, 1.8)
EGFR	BL	114.6 (110.4, 118.9)	112.9 (108.6, 117.3)	
	3	111.2 (107.3, 115.1)	109.0 (104.8, 113.2)	0.3 (-2.1, 2.7)
	4	108.7 (104.7, 112.7)	108.7 (104.6, 112.7)	-1.5 (-4.0, 1.0)
	5	111.1 (107.1, 115.2)	109.2 (105.1, 113.3)	0.6 (-1.9, 3.0)
	6	110.0 (106.0, 114.0)	108.2 (104.2, 112.2)	-0.3 (-2.8, 2.3)
Urea (mmol/L)	BL	5.5 (5.3, 5.7)	5.6 (5.4, 5.8)	
	3	4.1 (3.9, 4.2)	4.3 (4.2, 4.5)	-0.2 (-0.4, 0.0)
	4	5.3 (5.1, 5.5)	5.2 (5.1, 5.4)	0.1 (-0.1, 0.3)
	5	5.4 (5.3, 5.6)	5.5 (5.3, 5.7)	0.0 (-0.2, 0.2)
	6	5.6 (5.4, 5.8)	5.6 (5.4, 5.8)	0.0 (-0.2, 0.2)

DMC—Difference in mean change, BL=baseline assessment

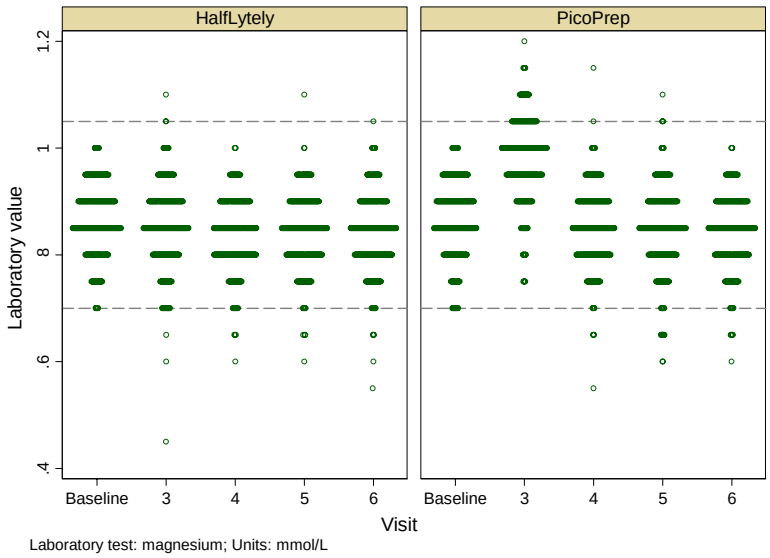
Study FE2009-02

Shift Analysis

The number of patients with an abnormal laboratory value for the electrolyte or renal parameters is displayed in Table 13.

Magnesium: At visit 3 significantly more patients in the PicoPrep group had an abnormal magnesium value compared to HalfLytely (8.7% versus 1.4%, RD=7.3%; 95% CI=3.8, 10.8). At visit 4, the percentage of abnormal values for PicoPrep decreased to 1.7%, which is similar to the 1.4% observed for HalfLytely. The return to normal in the PicoPrep group after visit 3 is shown in Figure 3.

Figure 3. Modified scatterplot of MG values by visits among patients with normal baseline (trial 2009-02)



Urea: At visit 3, there are slightly more patients in the PicoPrep with an abnormal value compared to HalfLytely (PicoPrep 17.2%, HalfLytely 14.2%); by visit 4 the percentages are considerably decreased from those seen at visit 3, with slightly more abnormal values for PicoPrep (6.8% versus 4.1%). At visit 6 the numbers are similar between treatment groups.

Chloride: For the PicoPrep group, there are 3 patients with an abnormal value at visit 3 and 0 by visit 5. There were no abnormal values in the HalfLytely group.

Potassium, Sodium, Calcium: At visit 3 both treatment groups had a similar percentage of patients with an abnormal potassium value, which decreased at subsequent visits. This same trend is observed for sodium and calcium.

Creatinine, and Creatinine Clearance: At each post-treatment visit there is a similar percentage of patients in both treatment groups with an abnormal creatinine value. The same trend is observed for creatinine clearance.

Table 13. Electrolyte and renal laboratory values outside normal range given normal range at baseline (Trial 2009-02)

Outside normal range	Visit	PicoPrep n/N (%)	HalfLytely n/N (%)	RD (95% CI)
Potassium	3	13/274 (4.7)	14/271 (5.2)	-0.4 (-4.1, 3.2)
	4	9/276 (3.3)	9/277 (3.2)	0.0 (-2.9, 3.0)
	5	8/276 (2.9)	14/278 (5.0)	-2.1 (-5.4, 1.1)
	6	8/275 (2.9)	11/284 (3.9)	-1.0 (-4.0, 2.0)
Sodium	3	3/286 (1.0)	3/295 (1.0)	0.0 (-1.6, 1.7)
	4	4/284 (1.4)	1/291 (0.3)	1.1 (-0.5, 2.6)
	5	1/285 (0.4)	1/291 (0.3)	0.0 (-1.0, 1.0)
	6	1/284 (0.4)	1/296 (0.3)	0.0 (-0.9, 1.0)
Chloride	3	3/287 (1.0)	0/297 (0.0)	1.0 (-0.1, 2.2)
	4	1/285 (0.4)	0/293 (0.0)	0.4 (-0.3, 1.0)
	5	0/285 (0.0)	0/293 (0.0)	0.0 (0.0, 0.0)
	6	0/285 (0.0)	0/298 (0.0)	0.0 (0.0, 0.0)
Magnesium	3	25/288 (8.7)	4/289 (1.4)	7.3 (3.8, 10.8)
	4	5/286 (1.7)	4/285 (1.4)	0.3 (-1.7, 2.4)
	5	11/286 (3.8)	5/285 (1.8)	2.1 (-0.6, 4.8)
	6	5/286 (1.7)	5/290 (1.7)	0.0 (-2.1, 2.2)
Calcium	3	9/276 (3.3)	8/282 (2.8)	0.4 (-2.4, 3.3)
	4	6/274 (2.2)	7/278 (2.5)	-0.3 (-2.9, 2.2)
	5	3/274 (1.1)	4/278 (1.4)	-0.3 (-2.2, 1.5)
	6	4/274 (1.5)	3/283 (1.1)	0.4 (-1.5, 2.3)
Creatinine	3	14/266 (5.3)	18/270 (6.7)	-1.4 (-5.4, 2.6)
	4	19/263 (7.2)	16/266 (6.0)	1.2 (-3.0, 5.4)
	5	13/264 (4.9)	12/265 (4.5)	0.4 (-3.2, 4.0)
	6	19/264 (7.2)	10/272 (3.7)	3.5 (-0.3, 7.4)
eGFR	3	26/199 (13.1)	25/224 (11.2)	1.9 (-4.3, 8.1)
	4	25/198 (12.6)	27/220 (12.3)	0.4 (-6.0, 6.7)
	5	11/198 (5.6)	28/219 (12.8)	-7.2 (-12.7, -1.8)
	6	21/199 (10.6)	24/224 (10.7)	-0.2 (-6.0, 5.7)
Urea	3	46/267 (17.2)	39/274 (14.2)	3.0 (-3.1, 9.1)
	4	18/263 (6.8)	11/269 (4.1)	2.8 (-1.1, 6.6)
	5	12/265 (4.5)	11/269 (4.1)	0.4 (-3.0, 3.9)
	6	15/264 (5.7)	16/274 (5.8)	-0.2 (-4.1, 3.8)

Mean Analysis

Table 14 below presents the mean laboratory value and the difference in mean change from baseline for PicoPrep compared to HalfLytely.

Chloride: At visit 3 patients that received PicoPrep compared to HalfLytely had a significantly greater decrease in mean levels from the baseline (DMC=-1.2 mmol/L; 95% CI=-1.6, -0.8). By visit 4 there is no difference between treatment groups.

Magnesium: Compared to HalfLytely, patients that received PicoPrep had a significantly greater increase in the mean change from baseline at visit 3 (DMC=0.13 mmol/L; 95% CI =0.11, 0.14). By visit 5 there is no difference between treatment groups.

Urea: Although PicoPrep and HalfLytely each had significantly lower mean values at visit 3 compared to baseline (see Figure 11), there is no statistical difference in the change from baseline between treatment groups. Values returned to near baseline after visit 4.

Potassium and Calcium: At visit 3, the difference in the change from baseline between treatment groups is statistically significantly (DMC = 0.08 mmol/L; 95% CI =0.01, 0.15), with the mean in the PicoPrep group increasing from 4.19 to 4.21, but decreasing from 4.19 to 4.13 for HalfLytely. After visit 3 there is no difference between groups. The same general trend is observed for calcium.

Sodium: At visit 3 both PicoPrep and HalfLytely had an increase in the mean sodium level from baseline, with difference between treatment groups not being statistically significant (DMC = -0.3 mmol/L; 95% CI =-0.6, 0.1).

Creatinine Clearance: At each post-treatment visit PicoPrep and HalfLytely had changes in mean levels from baseline that are statistically lower (see Figure 11). The differences in the mean change between groups is not statistically significant at visits 3, 5 and 6

Creatinine: At visit 3 there is no difference in the mean change from baseline between the two treatment groups. This result is also observed at visits 5 and 6.

Table 14. Mean laboratory value and difference in mean change from baseline (trial 2009-02)

Laboratory Paramter	Visit	PicoPrep mean (95% CI)	HalfLytely mean (95% CI)	DMC from baseline (95% CI)
Potassium (mmol/L)	BL	4.19 (4.15, 4.24)	4.19 (4.15, 4.24)	
	3	4.21 (4.16, 4.26)	4.13 (4.08, 4.17)	0.08 (0.01, 0.15)
	4	4.12 (4.07, 4.16)	4.09 (4.04, 4.13)	0.03 (-0.03, 0.09)
	5	4.18 (4.14, 4.22)	4.15 (4.10, 4.20)	0.02 (-0.05, 0.08)
	6	4.16 (4.12, 4.21)	4.14 (4.09, 4.18)	0.02 (-0.05, 0.08)
Sodium (mmol/L)	BL	139.4 (139.2, 139.6)	139.3 (139.1, 139.6)	
	3	139.6 (139.4, 139.9)	139.8 (139.6, 140.1)	-0.3 (-0.6, 0.1)
	4	139.3 (139.1, 139.5)	139.6 (139.3, 139.8)	-0.3 (-0.6, -0.0)
	5	139.5 (139.2, 139.7)	139.3 (139.1, 139.6)	0.0 (-0.3, 0.4)
	6	139.4 (139.1, 139.6)	139.3 (139.1, 139.6)	-0.0 (-0.4, 0.3)
Chloride (mmol/L)	BL	102.6 (102.4, 102.9)	102.4 (102.2, 102.7)	
	3	101.7 (101.3, 102.0)	102.7 (102.4, 103.0)	-1.2 (-1.6, -0.8)
	4	102.4 (102.1, 102.7)	103.0 (102.7, 103.2)	-0.7 (-1.1, -0.4)
	5	102.5 (102.2, 102.8)	102.4 (102.1, 102.7)	-0.1 (-0.5, 0.2)
	6	102.4 (102.1, 102.7)	102.5 (102.2, 102.8)	-0.4 (-0.7, 0.0)
Magnesium (mmol/L)	BL	0.86 (0.86, 0.87)	0.86 (0.85, 0.87)	
	3	0.98 (0.97, 0.99)	0.85 (0.84, 0.86)	0.13 (0.11, 0.14)
	4	0.85 (0.84, 0.86)	0.83 (0.83, 0.84)	0.01 (0.00, 0.03)
	5	0.85 (0.84, 0.85)	0.84 (0.83, 0.85)	0.00 (-0.01, 0.02)
	6	0.84 (0.83, 0.85)	0.84 (0.83, 0.85)	0.00 (-0.01, 0.01)
Calcium (mmol/L)	BL	2.38 (2.37, 2.39)	2.39 (2.38, 2.40)	
	3	2.39 (2.38, 2.40)	2.37 (2.36, 2.38)	0.02 (0.01, 0.04)
	4	2.37 (2.35, 2.38)	2.36 (2.35, 2.37)	0.01 (-0.00, 0.03)
	5	2.37 (2.36, 2.38)	2.36 (2.35, 2.37)	0.01 (-0.00, 0.03)
	6	2.36 (2.35, 2.38)	2.35 (2.34, 2.36)	0.02 (0.00, 0.03)
Creatinine (umol/L)	BL	73.5 (71.7, 75.4)	72.8 (71.0, 74.6)	
	3	76.1 (74.2, 78.0)	75.0 (73.1, 77.0)	0.3 (-1.1, 1.8)
	4	77.2 (75.1, 79.3)	74.7 (72.7, 76.7)	1.6 (0.0, 3.2)
	5	74.9 (73.0, 76.8)	73.6 (71.8, 75.4)	0.4 (-0.9, 1.6)
	6	75.5 (73.6, 77.5)	74.2 (72.4, 76.0)	0.3 (-1.1, 1.8)
EGFR	BL	108.3 (104.7, 111.9)	111.8 (108.0, 115.6)	
	3	103.5 (100.0, 107.0)	108.0 (104.0, 111.9)	-1.1 (-3.2, 1.1)
	4	103.2 (99.7, 106.7)	108.6 (104.7, 112.6)	-2.4 (-4.5, -0.2)
	5	106.0 (102.5, 109.5)	109.7 (105.8, 113.6)	-0.5 (-2.5, 1.4)
	6	105.8 (102.2, 109.5)	108.9 (105.1, 112.8)	-0.1 (-2.2, 2.1)
Urea (mmol/L)	BL	5.5 (5.3, 5.7)	5.7 (5.5, 5.9)	
	3	4.1 (4.0, 4.3)	4.5 (4.3, 4.6)	-0.2 (-0.4, 0.1)
	4	5.2 (5.0, 5.3)	5.2 (5.1, 5.4)	0.1 (-0.1, 0.3)
	5	5.6 (5.4, 5.8)	5.6 (5.4, 5.8)	0.1 (-0.1, 0.3)
	6	5.5 (5.4, 5.7)	5.7 (5.5, 5.8)	0.0 (-0.2, 0.3)

DMC—Difference in mean change, BL – baseline assessment

3.3.4.3 Adverse Events

Frequently occurring adverse events
Table 15 lists the AEs that are not findings from the colonoscopy procedure (e.g., hemorrhoids, colonic polyps) occurring in at least 2% of the patients

In trial 2009-01 there were slightly more headaches reported for PicoPrep compared to HalfLytely (4.3% versus 2.3%). The adverse events nausea, vomiting and melanosis coli, had either a smaller or similar percentage occurring in the PicoPrep group compared to HalfLytely.

In trial 2009-02 the adverse events headache, nausea, vomiting and melanosis coli had either a smaller or similar percentage occurring in the PicoPrep group compared to HalfLytely.

Table 15. Frequently occurring adverse events

	2009-01		2009-02	
Adverse Event	PicoPrep (N=305) n (%)	HalfLytely (N=298) n (%)	PicoPrep (N=296) n (%)	HalfLytely (N=302) n (%)
Headache	13 (4.3)	7 (2.3)	10 (3.4)	10 (3.3)
Nausea	15 (4.9)	14 (4.7)	11 (3.7)	16 (5.3)
Vomitting	5 (1.6)	11 (3.7)	6 (2.0)	8 (2.6)
Melanosis coli	1 (0.3)	7 (2.3)	4 (1.4)	4 (1.3)

As briefly discussed in Section 3.1, the incidence of vomiting and nausea for HalfLytely in the two trials are well below the estimates for these adverse events reported in the HalfLytely product label (Table 16). The incidence of nausea in trial 2009-01 and 2009-02 is 4.7% and 5.3%, respectively, which is notably smaller than the estimates of 34% and 42% that appear in the HalfLytely product label. The incidence of vomiting in the two trials is similar to the incidences reported in the HalfyLytely label.

Reviewer Comment: It may be hard to attribute such large differences in the incidences in the HalfLytely group to the limitations associated with cross-study comparisons given the well-known association of bowel preps with these adverse events. A possible explanation for this is that the investigators inadvertently thought these adverse events were also included in the list of commonly occurring adverse events that the protocol specified to collect in exceptional circumstances (See section below). Because of the potential for under-reporting, there is some concern regarding the overall integrity/accuracy of the safety data. If PicoPrep is approved for marketing, the product label should warn against comparing results across bowel preparation product labels. The label should also state that the true risks of adverse events known to be associated with bowel preparation products are likely to be larger than what is reported based on findings from the two trials.

Table 16. Excerpt from the HalfLytely product label

Table 1: Adverse Reactions Observed in at Least 3% of Randomized Patients

	HalfLytely and 5 mg Bisacodyl Tablet Bowel Prep Kit (N=154)	HalfLytely and 10 mg Bisacodyl Tablets Bowel Prep Kit (N=154)
Overall Discomfort	57%	66%
Abdominal fullness	40%	53%
Abdominal cramping	38%	46%
Nausea	34%	42%
Vomiting	10%	7%

Selectively collected adverse events

The protocol specified that the adverse events abdominal bloating, distension, pain/cramping, and watery diarrhea, which are known to occur in response to colon cleansing, were only to be documented as an adverse event if the findings induced an action, such as 1) changes in study drug or study discontinuation, 2) resulted in therapeutic or diagnostic procedures, 3) met the criteria for a serious adverse event, or 4) showed clinically significant worsening during study. Table 19 displays the adverse events that were selectively collected in both trials. There are few adverse events reported in either trial.

Table 17. Occurrence of selectively reported adverse events*

Trial	2009-01		2009-02	
	PicoPrep (N=305)	HalfLytely (N=298)	PicoPrep (N=296)	HalfLytely (N=302)
Adverse Event	n	n	n	n
Abdominal discomfort	1	0	0	0
Abdominal distension	0	1	0	0
Abdominal pain	3	3	3	1
Abdominal pain lower	1	0	0	1
Abdominal pain upper	2	0	0	0
Abdominal tenderness	1	0	4	1
Diarrhoea	3	2	1	1

*Per protocol only these AE were to be reported if the findings induced an action, such as 1) changes in study drug or study discontinuation, 2) resulted in therapeutic or diagnostic procedures, 3) met the criteria for a serious adverse event, or 4) showed clinically significant worsening during study.

Table 20 summarizes attributes of the adverse events in the above Table according to the protocol defined reporting criteria. From the safety dataset it was not possible to determine if the adverse events showed clinically worsening throughout the study. However, of the reported events, 71.0%, 16.1% and 12.9% are reported to be mild, moderate and severe in intensity, respectively. None of these adverse event are classified as a serious, had action taken with study medication, or lead to study discontinuation. Of the 8 reported that lead to '*Other action taken'*, 6 are related to study medication.

Reviewer comment: Because of the apparent discordance between the criteria for reporting and the events attributes, it is questionable whether all investigators adhered to the reporting guidelines specified in the protocol. If the investigators differentially reported these adverse

events, it is not possible to obtain unbiased risk estimates under the exceptional circumstance defined in the protocol.

Table 18. Characteristics of adverse events that were selectively collected

	2009-01		2009-02	
	PicoPrep (N=305)	**HalfLytely (N=298)**	**PicoPrep (N=296)**	**HalfLytely (N=302)**
Reporting criteria	**n**	**n**	**n**	**n**
Showed clinically significant worsening during study	NA	NA	NA	NA
Classified as a serious event	0	0	0	0
No action taken with study treatment	0	0	0	0
Adverse event leading to study discontinuation	0	0	0	0
Other action taken	3	2	2	1
Rest	0	0	1	0
Medication	3	1	1	1
CT scan	0	1	0	0

NA—not available

Adverse events of clinical interest

In the both studies there are no reported adverse events labeled cardiac arrhythmia, seizure, or ischemic colitis.

Table 19 reports the adverse events associated with the SMQ cardiac arrhythmia. In both trials there is no notable imbalance in the event frequency. Collectively, however, there are numerically more adverse events associated with the SMQ occurring in the PicoPrep arm compared to HalfLytely. Trial 2009-01 had only 3 events in patients that received PicoPrep compared to 1 for HalfLytely; trial 2009-02 had 7 events among patients that received PicoPrep compared to 1 for HalfLytely. *It is difficult to draw any meaningful conclusions from these small numbers.*

Table 19. Adverse events associated with the SMQ cardiac arrhythmia

	2009-01		2009-02	
	PicoPrep (N=305)	HalfLytely (N=298)	PicoPrep (N=296)	HalfLytely (N=302)
Adverse Event	n	n	n	n
Atrioventricular block first degree	0	0	3	1
Bundle branch block bilateral	0	0	1	0
Bundle branch block left	1	0	1	0
Bundle branch block right	0	0	2	0
Conduction disorder	0	0	0	1
Electrocardiogram QT prolonged	0	0	1	0
Electrocardiogram change	1	1	0	0
Heart rate irregular	0	0	0	1
Palpitations	0	0	1	0
Syncope	0	0	1	1
Tachycardia	0	0	0	1
Ventricular extrasystoles	1	0	0	1

4 FINDINGS IN SPECIAL /SUBGROUP POPULATIONS

Special/subgroup populations are not investigated in this review.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

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 specific for adverse events or abnormal laboratory parameters. Therefore, results from analyses of safety events and abnormal parameters should not be considered confirmatory. In addition, given the large number of comparisons performed without any adjustments for multiplicity, CIs that exclude the null value should not be taken as confirmatory evidence of statistical significance. However, because the two trials shared similar study designs differing with respect to the administration of PicoPrep (i.e., split-dose versus day before), trends in findings of safety from one trial can be viewed along with findings from the second trial as supportive evidence.

The safety of PicoPrep in high-risk patient population, such as those with either renal impairment or significant gastrointestinal disease can not be established from the data considered in this review since both RCTs excluded these patients. Future evaluations, such as post-approval studies, to explore the safety in these select populations may be necessary if it is anticipated that such populations would receive this product.

The protocol specified an unconventional reporting strategy for commonly occurring adverse events for the bowel preparation products, namely abdominal bloating, distension, pain/cramping, and watery diarrhea. Specifically, the protocol stated that only when these events

required changes in study drug or study discontinuation, resulted in therapeutic or diagnostic procedures, met the criteria for a serious adverse event, or showed clinically significant worsening during study were they to be reported. This reporting/data collecting strategy likely led to underreporting of events. Consequently, the incidence estimate for these events is likely biased. If PicoPrep is approved for marketing, the labeling of these adverse events should explicitly describe how the data were collected. The product label should also warn against contrasting results presented in the PicoPrep label against those presented in similar product labels (e.g., SUPREP or HalfLytely).

While the commonly occurring adverse events nausea and vomiting are not included in the list of adverse events that were to be selectively collected, these adverse events may have been under-reported. This concern is supported by a large difference in the reported incidences for HalfLytely in the two trial and the estimates reported in the HalfLytely product label. The difference is most pronounced for nausea, with estimates of 4.7% and 5.3% in the two RCTs compared to 34% and 42% that appear in the HalfLytely product label. It is unlikely these differences in the incidence between the product label and the two trials can be attributable to caveats associated with cross-study comparisons. Because of the potential for under-reporting, there is some concern regarding the overall integrity/accuracy of the safety data. The product label should state that the true risks of adverse events known to be associated with bowel preparation products are likely to be larger than what is reported based on findings from the two trials.

The effect of PicoPrep on laboratory parameters that might be influenced by race, in particular, Black race, can not be inferred from the two trials as each trial included a limited proportion of Black subjects (10.4% and 9.0% in trial 2009-01 and 2009-02, respectively).

In both trials, the laboratory test ALP, AST and potassium at visit 3 had disproportionately more missing values. In trial 2009-01 the missing values (PicoPrep 27, HalfLytely 16) make the results from the shift analysis for potassium and AST difficult to interpret. For AST the numerical imbalance for PicoPrep compared to HalfLytely at visit 3 (5.9% versus 3.4%) is not statistically significant but is at visit 4 (3.6% versus 0.7%). For potassium, there is a non-significant increase in the number of abnormal values for PicoPrep at visit 3 (10.0% versus 6.0%) and visit 4 (6.7% versus 3.9%).

Collective Evidence

The safety analysis population for trial 2009-01 includes 603 patients (305 PicoPrep and 298 Halflytely); trial 2009-02 includes 598 patients (296 Picoprep and 302 Halflytely).

For each of the 14 laboratory parameters investigated in the two studies, there is no evidence of statistically significant differences between PicoPrep and HalfLytely at baseline based on the mean laboratory value or the number of abnormal values.

Below is a listing and summary liver function parameters that have either a numerical imbalance in the number of abnormal values favoring PicoPrep or a difference in mean change from baseline:

Trial 2009-01

- *Albumin:* Compared to HalfLytely, at visit 3, the PicoPrep arm had a statistically significantly greater proportion of abnormal values (9.5% versus 4.5%; RD=5.0%; 95% CI= 0.9, 9.1) and a greater increase in mean levels from baseline that approached statistical significance (DMC=0.4 g/L; 95% CI=-0.02, 0.76). At visit 4 there are no differences between treatment groups.
- *AST:* At visit 3 the proportion of abnormal values was greater in the PicoPrep arm compared to HalfLytely (5.9% versus 3.4%). At visit 4 the overall proportion of abnormal values decreased from visit 3, but the proportion was statistically significantly higher in the PicoPrep arm compared to HalfLytely (3.6% versus 0.7%; RD=2.9%; 95% CI=0.5, 5.3). At visit 5 there is no difference between treatment arms.

Trial 2009-02

- *Albumin*: At visit 3, the PicoPrep arm had a greater proportion of abnormal values compared to HalfLytely (5.8% versus 2.8%), as well as a statistically significantly greater increase in mean levels from baseline (DMC=0.9 g/L; 95% CI = 0.5, 1.3). By visit 5 there is no difference between treatment groups.
- *AST:* At visit 3 there are numerically more abnormal values in the PicoPrep group compared to HalfLytely (7.0% versus 3.8%). At visit 4 the percentage of abnormal values for PicoPrep decreased to 2.9%, which is slightly below 4.1% reported for HalfLytely.

Below is a listing and summary of electrolyte and renal laboratory parameters that have either a numerical imbalance in the number of abnormal values disfavoring PicoPrep or a difference in mean change from baseline:

Trial 2009-01

- *Chloride*: Compared to HalfLytely, at visit 3, the PicoPrep arm had a statistically significantly higher proportion of abnormal values (3.7% versus 0.3%; RD=3.3%; 95% CI=1.1, 5.5) and a significantly greater decrease in mean levels from baseline (DMC=-1.6 mmol/L; 95% CI=-2.0, -1.2). By visit 4 there are no differences between treatment groups.
- *Magnesium*: Compared to HalfLytely, at visit 3, the PicoPrep arm PicoPrep had a statistically significantly higher proportion of abnormal values (11.6% versus 0%, RD=11.6%; 95% CI=7.9, 15.2) and a significantly greater increase in mean levels from the baseline (DMC=0.12 mmol/L; 95% CI=0.11, 0.14). By visit 4 there are no differences between treatment groups.
- *Urea:* At visit 3 the proportion of abnormal values was statistically significantly higher in the PicoPrep arm compared to HalfLytely (20.9% versus 12.0%; RD=8.9%; 95% CI=2.9, 15.0). At visit 4 the proportion of abnormal values remained higher in the PicoPrep arm (5.6% versus 3.3%), but the difference was not statistically significant. Based on changes in mean levels from baseline there is no evidence the treatment groups differed at any follow-up visit.

- *Potassium:* There is a non-significant increase in the number of abnormal values for PicoPrep compared to HalfLytely at visit 3 (10.0% versus 6.0%) and visit 4 (6.7% versus 3.9%). The numbers are similar after visit 4.
- *Sodium*: Compared to HalfLytely, at visit 3, there is a non-significant increase of abnormal values for PicoPrep (3.7% versus 1.7%) but a significantly greater decrease in mean levels from baseline (DMC=-0.6 mmol/L; 95% CI=-0.9, -0.2). By visit 4 there is no statistical difference for either summary.

Trial 2009-02

- *Magnesium*: Compared to HalfLytely, at visit 3, the PicoPrep arm had a statistically significantly higher proportion of abnormal values (8.7% versus 1.4%, RD=7.3%; 95% CI=3.8, 10.8) and a significantly greater increase in mean levels from the baseline (DMC=0.13 mmol/L; 95% CI =0.11, 0.14). By visit 4, there is no evidence of differences existing between treatment groups based on either summary.
- *Chloride:* Compared to HalfLytely, at visit 3, the PicoPrep arm had a higher but not statistically significant proportion of abnormal values (1.0% versus 0%), and a significantly greater decrease in mean levels from baseline (DMC=-1.2 mmol/L; 95% CI=-1.6, -0.8). By visit 5 there is no statistical difference between treatment groups.

In the both trials there were no reported adverse events labeled cardiac arrhythmia, seizure, or ischemic colitis and no patient deaths.

In trial 2009-01 the most commonly reported adverse event was nausea (PicoPrep 4.9%, HalfLytely 4.7%), followed by headache (PicoPrep 4.3%, HalfLytely 2.3%) and vomiting (PicoPrep 1.6%, HalfLytely 3.7%). In trial 2009-02 the most commonly reported adverse event was nausea (PicoPrep 3.7%, HalfLytely 5.3%), followed by headache (PicoPrep 3.4%, HalfLytely 3.3%) and vomiting (PicoPrep 2.0%, HalfLytely 2.6%).

5.2 Conclusions and Recommendations

Due in part to some potential safety concerns associated with bowel preps, laboratory parameters associated with the liver and kidney function and electrolytes balance were evaluated in this review. The focus was on differences following administration of study drug and whether differences persisted throughout the one month study follow-up. In both trials, based on laboratory values collected on the day of the colonoscopy (visit 3), there is evidence that PicoPrep differed from HalfLytely with respect to either the number of abnormal values or difference in mean change from baseline for the following parameters: albumin, AST, chloride and magnesium. In trial 2009-01 specifically (not 2009-02) there were noted imbalances between treatment groups disfavoring PicoPrep in urea, potassium and sodium laboratory values collected on day of colonoscopy. In both trials, by the end of the study, there was no evidence of imbalances between treatment groups for any of the laboratory parameters investigated.

Due to the atypical collection of select adverse events, safety labeling of this product needs to clearly describe the limited collection of the adverse events of abdominal bloating, distension, pain/cramping, and watery diarrhea in both trials and warn against comparing incidences to those in other bowel preparation product labels. The product label should also state that the true risks

of adverse events nausea and vomiting, which were not part of the selective reporting strategy, are likely to be larger than what was reported from the two confirmatory clinical trials.

6 APPENDIX

Table 20. Number of missing laboratory tests by study, visit and treatment arm

	PicoPrep				HalfLytely			
Laboratory Parameter	**Visit 3 n (%)**	**Visit 4 n (%)**	**Visit 5 n (%)**	**Visit 6 n (%)**	**Visit 3 n (%)**	**Visit 4 n (%)**	**Visit 5 n (%)**	**Visit 6 n (%)**
Trial 2009-01	*N=303*	*N=303*	*N=304*	*N=304*	*N=298*	*N=296*	*N=295*	*N=294*
ALB	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
ALP	27 (8.9)	1 (0.3)	0 (0.0)	1 (0.3)	16 (5.4)	1 (0.3)	1 (0.3)	1 (0.3)
ALT	3 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)	2 (0.7)	2 (0.7)	0 (0.0)	0 (0.0)
AST	27 (8.9)	1 (0.3)	0 (0.0)	1 (0.3)	16 (5.4)	2 (0.7)	1 (0.3)	1 (0.3)
CA	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
CBILI	3 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)	2 (0.7)	1 (0.3)	0 (0.0)	0 (0.0)
CL	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
CREATENZ	3 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)	2 (0.7)	1 (0.3)	0 (0.0)	0 (0.0)
EGFR	3 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
GGT	2 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
K	27 (8.9)	1 (0.3)	0 (0.0)	1 (0.3)	16 (5.4)	2 (0.7)	1 (0.3)	1 (0.3)
MG	2 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
SODIUM	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
UREA	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Trial 2009-02	*N=291*	*N=289*	*N=289*	*N=288*	*N=297*	*N=293*	*N=296*	*N=298*
ALB	1 (0.3)	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.0)	0 (0.0)
ALP	5 (1.7)	1 (0.3)	1 (0.3)	2 (0.7)	12 (4.0)	1 (0.3)	4 (1.4)	0 (0.0)
ALT	1 (0.3)	1 (0.3)	1 (0.3)	0 (0.0)	2 (0.7)	0 (0.0)	3 (1.0)	0 (0.0)
AST	5 (1.7)	1 (0.3)	1 (0.3)	2 (0.7)	12 (4.0)	1 (0.3)	4 (1.4)	0 (0.0)
CA	1 (0.3)	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.0)	0 (0.0)
CBILI	1 (0.3)	1 (0.3)	1 (0.3)	0 (0.0)	2 (0.7)	0 (0.0)	3 (1.0)	0 (0.0)
CL	1 (0.3)	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.0)	0 (0.0)
CREATENZ	1 (0.3)	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.0)	0 (0.0)
EGFR	1 (0.3)	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.0)	0 (0.0)
GGT	1 (0.3)	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.0)	0 (0.0)
K	5 (1.7)	1 (0.3)	1 (0.3)	2 (0.7)	12 (4.0)	1 (0.3)	4 (1.4)	0 (0.0)
MG	1 (0.3)	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.0)	0 (0.0)
SODIUM	1 (0.3)	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.0)	0 (0.0)
UREA	1 (0.3)	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.0)	0 (0.0)

Table 21. Reason laboratory tests were not performed by study and visit. Counts collapsed over laboratory tests and treatment arms.

Reason no laboratory value	Visit 3	Visit 4	Visit 5	Visit 6
Study 2009-01				
Leaked in transit	0	13	0	13
Pre-analytical contamination	13	0	0	0
Hemolyzed serum	138	6	3	3
Study 2009-02				
Leaked in transit	0	14	14	0
Pre-analytical contamination	0	0	14	0
Hemolyzed serum	52	3	3	6
Insufficient quantity	14	0	28	0

Table 22. Reference ranges for laboratory parameters

Laboratory Parameter (abbreviation, units)	Lower Limit	Upper Limit
Albumin (ALB, g/L)	37	49
Alkaline Phosphatase (ALP, IU/L)	40	135
Alanine Transaminase (ALT, IU/L)	0	47
Aspirate Transaminase (AST, IU/L)	0	37
Calcium (CA, mmol/L)	2.1	2.55
Bilirubin (CBILI, umol/L)	0	19
Chloride (CL, mmol/L)	95	113
Creatine Clearance (EGFR,)	90	
Creatinine (CREATENZ, umol/L)	45 (F); 59 (M)	84 (F); 104 (M)
Gamma Glutamly Transpeptiase (GGT, IU/L)	0	33 (F); 51 (M)
Potassium (K, mmol/L)	3.6	5.2
Magnesium (MG, mmol/L)	0.7	1.05
Sodium (SODIUM, mmol/L)	134	146
Urea (UREA, mmol/L)	3.2	8.6

F—females; M—males.

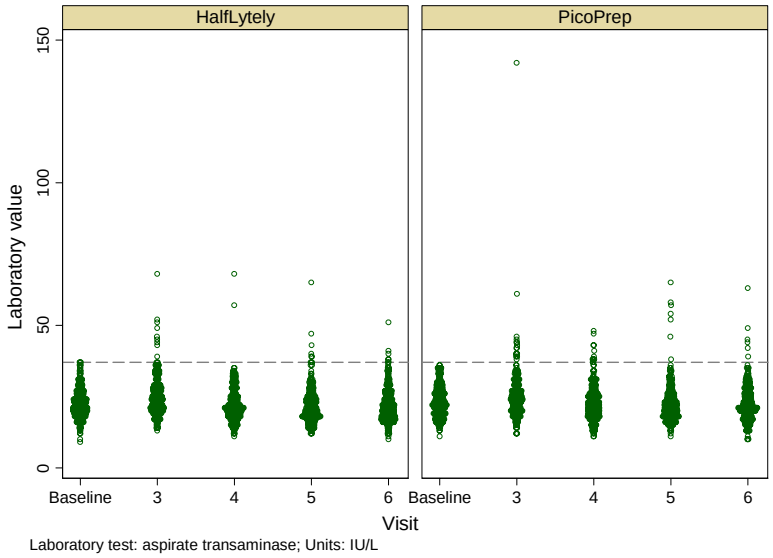
6.1 Liver Function Tests

6.1.1 Trial 2009-01

Table 23. Number of patients above or below normal range (trial 2009-01)

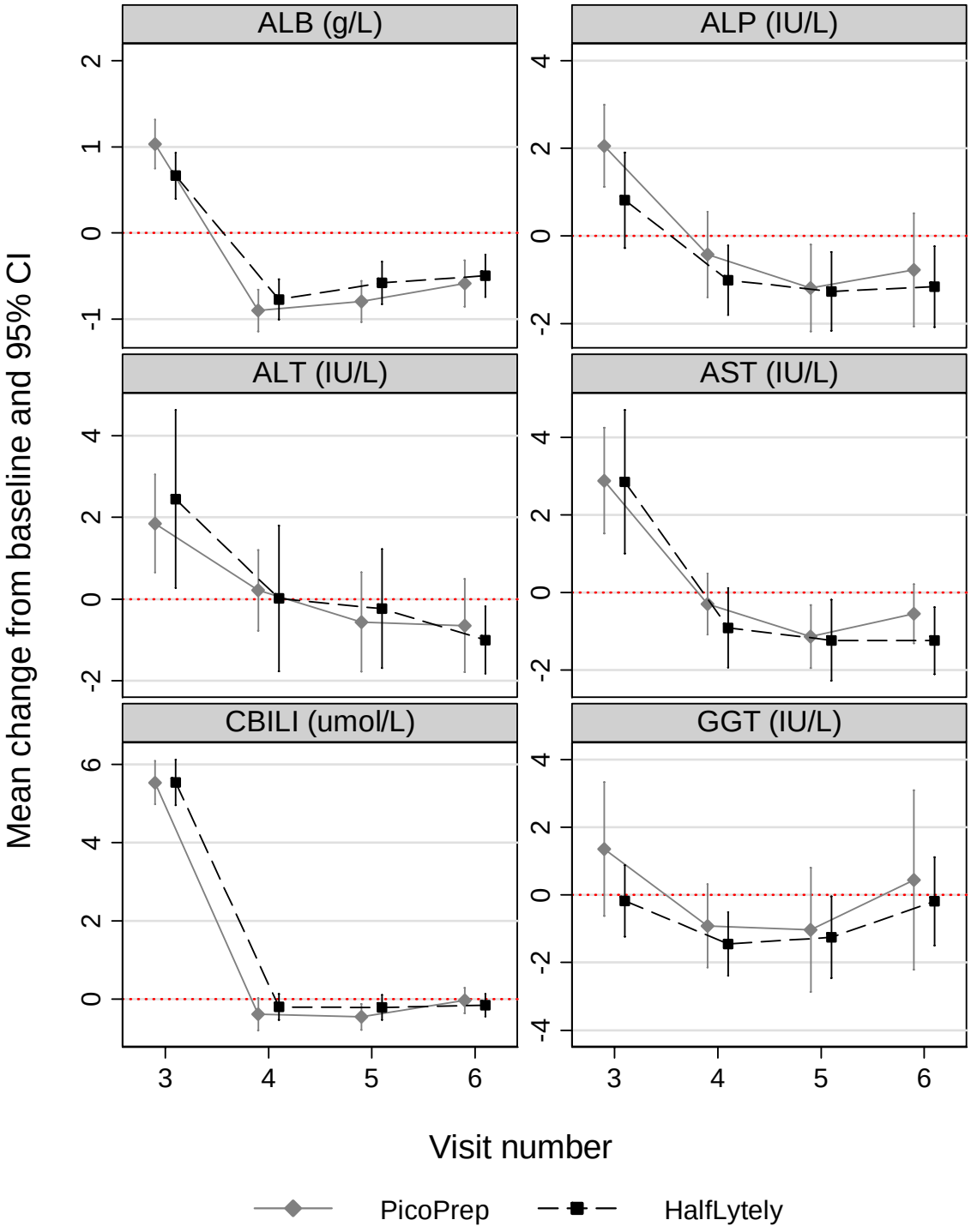
		Below		Above	
Laboratory Parameter	**Visit**	**PicoPrep n/N (%)**	**HalfLytely n/N (%)**	**PicoPrep n/N (%)**	**HalfLytely n/N (%)**
Albumin	3	2/294 (0.7)	1/289 (0.3)	26/294 (8.8)	12/289 (4.2)
	4	3/295 (1.0)	0/286 (0.0)	3/295 (1.0)	1/286 (0.3)
	5	1/296 (0.3)	1/286 (0.3)	4/296 (1.4)	3/286 (1.0)
	6	3/295 (1.0)	0/285 (0.0)	3/295 (1.0)	3/285 (1.1)
ALP	3	2/263 (0.8)	3/268 (1.1)	2/263 (0.8)	2/268 (0.7)
	4	2/285 (0.7)	2/281 (0.7)	0/285 (0.0)	2/281 (0.7)
	5	1/287 (0.3)	2/281 (0.7)	0/287 (0.0)	3/281 (1.1)
	6	3/286 (1.0)	2/280 (0.7)	1/286 (0.3)	1/280 (0.4)
ALT	3	0/275 (0.0)	0/281 (0.0)	9/275 (3.3)	5/281 (1.8)
	4	0/278 (0.0)	0/279 (0.0)	9/278 (3.2)	2/279 (0.7)
	5	0/279 (0.0)	0/280 (0.0)	9/279 (3.2)	5/280 (1.8)
	6	0/278 (0.0)	0/279 (0.0)	6/278 (2.2)	3/279 (1.1)
AST	3	0/255 (0.0)	0/265 (0.0)	15/255 (5.9)	9/265 (3.4)
	4	0/276 (0.0)	0/276 (0.0)	10/276 (3.6)	2/276 (0.7)
	5	0/278 (0.0)	0/276 (0.0)	7/278 (2.5)	6/276 (2.2)
	6	0/277 (0.0)	0/275 (0.0)	6/277 (2.2)	5/275 (1.8)
Bilirubin	3	0/296 (0.0)	0/293 (0.0)	36/296 (12.2)	41/293 (14.0)
	4	0/298 (0.0)	0/292 (0.0)	7/298 (2.3)	2/292 (0.7)
	5	0/299 (0.0)	0/292 (0.0)	4/299 (1.3)	0/292 (0.0)
	6	0/298 (0.0)	0/291 (0.0)	4/298 (1.3)	0/291 (0.0)
GGT	3	0/251 (0.0)	0/255 (0.0)	6/251 (2.4)	5/255 (2.0)
	4	0/252 (0.0)	0/252 (0.0)	6/252 (2.4)	1/252 (0.4)
	5	0/253 (0.0)	0/253 (0.0)	7/253 (2.8)	2/253 (0.8)
	6	0/252 (0.0)	0/252 (0.0)	6/252 (2.4)	8/252 (3.2)

Figure 4. Modified scatterplot of AST values by visits among patients with normal baseline (trial 2009-01)



Laboratory test: aspirate transaminase; Units: IU/L

Figure 5. Liver function parameters: Mean change from baseline (trial 2009-01)

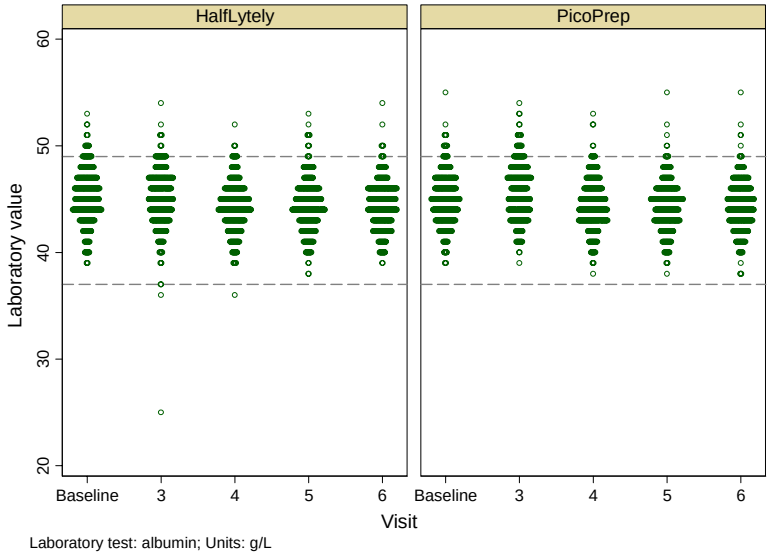


6.1.2 Trial 2009-02

Table 24. Number of patients above or below normal range (Trial 2009-02)

		Below		Above	
Laboratory Parameter	**Visit**	**PicoPrep n/N (%)**	**HalfLytely n/N (%)**	**PicoPrep n/N (%)**	**HalfLytely n/N (%)**
Albumin	3	0/277 (0.0)	2/283 (0.7)	16/277 (5.8)	6/283 (2.1)
	4	0/275 (0.0)	1/279 (0.4)	2/275 (0.7)	2/279 (0.7)
	5	0/275 (0.0)	0/279 (0.0)	2/275 (0.7)	7/279 (2.5)
	6	0/275 (0.0)	0/284 (0.0)	1/275 (0.4)	3/284 (1.1)
ALP	3	2/276 (0.7)	2/276 (0.7)	0/276 (0.0)	1/276 (0.4)
	4	2/278 (0.7)	1/283 (0.4)	0/278 (0.0)	1/283 (0.4)
	5	2/277 (0.7)	4/283 (1.4)	1/277 (0.4)	0/283 (0.0)
	6	0/275 (0.0)	2/289 (0.7)	1/275 (0.4)	0/289 (0.0)
ALT	3	0/271 (0.0)	0/277 (0.0)	10/271 (3.7)	9/277 (3.2)
	4	0/269 (0.0)	0/275 (0.0)	10/269 (3.7)	7/275 (2.5)
	5	0/269 (0.0)	0/276 (0.0)	3/269 (1.1)	10/276 (3.6)
	6	0/269 (0.0)	0/280 (0.0)	5/269 (1.9)	12/280 (4.3)
AST	3	0/272 (0.0)	0/265 (0.0)	19/272 (7.0)	10/265 (3.8)
	4	0/273 (0.0)	0/271 (0.0)	8/273 (2.9)	11/271 (4.1)
	5	0/273 (0.0)	0/271 (0.0)	2/273 (0.7)	4/271 (1.5)
	6	0/271 (0.0)	0/277 (0.0)	5/271 (1.8)	10/277 (3.6)
Bilirubin	3	0/281 (0.0)	0/289 (0.0)	24/281 (8.5)	23/289 (8.0)
	4	0/280 (0.0)	0/287 (0.0)	2/280 (0.7)	1/287 (0.3)
	5	0/279 (0.0)	0/288 (0.0)	1/279 (0.4)	0/288 (0.0)
	6	0/279 (0.0)	0/292 (0.0)	3/279 (1.1)	3/292 (1.0)
GGT	3	0/245 (0.0)	0/244 (0.0)	11/245 (4.5)	4/244 (1.6)
	4	0/242 (0.0)	0/239 (0.0)	10/242 (4.1)	3/239 (1.3)
	5	0/241 (0.0)	0/240 (0.0)	7/241 (2.9)	4/240 (1.7)
	6	0/241 (0.0)	0/244 (0.0)	12/241 (5.0)	9/244 (3.7)

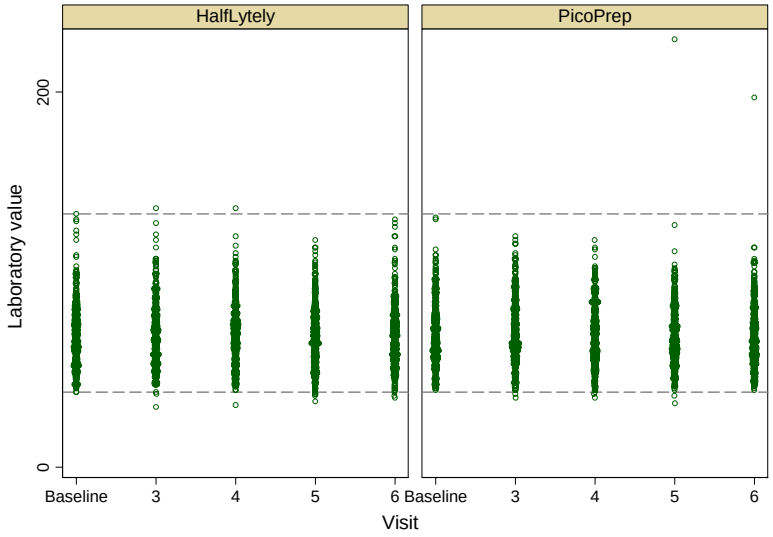
Figure 6. Modified scatterplot of albumin values by visits for the full sample (trial 2009-02).



Laboratory test: albumin; Units: g/L

Dotted lines represent upper and lower normal values

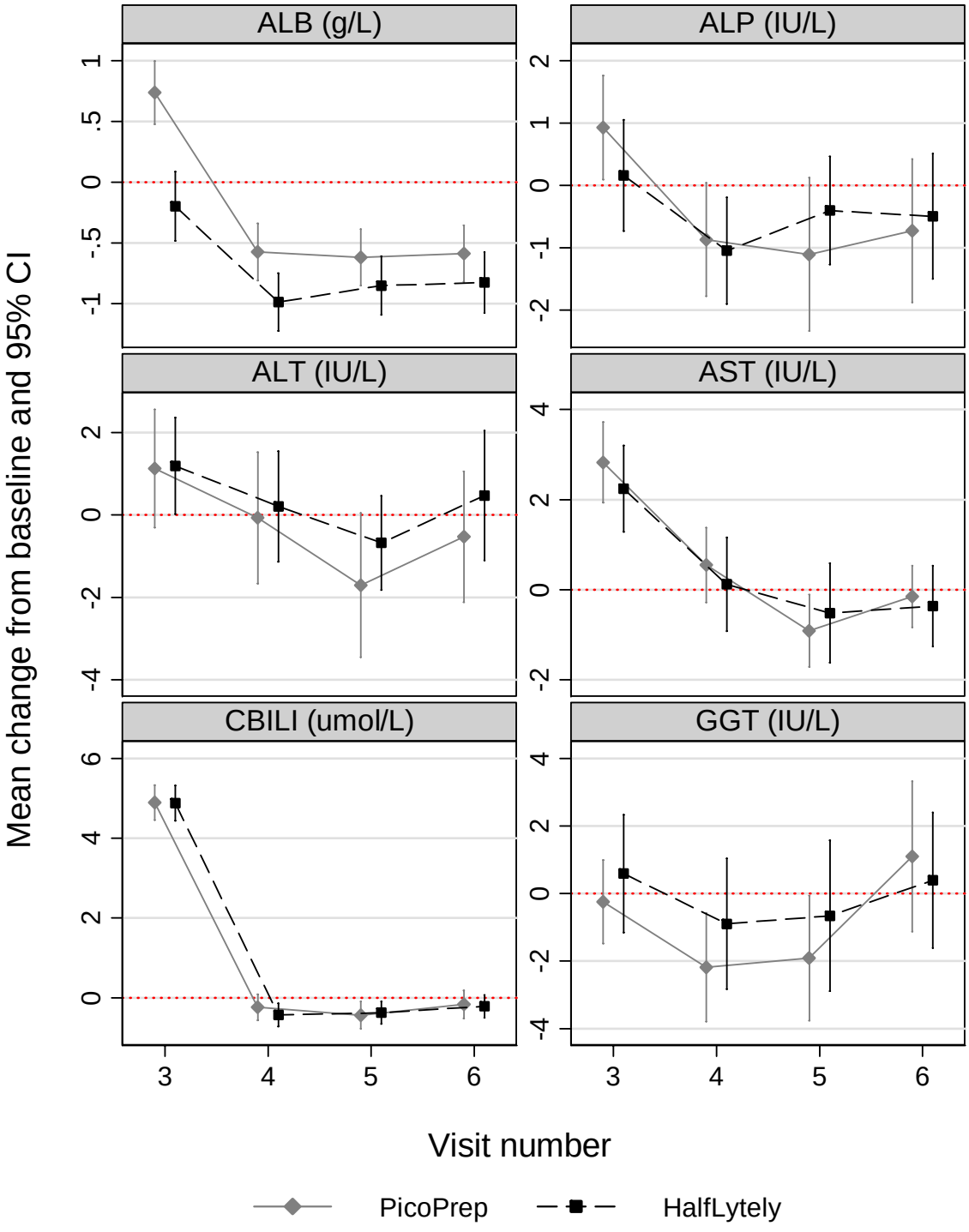
Figure 7. Modified scatterplot of ALP values by visits among patients with normal baseline (trial 2009-02)



Laboratory test: alkaline phosphatase; Units: IU/L

Dotted lines represent upper and lower normal values

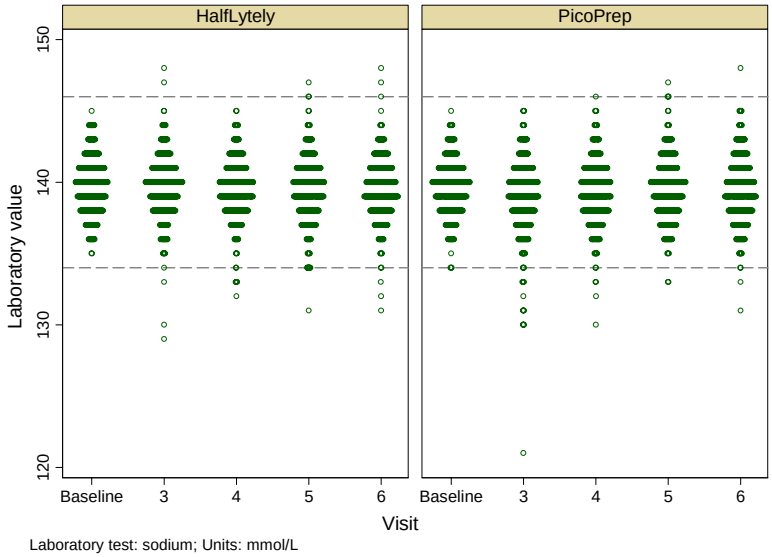
Figure 8. Liver function parameters: Mean change from baseline (trial 2009-02)



6.2 Electrolyte and renal laboratory tests

6.2.1 Trial 2009-01

Figure 9. Modified scatterplot of sodium values by visits among patients with normal baseline (trial 2009-01)



Dotted lines represent upper and lower normal values

Table 25. Number of patients above or below normal range (trial 2009-01)

		Below		Above	
Laboratory Parameter	**Visit**	**PicoPrep n/N (%)**	**HalfLytely n/N (%)**	**PicoPrep n/N (%)**	**HalfLytely n/N (%)**
Potassium	3	19/260 (7.3)	11/268 (4.1)	7/260 (2.7)	5/268 (1.9)
	4	15/282 (5.3)	10/279 (3.6)	4/282 (1.4)	1/279 (0.4)
	5	11/285 (3.9)	8/279 (2.9)	5/285 (1.8)	8/279 (2.9)
	6	11/284 (3.9)	8/278 (2.9)	2/284 (0.7)	2/278 (0.7)
Sodium	3	11/298 (3.7)	3/295 (1.0)	0/298 (0.0)	2/295 (0.7)
	4	4/299 (1.3)	5/292 (1.7)	0/299 (0.0)	0/292 (0.0)
	5	2/300 (0.7)	1/292 (0.3)	1/300 (0.3)	1/292 (0.3)
	6	2/299 (0.7)	3/291 (1.0)	1/299 (0.3)	2/291 (0.7)
Chloride	3	11/301 (3.7)	1/298 (0.3)	0/301 (0.0)	0/298 (0.0)
	4	2/302 (0.7)	2/295 (0.7)	0/302 (0.0)	0/295 (0.0)
	5	1/303 (0.3)	3/295 (1.0)	0/303 (0.0)	0/295 (0.0)
	6	2/302 (0.7)	3/294 (1.0)	0/302 (0.0)	0/294 (0.0)
Magnesium	3	0/294 (0.0)	0/294 (0.0)	34/294 (11.6)	0/294 (0.0)
	4	2/296 (0.7)	2/291 (0.7)	0/296 (0.0)	0/291 (0.0)
	5	4/297 (1.3)	0/291 (0.0)	0/297 (0.0)	1/291 (0.3)
	6	7/296 (2.4)	1/290 (0.3)	1/296 (0.3)	2/290 (0.7)
Calcium	3	2/292 (0.7)	1/286 (0.3)	4/292 (1.4)	6/286 (2.1)
	4	0/292 (0.0)	1/283 (0.4)	2/292 (0.7)	5/283 (1.8)
	5	0/293 (0.0)	1/283 (0.4)	5/293 (1.7)	3/283 (1.1)
	6	0/292 (0.0)	1/282 (0.4)	7/292 (2.4)	4/282 (1.4)
Creatinine	3	2/260 (0.8)	2/268 (0.7)	5/260 (1.9)	13/268 (4.9)
	4	2/264 (0.8)	1/267 (0.4)	18/264 (6.8)	11/267 (4.1)
	5	1/264 (0.4)	0/267 (0.0)	10/264 (3.8)	13/267 (4.9)
	6	1/264 (0.4)	1/265 (0.4)	11/264 (4.2)	14/265 (5.3)
eGFR	3	22/221 (10.0)	17/214 (7.9)	0/221 (0.0)	0/214 (0.0)
	4	32/223 (14.3)	22/212 (10.4)	0/223 (0.0)	0/212 (0.0)
	5	22/223 (9.9)	17/213 (8.0)	0/223 (0.0)	0/213 (0.0)
	6	24/223 (10.8)	21/211 (10.0)	0/223 (0.0)	0/211 (0.0)
Urea	3	60/287 (20.9)	33/276 (12.0)	0/287 (0.0)	0/276 (0.0)
	4	12/287 (4.2)	6/274 (2.2)	4/287 (1.4)	3/274 (1.1)
	5	13/288 (4.5)	4/274 (1.5)	4/288 (1.4)	7/274 (2.6)
	6	8/287 (2.8)	5/272 (1.8)	9/287 (3.1)	7/272 (2.6)

6.2.2 Trial 2009-02

Table 26. Number of patients above or below normal range (trial 2009-02)

		Below		Above	
Laboratory Parameter	**Visit**	**PicoPrep n/N (%)**	**HalfLytely n/N (%)**	**PicoPrep n/N (%)**	**HalfLytely n/N (%)**
Potassium	3	13/274 (4.7)	13/271 (4.8)	0/274 (0.0)	1/271 (0.4)
	4	8/276 (2.9)	9/277 (3.2)	1/276 (0.4)	0/277 (0.0)
	5	6/276 (2.2)	14/278 (5.0)	2/276 (0.7)	0/278 (0.0)
	6	7/275 (2.5)	8/284 (2.8)	1/275 (0.4)	3/284 (1.1)
Sodium	3	3/286 (1.0)	3/295 (1.0)	0/286 (0.0)	0/295 (0.0)
	4	4/284 (1.4)	1/291 (0.3)	0/284 (0.0)	0/291 (0.0)
	5	1/285 (0.4)	1/291 (0.3)	0/285 (0.0)	0/291 (0.0)
	6	1/284 (0.4)	1/296 (0.3)	0/284 (0.0)	0/296 (0.0)
Chloride	3	3/287 (1.0)	0/297 (0.0)	0/287 (0.0)	0/297 (0.0)
	4	1/285 (0.4)	0/293 (0.0)	0/285 (0.0)	0/293 (0.0)
	5	0/285 (0.0)	0/293 (0.0)	0/285 (0.0)	0/293 (0.0)
	6	0/285 (0.0)	0/298 (0.0)	0/285 (0.0)	0/298 (0.0)
Magnesium	3	0/288 (0.0)	3/289 (1.0)	25/288 (8.7)	1/289 (0.3)
	4	4/286 (1.4)	4/285 (1.4)	1/286 (0.3)	0/285 (0.0)
	5	10/286 (3.5)	4/285 (1.4)	1/286 (0.3)	1/285 (0.4)
	6	5/286 (1.7)	5/290 (1.7)	0/286 (0.0)	0/290 (0.0)
Calcium	3	0/276 (0.0)	2/282 (0.7)	9/276 (3.3)	6/282 (2.1)
	4	2/274 (0.7)	1/278 (0.4)	4/274 (1.5)	6/278 (2.2)
	5	0/274 (0.0)	0/278 (0.0)	3/274 (1.1)	4/278 (1.4)
	6	0/274 (0.0)	1/283 (0.4)	4/274 (1.5)	2/283 (0.7)
Creatinine	3	2/266 (0.8)	2/270 (0.7)	12/266 (4.5)	16/270 (5.9)
	4	0/263 (0.0)	1/266 (0.4)	19/263 (7.2)	15/266 (5.6)
	5	3/264 (1.1)	2/265 (0.8)	10/264 (3.8)	10/265 (3.8)
	6	1/264 (0.4)	0/272 (0.0)	18/264 (6.8)	10/272 (3.7)
eGFR	3	26/199 (13.1)	25/224 (11.2)	0/199 (0.0)	0/224 (0.0)
	4	25/198 (12.6)	27/220 (12.3)	0/198 (0.0)	0/220 (0.0)
	5	11/198 (5.6)	28/219 (12.8)	0/198 (0.0)	0/219 (0.0)
	6	21/199 (10.6)	24/224 (10.7)	0/199 (0.0)	0/224 (0.0)
Urea	3	45/267 (16.9)	37/274 (13.5)	1/267 (0.4)	2/274 (0.7)
	4	14/263 (5.3)	7/269 (2.6)	4/263 (1.5)	4/269 (1.5)
	5	5/265 (1.9)	5/269 (1.9)	7/265 (2.6)	6/269 (2.2)
	6	9/264 (3.4)	7/274 (2.6)	6/264 (2.3)	9/274 (3.3)

Figure 10. Electrolyte and renal parameters: Mean change from baseline (trial 2009-01)

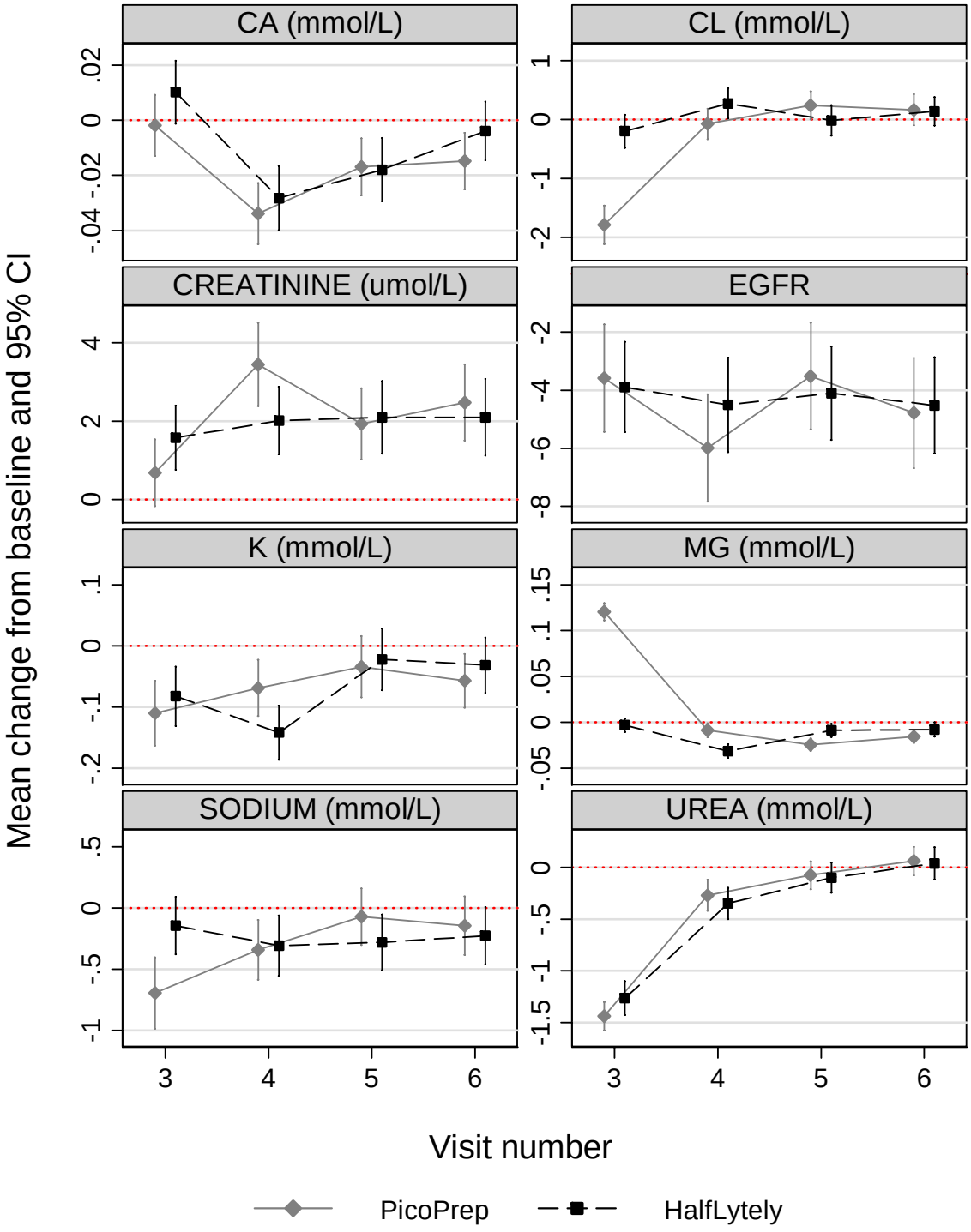
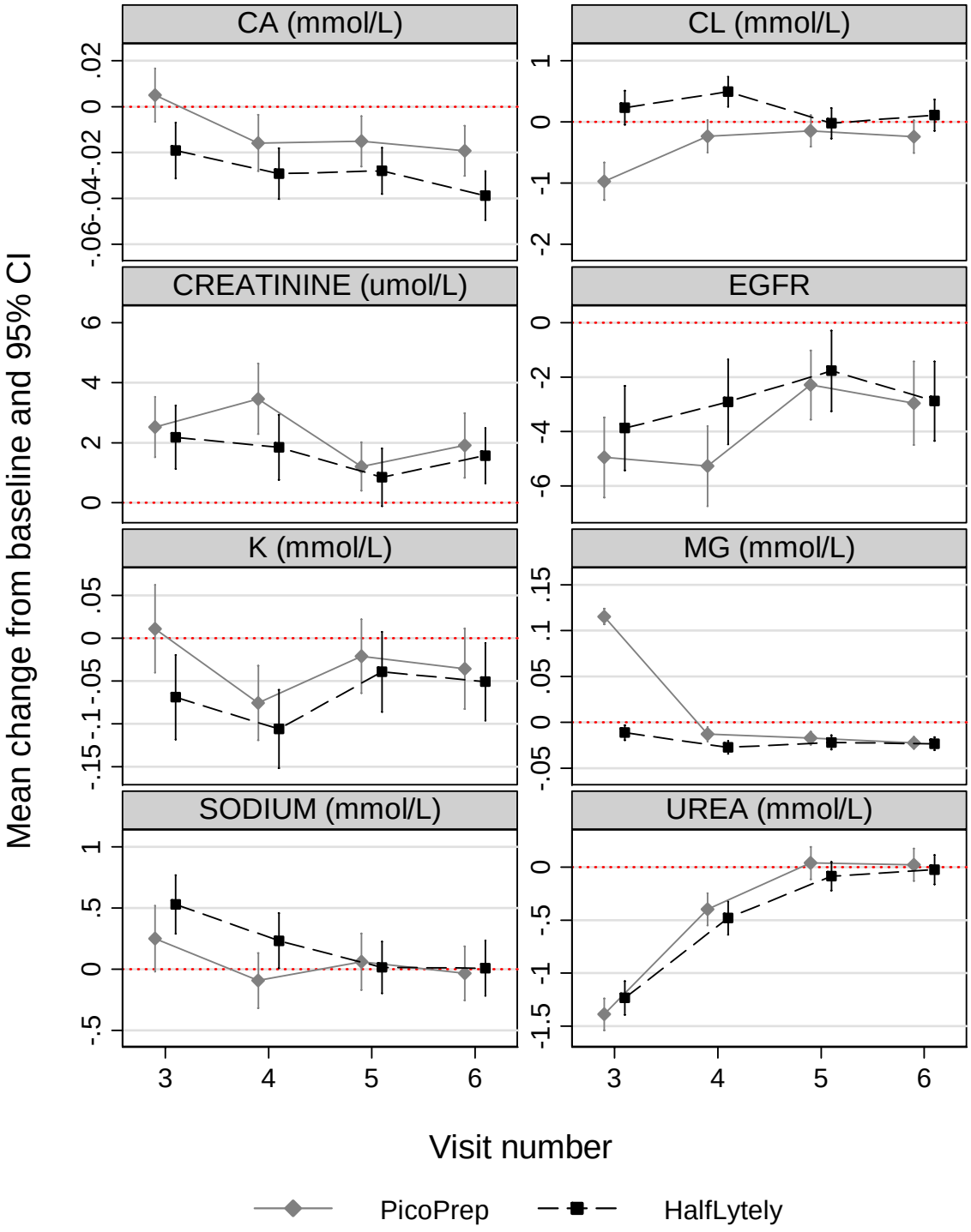


Figure 11. Electrolyte and renal parameters: Mean change from baseline (trial 2009-02)



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/s/

BRADLEY W MCEVOY
05/11/2012

LAREE A TRACY
05/14/2012

ALOKA G CHAKRAVARTY
05/14/2012

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 202535	**Applicant: Ferring Pharmaceuticals**	**Stamp Date: September 16, 2011**
Drug Name: PicoPrep	**NDA/BLA Type: NME/Standard**	**Indication: Bowel cleansing prior to colonoscopy**

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

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	X			
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			The applicant had not included the datasets for the 2nd study at the time of submission. However, this matter was resolved later.

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ___Yes_____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

The SAS datasets for Study 2009-02 have not been provided. The applicant has submitted the Study 2009-01 datasets for Study 2009-02.

Please identify and list any potential review issues.

At this point in the review, I have noticed the following:

- Although the statistical reviewer of the IND had brought up the weakness of choosing a 10 mg dosage for the active comparator and had recommended the sponsor to use the 20 mg dosage instead, nonetheless, the sponsor used the 10 mg dosage in the study.

- In the protocol, the sponsor had specified the method of finding the Non-Inferiority (NI) margin for the two studies and reported this value as 9%. However, the statistical reviewer had suggested a NI margin of 4% based on a 5% relative decrease if that was more acceptable from a clinical standpoint. Regardless, the sponsor still used a 9% NI margin. However, if the superiority objectives of the studies have been met, the NI margin may not be a review issue.

- The Sponsor has defined the Intent-to-Treat analysis set as: "All randomized subjects who received any study treatment and produced efficacy assessment data. However, the statistical reviewer of the IND had informed the sponsor that this was a modified ITT data set and they should use the ITT as defined by all randomized subjects for the primary analysis. The Applicant has ignored the statistical reviewer's advice. Further sensitivity analyses will be required.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

- In both Studies 2009-01 and 2009-02, there are discrepancies in the number of subject-discontinuations between Table 7-1 in the study report and Table 14.1.1 under Subject Disposition of the "demographic" file.

Discrepancies are as follows:

Study 2009-01

	Table 7-1 Study Report			Table 14.1.1 Subject Disposition		
	PicoPrep	HalfLytely	Total	PicoPrep	HalfLytely	Total
Discontinuation from the Study	1	3	4	3	6	9
Subject Withdrawal	1	0	1	3	2	5

Study 2009-02

	Table 7-1 Study Report			Table 14.1.1 Subject Disposition		
	PicoPrep	HalfLytely	Total	PicoPrep	HalfLytely	Total
Discontinuation from the Study	9	7	16	13	8	21
Subject Withdrawal	5	1	6	8	2	10

Please clarify these discrepancies.

Content Parameter (possible review concerns for 74-day letter)	**Yes**	**No**	**NA**	**Comment**
Designs utilized are appropriate for the indications requested.	**X**			At this point in the review, it seems OK. However, this would be a review issue
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**			Only 1 subject in PicoPrep and 3 subjects in HalfLytely did not complete the study.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Brief summary of controlled clinical trials

The following table contains information on the relevant trials contained in the submission.

Study number	Design	Treatment Arms /Sample Size	Primary Endpoint /Analysis	Sponsor's Findings
2009-01	a 7-month, phase III, randomized, multicenter, assessor-blinded, active-control, non-inferiority (NI) study investigating the efficacy, safety, and tolerability of "**Split-Dose**" dosing of PicoPrep versus HalfLytely for colon cleansing in preparation for colonoscopy in adult subjects.	**Planned:** All: 600 PicoPrep: 300 HalfLytely: 300 **Actual:** All: 603 PicoPrep: 305 HalfLytely: 298	**Aronchick Scale**: Cleanliness was reported by describing the overall preparation of the colon, assigning a grade of excellent, good, fair, or inadequate, according to the definitions given in **Aronchick Scale.** For the purpose of analysis, a subject was considered a responder following administration of the preparation if overall colon cleansing was rated as excellent or good on the 4-point scale.	PicoPrep showed superiority to the active control HalfLytely.
2009-02	a 7-month, phase III, randomized, multicenter, assessor-blinded, active-control, non-inferiority (NI) study investigating the efficacy, safety, and tolerability of "**Day-Before**" dosing of PicoPrep versus HalfLytely for colon cleansing in preparation for colonoscopy in adult subjects**.**	**Planned:** All: 600 PicoPrep: 300 HalfLytely: 300 **Actual:** All: 598 PicoPrep: 296 HalfLytely: 302	**Aronchick Scale**: Cleanliness was reported by describing the overall preparation of the colon, assigning a grade of excellent, good, fair, or inadequate, according to the definitions given in **Aronchick Scale.** For the purpose of analysis, a subject was considered a responder following administration of the preparation if overall colon cleansing was rated as excellent or good on the 4-point scale.	PicoPrep showed superiority to the active control HalfLytely.

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/s/

SHAHLA S FARR
11/15/2011

MICHAEL E WELCH
11/15/2011