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** | 21-551/SE2 |
| **Drug Name** | HalfLytely ® Solution with 5 mg and 10 mg bisacodyl |
| **Indication(s)** | Cleansing of the colon as a preparation for colonoscopy in adults. |
| **Applicant** | Braintree Laboratories, Inc. |
| **Document Reviewed** | NDA volumes 1 to 3 dated September 17, 2009<br>PDUFA: July 17, 2010 |
| **Review Priority** | Standard |
| **Biometrics Division** | Division of Biometrics III |
| **Statistical Reviewer** | Wen-Jen Chen, Ph.D. |
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| **Project Manager** | Ms. Diane Munro |
| **Keywords** | NDA review, Clinical studies, Non-inferiority analysis |

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# 1.0 EXECTIVE SUMMARY OF STATISTICAL FINDINGS

## 1.1 Conclusions and Recommendations

Following the comments made for the non-inferiority analysis, the non-inferiority of HalfLytely with 5 mg bisacodyl (H5) to HalfLytely with 10 mg bisacodyl (H10) is not established. Consequently the results do not support a labeling claim that the efficacy of H5 is non-inferior to H10 for cleansing of the colon as a preparation for colonoscopy in adults.

However, analysis of the cleansing success rate for HalfLytely 5 mg shows that a lower bound of 95% two-sided confidence interval is 69.0%. If the medical division deems that a success rate around 70.0% would be much higher than a placebo success rate, then, H5 formulation can be considered effective.

## 1.2 Brief Overview of Clinical Studies

In the approval letter (dated September 24, 2007) for HalfLytely kit combining a dose of 10mg bisacodyl submitted through NDA 21-551/S006, FDA requested the applicant to conduct a dose-response study evaluating lower doses of bisacodyl (e.g., 7.5 mg, 5 mg, and/or 2.5 mg) for efficacy and safety in cleansing the colon as a preparation for colonoscopy in adults. In accordance with this commitment, protocol F38-27 was submitted (IND 57,673) on December 28, 2007. Then, one year and five months later (May 28, 2009), a statistical analysis plan (SAP) was submitted. However, instead of planning a dose-response study, in the protocol along with SAP, the applicant discussed the study design and analysis method to evaluate whether or not a HalfLytely kit containing a dose of 5 mg bisacodyl was as effective as the approved kit containing 10 mg bisacodyl.

Accordingly, the objective of this study was to evaluate the safety and efficacy of HalfLytely with 10 mg bisacodyl (the approved product) to HalfLytely with 5 mg bisacodyl in normal outpatients requiring colonoscopy. In addition, in the study report, the approved HalfLytely with 10 mg bisacodyl is simply referred to as H10 and the test product, HalfLytely with 5 mg bisacodyl is referred to as H5.

This was a single blind (study investigator blinded) active controlled study. The active control was the approved HalfLytely and Bisacodyl Tablets Bowel Prep Kit which includes a bisacodyl dose of 10 mg (two 5 mg tablets). H10 or H5 bowel preparation kits were provided in identically labeled packages to patients requiring colonoscopy for routinely accepted indications. The only difference in the test preparations was the number of bisacodyl tablets (two versus one) contained inside the kit. The order of preparation assignment was determined according to a computer generated randomization schedule.

Total of 308 patients who met the inclusion and exclusion criteria were randomly assigned in a 1: 1 ratio within each participating site to receive either H5 or H110. Of these patients, 82 individuals were 65 years of age or older.

At Visit 2 (prior to the scheduled colonoscopy), patients completed a symptom scale questionnaire which asked them to provide an overall rating of their preparation related symptoms of stomach cramping, stomach bloating, nausea and overall discomfort. Patients used a five point scale for each symptom where a score of 1 = "None", 2 = "Mild", 3 = "Bothersome", 4 = "Distressing" and 5 = "Severely distressing". In addition, safety assessments also included adverse event monitoring as well as a pre and post physical examination.

Subjects self-administered the assigned study preparation on the day before their scheduled colonoscopy. Study subjects were instructed to first take their bisacodyl tablets according to the drug kit received. Following their first bowel movement (or a maximum of 6 hours), study subjects were instructed to begin consuming the 2 liters of HalfLytely solution.

Study subjects were provided with a treatment questionnaire to report their experience with the study treatment. Prior to the colonoscopy, study subjects also completed a symptom scale questionnaire to report their overall experience with the preparation.

The primary efficacy endpoint was based on the colonoscopists assessment of colon cleansing using a four point scale (poor, fair, good, and excellent). For the primary efficacy analysis, grades 3 (“good”) and 4 (“excellent”) were considered "successful" and grades 1 (“poor”) and 2 (“fair”) were considered "failure". Failing scores also included any patient exposed to the preparation who was not examined due to an adverse event, non-compliance or lack of efficacy.

Each examination was also rated as to whether or not cleansing was adequate for examination, the need for re-preparation and the colonoscopists ability to reach the cecum.

The primary analysis was based upon an intent-to-treat (ITT) analysis and included all patients randomized and receiving any treatment. Patients that did not undergo colonoscopy because of inadequate preparation, preparation or dietary non-compliance or preparation related adverse events were considered failures. Patients that took study preparation but withdrew prior to colonoscopy for reasons unrelated to safety or efficacy were excluded from efficacy analyses.

### 1.3 Statistical Issues and Findings

✓ In the protocol, the applicant proposed non-inferiority margin of 15% to assess the efficacy of the study drug H5 (HalfLytely with 5 mg bisacodyl) versus H10 (HalfLytely with 10 mg bisacodyl) using a non-inferiority analysis. However, the applicant did not submit any justification to support the non-inferiority margin of 15%. Since the non-inferiority margin of 15% selected by the applicant was not supported by the well-controlled historical studies conducted under conditions similar to those planned for the new trial as recommended by ICH E10, the non-inferiority margin of 15% is debatable and might not be acceptable.

Furthermore, since the colonoscopy exam is a risky procedure, from an ethical perspective, in the non-inferiority analysis, the success rate for the bowel preparation of the study drug should be close to that of the active control drug in the sense of not allowing more than 10%

reduction in active control treatment level. By this criterion, since the successful bowel preparation rate for H10 is around 80%, the non-inferiority margin should be around 8% (10% of 80%).

- ✓ Since this is a single blinded study, patients knew which drug was used for their bowel preparation. There was possibility for the investigators to be informed of the bowl preparation drug used by patients. Therefore, in reality, the single blinded trial had potential to be an open label trial. Furthermore, the ratings of "fair" (enough feces or fluid to prevent a completely reliable exam) and "good" (small amounts of feces or fluid not interfering with exam) in bowel cleansing quality are not completely distinguishable and might be assessed subjectively. Accordingly, as long as the investigator realized which drug was used by the patient, the assessment on the successful bowel preparation (scored as "good" by investigators) could be biased in favor of the study drug H5.

  The ICH E10 Guidance for Industry states that for the comparative trial to be informative concerning relative safety and/or efficacy, the trial needs to be fair; i.e., the conditions of the trial should not inappropriately favor one treatment over the other. Accordingly, in order to avoid the potential for biased assessments in this single blinded trial, the study could have been double blind, where patients in both groups could have been given two tablets without different appearance: H10 giving two 5 mg bisacodyl tablets and H5 giving one 5 mg bisacodyl tablet and one placebo tablet.

  To avoid biase in favor of H5, the applicant could have included a 0 mg bisacodyl plus HalfLytely arm (H0) in this trial. This would then have required the applicant to demonstrate superiority of the test arm H5 over H0, which would have been a more valid study design consistent with good statistical principles.

  Finally, since no non-inferiority margin was pre-specified for the secondary endpoint "Was cleansing adequate for evaluation", the results from the secondary endpoints can not be validly assessed. Accordingly, these results can not be put in the labeling package kit.

- ✓ From the active controlled arms selected by the applicant for the bowel preparation drugs H20 and H10 studied by previous submitted NDAs, we realize that as long as the study drug (e.g., H20) was approved, then it was used as an active control arm for the next new study drug (e.g., H10). Since the active control arm is changing to the previous study drug, by the insight of the non-inferiority comparison theory, the effect of the newly selected active control arm may be decreased when compared to the previous one. It follows that the non-inferiority of H5 to H10 shown by this study (F38-27) may not be held if H20 was the active controlled arm for the study. Accordingly, in order to preserve the acceptable quality of the non-inferiority analysis, the active controlled arm used for the new bowel preparation drug should not keep changing to the most recently approved drug.

- ✓ The result of this reviewer's primary efficacy endpoint (successful bowel preparation) analysis using data of H5 alone shows that lower bound of the two-sided 95% confidence

interval on the success rate of H5 in bowel cleansing quality is around 70.0% using ITT and Per-Protocol patients for Study F38-27. However, due to potential bias in the investigator assessments in favor of the study drug H5, the true success rate of H5 in bowel cleansing quality might be less than 70.0%.

## 2.0 INTRODUCTION

In the approval letter (dated September 24, 2007) for drug 10mg bisacodyl submitted through NDA 21-551/S006, FDA requested Braintree to conduct a dose-response study evaluating lower doses of bisacodyl (e.g., 7.5 mg, 5 mg, and/or 2.5 mg) for efficacy and safety in cleansing the colon as a preparation for colonoscopy in adults. In accordance with this commitment, protocol F38-27 was submitted by Braintree to FDA (IND 57,673) on December 28, 2007. Then, one year and five months later (May 28, 2009), a statistical analysis plan (SAP) was submitted to the Agency. However, instead of planning a dose-response study, in the protocol along with SAP, the applicant discussed the study design and analysis method to evaluate whether or not a HalfLytely kit containing a dose of 5mg bisacodyl was as effective as the approved kit containing 10 mg bisacodyL.

Accordingly, the goal of this submission for the completed F38-27 study report was to demonstrate that a HalfLytely kit with 5mg bisacodyl provides safe and effective cleansing equivalent to the HalfLytely kit with 10mg bisacodyl.

### 2.1 Overview

The objective of this study was to evaluate the safety and efficacy of HalfLytely with 10mg bisacodyl (the approved product) to HalfLytely with 5mg bisacodyl in normal outpatients requiring colonoscopy. In addition, in the study report, the approved HalfLytely with 10 mg bisacodyl is simply referred to as H10 and the test product, HalfLytely with 5 mg bisacodyl is referred to as H5.

This was a single blind (study investigator blinded) active controlled study. H10 or H5 bowel preparation kits were provided in identically labeled packages to patients requiring colonoscopy for routinely accepted indications. The order of preparation assignment was determined according to a computer generated randomization schedule.

The active control was the approved HalfLytely and Bisacodyl Tablets Bowel Prep Kit which includes a bisacodyl dose of 10 mg (two 5 mg tablets). The study medications were provided to patients in identically labeled packages. The only difference in the test preparations was the number of bisacodyl tablets (two versus one) contained inside the kit.

Subjects self-administered the assigned study preparation on the day before their scheduled colonoscopy. Study subjects were instructed to first take their bisacodyl tablets according to the drug kit received. Following their first bowel movement (or a maximum of 6 hours), study subjects were instructed to begin consuming the 2 liters of HalfLytely solution.

Study subjects were provided with a treatment questionnaire to report their experience with the study treatment. Prior to the colonoscopy, study subjects also completed a symptom scale questionnaire to report their overall experience with the preparation.

Total of 308 male and female patients who met the inclusion and exclusion criteria were randomly assigned in a 1: 1 ratio within each participating site to receive either H5 or H10. Of these patients, 82 individuals were 65 years of age or older.

The randomization schedule for the study was created by (b) (4) Statistical Services Network and was constructed using random blocks of 2 balanced treatment assignments at each site. The randomization schedule was implemented by Braintree Laboratories prior to kit distribution to the site. Following receipt of a sequential series of drug kits, site personnel dispensed the lowest numbered kit available to patients who met eligibility criteria in order to maintain the randomization schedule.

The primary efficacy endpoint was based on the colonoscopists assessment of colon cleansing using a four point scale (poor, fair, good, and excellent). For the primary efficacy analysis, grades 3 (“good”) and 4 (“excellent”) were considered "successful" and grades 1 (“poor”) and 2 (“fair”) were considered "failure". Failing scores was also given to any patient exposed to the preparation who was not examined due to an adverse event, non-compliance or lack of efficacy.

Each examination was also rated as to whether or not cleansing was adequate for examination, the need for re-preparation and the colonoscopists ability to reach the cecum.

At Visit 2 (prior to the scheduled colonoscopy), patients completed a symptom scale questionnaire which asked them to provide an overall rating of their preparation related symptoms of stomach cramping, stomach bloating, nausea and overall discomfort. Patients used a five point scale for each symptom where a score of 1 = "None", 2 = "Mild", 3 = "Bothersome", 4 = "Distressing" and a score of 5 = "Severely distressing". In addition, safety assessments also included adverse event monitoring as well as pre and post physical examination.

The primary analysis was based upon an intent-to-treat (ITT) analysis and included all patients randomized and receiving any treatment. Patients that did not undergo colonoscopy because of inadequate preparation, preparation or dietary non-compliance or preparation related adverse events were considered failures. Patients that took study preparation but withdrew prior to colonoscopy for reasons unrelated to safety or efficacy were excluded from efficacy analyses.

## 2.2 Data Sources

Documents reviewed include NDA volumes 1 to 3 submitted by the applicant on September 17, 2009. Data used in this reviewer’s analysis were submitted by the applicant on September 17, 2009 and located at \\FDSWA150\NONECTD\N21551\S_013\2009-09-11.

# 3.0 STATISTICAL EVALUATION

## 3.1 Evaluation of Efficacy for Study F38-27

### 3.1.1 Study Design and Endpoints

The objective of this study was to evaluate the safety and efficacy of HalfLytely with 10mg bisacodyl (the approved product) to HalfLytely with 5mg bisacodyl in normal outpatients requiring colonoscopy. In addition, in the study report, the approved HalfLytely with 10 mg bisacodyl is simply referred to as H10 and the test product, HalfLytely with 5 mg bisacodyl is referred to as H5.

This was a single blind (study investigator blinded) active controlled study. H10 or H5 bowel preparation kits were provided in identically labeled packages to patients requiring colonoscopy for routinely accepted indications. The order of preparation assignment was determined according to a computer generated randomization schedule.

The active control was the approved HalfLytelyCI and Bisacodyl Tablets Bowel Prep Kit which includes a bisacodyl dose of 10 mg (two 5 mg tablets). The study medications were provided to patients in identically labeled packages. The only difference in the test preparations was the number of bisacodyl tablets (two versus one) contained inside the kit.

Subjects self-administered the assigned study preparation on the day before their scheduled colonoscopy. Study subjects were instructed to first take their bisacodyl tablets according to the drug kit received. Following their first bowel movement (or a maximum of 6 hours), study subjects were instructed to begin consuming the 2 liters of HalfLytely solution.

Study subjects were provided with a treatment questionnaire to report their experience with the study treatment. Prior to the colonoscopy, study subjects also completed a symptom scale questionnaire to report their overall experience with the preparation.
A total of 308 male and female patients who met the inclusion and exclusion criteria were randomly assigned in a 1: 1 ratio within each participating site to receive either H5 or H10. Of these patients, 82 individuals were 65 years of age or older.

The randomization schedule for the study was created by (b) (4) Statistical Services Network and was constructed using random blocks of 2 balanced treatment assignments at each site. The randomization schedule was implemented by Braintree Laboratories prior to kit distribution to the site. Following receipt of a sequential series of drug kits, site personnel dispensed the lowest numbered kit available to patients who met eligibility criteria in order to maintain the randomization schedule.

The primary efficacy endpoint was based on the colonoscopists assessment of colon cleansing using a four point scale (poor, fair, good, and excellent). This scale is shown in Table 3.1.1.1.

**Table 3.1.1.1 (Applicant's) Colonoscopist Colon Cleansing Scores**

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

For the primary efficacy analysis, grades 3 and 4 were considered "successful" and grades 1 and 2 were considered "failure". Failing scores also included any patient exposed to the preparation who was not examined due to an adverse event, non-compliance or lack of efficacy.

Each examination was also rated as to whether or not cleansing was adequate for examination, the need for re-preparation and the colonoscopists ability to reach the cecum.

At Visit 2 (prior to the scheduled colonoscopy), patients completed a symptom scale questionnaire which asked them to provide an overall rating of their preparation related symptoms of stomach cramping, stomach bloating, nausea and overall discomfort. Patients used a five point scale for each symptom where a score of 1 = "None", 2 = "Mild", 3 = "Bothersome", 4 = "Distressing" and a score of 5 = "Severely distressing". In addition, safety assessments also included adverse event monitoring as well as pre and post physical examination.

### 3.1.2 Statistical Methodologies

The primary analysis was based upon an intent-to-treat (ITT) analysis and included all patients randomized and receiving any treatment. Patients that did not undergo colonoscopy because of inadequate preparation, preparation or dietary non-compliance or preparation related adverse events were considered failures. Patients that took study preparation but withdrew prior to colonoscopy for reasons unrelated to safety or efficacy were excluded from efficacy analyses. Success rate was analyzed using a CMH Chi-square adjusting for the effect of investigator site. The formal hypothesis test result (p-value) for treatment difference was presented together with a one-sided 95% confidence interval for the difference [Based upon the applicant's SAS program T2-1Z.sas, the applicant used SAS PROC FREQ procedure to calculate the 95% two-sided confidence interval for the proportion difference of H5 minus H10].

The primary endpoint of treatment success was tested using a non-inferiority test based upon the difference $D=P_1-P_2$ for the null hypothesis $H_0$: $P_1-P_2 \leq -D_0$ versus alternative hypothesis $H_1$: $P_1-P_2 > -D_0$, Where $P_1$ is the HalfLytely 5 mg group (treatment group) and $P_2$ is the HalfLytely 10 mg group (control group) and $D_0$ (>0) is the acceptable margin of equivalence equal to an absolute margin of 15%.

Secondary endpoints were analyzed in a manner similar to the primary analysis using CMH Chi-Square adjusting for any site effects for counts (percentages) and a two-way ANOVA with terms

for treatment, site, and their interaction for mean responses. Results were presented for the effect results (p-values) and 95% confidence intervals for the treatment difference.

Treatment emergent adverse event rates were descriptively presented by body system, preferred term, severity, and relationship to treatment for each treatment group. Differences in adverse event rates between treatment groups were assessed using Fishers Exact Test.

The applicant indicated that the protocol planed study size was three hundred (300) patients. Patients were randomly assigned to one of the two preparations in a ratio of 1: 1 (150 patients per group). A dropout rate of approximately 5% per treatment group was expected. The efficacy of H10 administered as a one-day preparation has been previously reported as 87%. Assuming a success rate for H5 of 81 %, a two-sided 95% confidence interval (asymptotic Pearson Chi-square method) for the between group success rates (H5 – H10) will result in a lower CI bound greater than - 15%. This result will establish non-inferiority between H5 and H10 for a non-inferiority margin of 15%.

### 3.1.3 Patient Disposition

This study was conducted at 6 centers. 308 patients were enrolled, including 82 elderly. 295 patients took study medication and were included in the Intent-to-Treat (ITT) analysis. All 13 non-ITT patient withdrawals were due to withdrawal of consent (6 for H5, 7 for H10). The reasons for discontinuation in the ITT group are given below in Table 3.1.3.1.

**Table 3.1.3.1 (Applicant's) Reasons for Patient Discontinuation by Intent-to-Treat Population***

| | H5 (n) | H10 (n) |
|---|---|---|
| Total Randomized | 154 | 154 |
| Total ITT Patients[1] | 148 (100%) | 147 (100%) |
| Completing Patients | 145 (98.0%) | 145 (98.6%) |
| Patients Discontinued | 3 (2.0%) | 2 (1.4%) |
| Reasons for discontinuation: | | |
| Non-compliance | 1 (33.3%) | 1 (50.0%) |
| Patient withdrew consent | 1 (33.3%) | 0 (0%) |
| Adverse event | 1 (33.3%) | 0 (0%) |
| Insurance Coverage Issues | 0 | 1 (50.0%) |

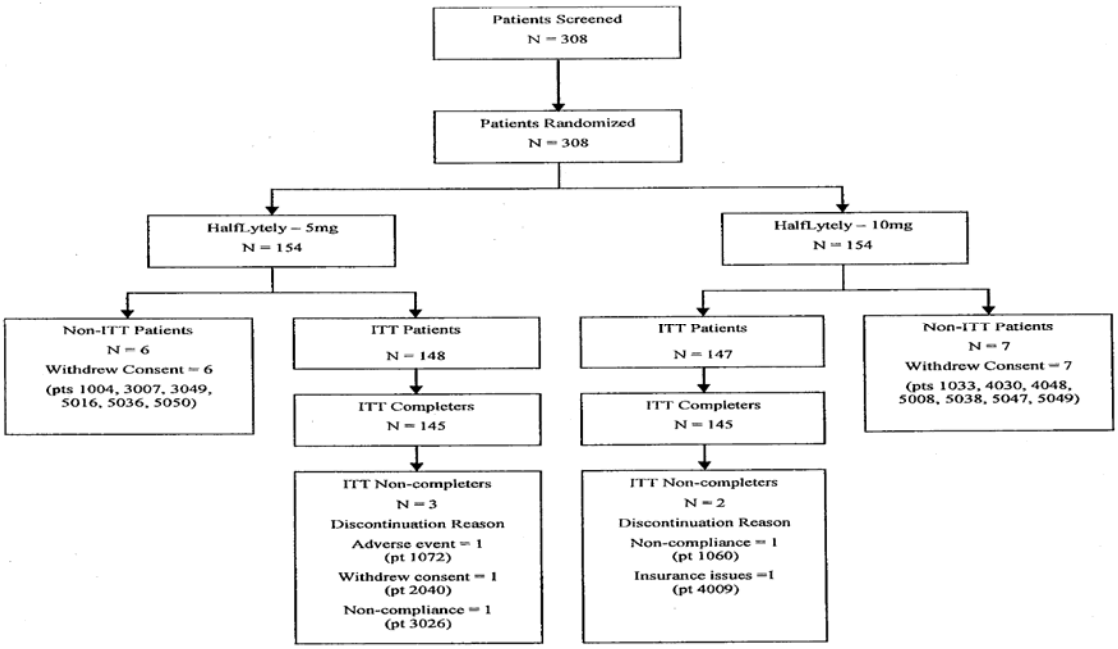
*ITT is defined as any patient that took any amount of study preparation

Based upon Table 3.1.3.1, the applicant indicated that 290 patients of the 295 ITT patients that took their study preparation fully completed the study (defined as patients that had a colonoscopy). Five patients (numbers 1060, 1072, 2040, 3026 and 4009) took at least a portion of their preparation but were withdrawn prior to colonoscopy. Patients 1060 (H10) and 3026 (H5) were noncompliant with preparation specific dietary restrictions and were withdrawn, but were included in the efficacy analysis as non-responders. Patient 2040 (H5) was noncompliant with site-specific NPO restrictions (not mandated by the protocol) and decided to withdraw consent. Patient 1072 (H5) experienced nausea and vomiting and decided to discontinue the preparation. This patient was also included in the efficacy analysis as a non-responder. Patient

4009 (H10) withdrew prior to colonoscopy due to an insurance coverage issue. In conclusion, the applicant emphasized that the primary efficacy analysis was based on 293 patients..

Figure 3.1.3.1 demonstrated the diagram for the patient disposition.

**Figure 3.1.3.1 (Applicant's) Diagram for patient disposition**




### 3.1.4 Demographics and Baseline Characteristics

The applicant indicated that the study populations were well-matched. There were similar proportions of male and female patients. The average age of study participants was about 55 years, ranging in age from 19 to 87 years of age. There were 82 patients age 65 or older (44 in the H5 group and 38 in the H10 group), and 19 patients were 75 years of age or older (l1 in the H5 group and 8 in the H10 group). About 83 % of study enrollees were white, 12% were African American and 8% were Hispanic or Latino. Study patients weighed an average of about 185 lbs. There were no demographic related statistically significant differences between treatment groups.

The study population demographics are summarized in Table 3.1.4.1 below.

**Table 3.1.4.1 (Applicant's) Study Demographics by ITT Population**

| | H5 | H10 | p[1] |
|---|---|---|---|
| **Age** (years)[2] | | | |
| n | 148 | 147 | 0.216 |
| Mean (SD) | 56.8 (12.1) | 55.0 (13.0) | |
| **Gender** | | | |
| Female | 73 (49%) | 61 (42%) | 0.199 |
| Male | 75 (51%) | 86 (58%) | |
| **Race** | | | |
| White | 123 (83%) | 122 (83%) | 0.198 |
| A. Am. | 19 (13%) | 16 (11%) | |
| Other | 4 (3%) | 9 (6%) | |
| **Ethnicity** | | | |
| Hispanic | 8 (5%) | 14 (10%) | 0.192 |
| Non Hispanic | 140 (95%) | 133 (90%) | |
| **Weight** (lbs) | | | |
| Mean (SD) | 188 (44) | 183 (47) | 0.309 |

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

For baseline characteristics, the applicant indicated that patients returned to their study center for scheduled colonoscopy after completing their bowel preparation where issued study drug materials were reviewed for treatment compliance.

Compliance for each patient was calculated based on the number of bisacodyl tablets returned and the volume of liquid remaining in the PEG lavage component. Patients that took all bisacodyl tablets and returned less than 4 oz (118 ml) of unconsumed liquid were considered to have completed preparation.

### 3.1.5 Applicant's Efficacy Analysis Results and Conclusions

#### 3.1.5.1 Distribution of cleansing scores

The examining physician rated each colonoscopy for cleansing according to a four point scale where a score of 1 = "poor" and a score of 4= "excellent". Table 3.1.5.1 presented Cleansing scores for the H5 and H10 bowel preparations.

**Table 3.1.5.1 (Applicant's) Preparation cleansing score by treatment group using ITT completers**

| Score | H5<br>n (%) | H10<br>n (%) |
|---|---|---|
| 4<br>Excellent | 26<br>(17.7%) | 23<br>(15.8%) |
| 3<br>Good | 88<br>(59.9%) | 94<br>(64.4%) |
| 2<br>Fair | 22<br>(15.0%) | 22<br>(15.1%) |
| 1<br>Poor | 9<br>(6.1%) | 6<br>(4.1%) |

The applicant indicated that in Table 3.1.5.1, all 290 patients (ITT completers) with a colonoscopy were included while the other three patients (1060, 1072 and 3026) without a colonoscopy were not included. Based upon Table 3.5.1.1, the applicant claimed that the distribution of scores for each cleansing category was numerically similar.

### 3.1.5.2 Primary efficacy responder analysis

The primary efficacy responder analysis included the 290 patients that underwent colonoscopy as well as thee patients that were counted as failures because they could not undergo a colonoscopy due to inability to complete the preparation due to adverse event (patient 1072) or non-compliance with protocol dietary restrictions (patients 1060 and 3026). In addition, two patients (patients 4009 and 2040) were excluded from the responder analysis because of withdrawing consent forms.

The responder was defined as a successful preparation: physician rate scores 3 (Good) and 4 (Excellent). Table 3.1.5.2 presented the result regarding the responder analysis using the ITT patients without the two patients withdrawing consent forms.

**Table 3.1.5.2 (Applicant's) Result for primary efficacy responder analysis using ITT patients**

| Responder | H5<br>% (m/n) | H10<br>% (m/n) | Percent Diff<br>% (H5 – H10) | Two-sided 95% Confidence Interval<br>for Percent Diff (H5 – H10) |
|---|---|---|---|---|
| All Patients (n) | 147 | 146 | | |
| Success | 77.6% (114/147) | 80.1% (117/146) | -2.5% | (-11.9%, 6.8%) |

(1) A successful treatment is defined as bowel cleansing graded either "excellent" or "good "by the blinded colonoscopist (grading score = 3 or 4).

(2) 95% confidence interval (CI) for the difference between treatments was obtained by Chi-Square Test.

Based upon Table 3.1.5.2, the applicant indicated that the two-sided 95% confidence intervals reported in Cochran-Mantel-Haenszel Chi-Square testing (-11.9%, 6.8%) fall between the predetermined equivalence margin of ±15%, H5 can be considered equivalent with respect to cleansing efficacy to the approved H10.

### 3.1.5.3 Secondary endpoint analysis

The secondary endpoint was the physician response to the question "Was cleansing adequate for evaluation?" on the physician's colonoscopy examination form. Table 3.1.5.3 demonstrated the analysis results for the secondary endpoint.

**Table 3.1.5.3 (Applicant's) Number and Percent of Adequate Preparations**

| | H5<br>n (%) | H10<br>n (%) | 95% CI[1] | P |
|---|---|---|---|---|
| **Adequate? (n)** | 145 | 145 | | |
| Yes | 132 (91%) | 139 (96%) | -10.5, 0.8 | 0.153 |
| No | 13 (9%) | 6 (4%) | | |
| **Cecum reached? (n)** | 145 | 145 | | |
| Yes | 135 (93%) | 138 (95%) | -7.5, 3.3 | 0.472 |
| No | 10 (7%) | 7 (5%) | | |

(1) Confidence interval (CI) for the difference between treatments was by Chi-Square Test.

The applicant indicated that as shown in Table 3.1.5.3, more than 90% of preparations for either kit were considered to be adequate. Similarly, examining physicians were able to reach the cecum in over the 90% of the colonoscopies performed.

### 3.1.6. Reviewer's comments and efficacy analysis

In order to assess the efficacy results claimed by the applicant, this reviewer first comments on the following issues with regard to the study design: 1) the non-inferiority margin, 2) assessment quality for colon cleansing, and 3) active control selection. Then, this reviewer performs the efficacy analysis for H5.

### 3.1.6.1 Non-inferiority margin

In the protocol, the applicant proposed the non-inferiority margin of 15% to assess the efficacy of the study drug H5 (HalfLytely with 5mg bisacodyl) versus H10 (HalfLytely with 10mg bisacodyl) using a non-inferiority analysis. However, the applicant did not submit justification to support the selection for the non-inferiority margin of 15%.

Basically, ICH E10 emphasized that the margin chosen for a non-inferiority trial cannot be greater than the smallest effect size that the active-control drug would be reliably expected to have as compared with placebo in the setting of the planned trial. Identification of the smallest effect size that the active drug would be reliably expected to have is only possible when there is historical evidence of sensitivity to drug effects and, indeed, identification of the margin is based upon that evidence. In addition, the margin should also be identified based on past experience in placebo-control trials with adequate design under conditions similar to those planned for the new trial. Since no historical study as recommended by ICH E10 was submitted to support the non-inferiority margin of 15%, the non-inferiority margin of 15% is debatable. Accordingly, the non-inferiority of H5 to H10 claimed by the sponsor based upon non-inferiority margin of 15% is not established.

Finally, since the colonoscopy exam is a risky procedure, from ethical perspective, in the non-inferiority analysis, the successful rate for the bowel preparation of the study drug should be close to that of the active control drug in the sense of not allowing more than 10% reduction in active control treatment level. By this criterion, since the successful bowel preparation rate for H10 is around 80%, the non-inferiority margin should be around 8% (10% of 80%).

**3.1.6.2 Assessment of quality for colon cleansing**

Based on the applicant's study design, biased assessments of colon cleansing quality could be induced by i) the single blinded design and ii) problems with the non-inferiority analysis method.

**3.1.6.2.1 Single blinded design**

As indicated by the applicant, this trial was a single blinded study in which investigators were blinded to the methods of preparation. However, since patients knew which drug was used for their bowel preparations, there was opportunity for the investigators to be informed of the bowl preparation drug used by patients. Therefore, in reality, the single blinded trial was highly potential to be an open label trial.

Furthermore, the ratings of "fair" (enough feces or fluid to prevent a completely reliable exam) and "good" (small amounts of feces or fluid not interfering with exam) in bowel cleansing quality are not completely distinguished and would be assessed subjectively. Accordingly, as long as the investigator realized which drug was used by the patient, the assessment on the successful bowel preparation (scored as "excellent" and "good" by investigators) could be biased in favor of the study drug H5.

The ICH E10 Guidance for Industry states that for the comparative trial to be informative concerning relative safety and/or efficacy, the trial needs to be fair; i.e., the conditions of the trial should not inappropriately favor one treatment over the other. Accordingly, in order to avoid the potential for biased assessments from this single blinded trial, the study could have been double blind where patients in both groups could have been given two tablets without different appearance: H10 - two 5 mg bisacodyl tablets and H5 – one 5 mg bisacodyl tablet and one placebo tablet.

**3.1.6.2.2. Problems with non-inferiority analysis method**

Based on the efficacy non-inferiority analysis criteria, one notes that if the outcomes of the bowel preparations for the two treatment groups, H5 and H10, were consistently rated "successful", then the H5 drugs would be claimed to be non-inferior to H10. As indicated above, due to the single blind study and the ambiguous definition for bowel cleansing quality scores "good" and "fair", bowel preparation quality might not be assessed objectively. Therefore, with only two arms H5 and H10 in the trial, the investigators could easily have assigned similar scores to the two treatment groups. If investigators assessed the outcomes of the bowel preparations for the two treatment groups as close as possible, the chance of the efficacy "non-

inferiority" for the two drugs would be greatly increased. However, any such "non-inferiority" of H5 to H10 would be a biased result in favor of study drug H5.

To avoid bias in favor of H5, the applicant could have included a 0 mg bisacodyl plus HalfLytely arm (H0) in this trial. This would then have required the applicant to demonstrate superiority of the test arm H5 over H0, which would have been a more valid study design consistent with good statistical principles.

Finally, since no non-inferiority margin was pre-specified for the secondary endpoint "Was cleansing adequate for evaluation", the results from the secondary endpoints can not be validly assessed. Accordingly, these results can not be put in the labeling package kit.

**3.1.6.2.3 Active control selection**

It is noted that the active control arm selected by the applicant for this study is not the same as the one (4L NuLytely) selected by the applicant for the first bowel preparation study drug H20. The study drugs and the associated active control arms selected by the applicant are listed by Table 3.1.6.1 below.

**Table 3.1.6.1 (Reviewer's) Summary of study drug and its selected active control arm**

| Study Number | Study Drug | Active Control Arm |
|---|---|---|
| F38-13/14 | 2L + 20 mg Bis (H20) | 4L NuLytely |
| F38-26 | 2L+10 mg Bis (H10) | H20 |
| F38-27 | 2L+5mg Bis (H5) | H10 |

From the above list, we realized that as long as the study drug (e.g., H20) was approved. Then it was used as an active control arm for the next new study drug (e.g., H10). We note that the theory of the non-inferiority analysis only indicates that the effect of the approved study drug is not inferior to that of the active controlled arm by more than the selected non-inferiority margin. In other words, the study drug effect may be worse than that of the active controlled arm. Therefore, the way of the active controlled arms selected by the applicant is potentially deteriorating the effect of the active controlled arm.

The success rates along with the associated studies of the bowel preparations (based upon ITT population) for each of the selected active control arms are listed in Table 3.1.6.2 below.

**Table 3.1.6.2 (Reviewer's) Success rate of active control arm by study**

| Study Number | Active Control Arm | Success rate |
|---|---|---|
| F38-13/14 | 4L NuLytely | 90.0% (86/96) |
| F38-20 | 4L NuLytely | 78.0% (76/97) |
| F38-26 | H20 | 88.0% (196/223) |
| F38-27 | H10 | 80.0% (117/146) |

From Table 3.1.6.2, we note that except Study 38-20, the success rates of the bowel preparations for the active control arms decreased from 4L NuLytely to H10; it might indicate that the effect

size of the active control arm dwindled. By the light of the above information, for the current Study F38-27, if instead of using H10 as the active controlled arm, H20 was used by the applicant as the active controlled arm then, since the success rate (88.0%) of H20 was obtained from Study F38-26, the two-sided 95% confidence interval for the success rate of H5 minus that of H20 is (-19.0%, -2.3%). The lower bound (-19.0%) is less than -15% (selected non-inferiority margin). Based upon this result, even if using the non-inferiority margin of 15%, the result of the non-inferiority of H5 to H20 shown by this study is not supported. Accordingly, in order to preserve the acceptable quality of non-inferiority analysis, the active controlled arm used for the new bowel preparation drug should not keep changing to the most recently approved drug.

As seen above, there may be a concern for "biocreep". In order to avoid for "biocreep", the standard regimen should be used as control.

### 3.1.6.2.4 Reviewer's Efficacy Analysis for H5

Since the non-significant margin of 15% selected by the applicant for testing the null hypothesis of H5 inferior to H10 by more than 15% was not supported by historical data, the non-inferiority claim of H5 to H10 can not be officially established. In order to determine if the test drug H5 has efficacy (superior to placebo), this reviewer calculated the two-sided 95% confidence interval on the success rate of H5 ($P_{H5}$) using ITT and Per-Protocol patient populations. Table 3.1.6.3 presents the result.

**Table 3.1.6.3 (Reviewer's) 95% two-sided confidence intervals on $P_{H5}$**

| | H5 | | 95% Confidence Interval on |
|---|---|---|---|
| Patient Population | No. Success | Success Rate (n/N) | $P_{H5}$ |
| Per-Protocol Patients | 78.0% | (114/147) | (70.0%, 84.0%) |
| Intent-to-Treat Population | 77.0% | (114/148) | (69.0%, 84.0%) |

Table 3.1.6.3 shows the lower bounds for the two-sided 95% confidence intervals of the success rate of bowel cleansing quality are 70.0% and 69.0% for per-protocol and ITT populations, respectively. Since the assessments on the bowel preparations were potentially biased in favor of the test drug H5, the lower bound of the 95% two-sided interval for H5 calculated using the data from a more reliable study may be less than 69%. However, based upon the assumed placebo response rates of 20% to 30% estimated by the medical division, using the results in Table 3.1.6.3 as a reference, the medical division may deem that a success rate of H5 around 70% is effective.

## 3.2 Evaluation of Safety

The applicant indicated that for the 295 patients prepared for colonoscopy with either receiving H10 or H5, no differences in treatment emergent adverse reports were observed for the general population or on the basis of age, gender, race or medical risk. As expected, the most frequent reports involved gastrointestinal complaints generally consistent with use of a bowel preparation.

The majority of these reports were mild to moderate in intensity and quickly resolved. Patient symptom ratings of cramping, bloating, nausea and overall discomfort were generally lower with H5, with bloating reaching statistical significance. This difference was seen not only in the general population, but also in the elderly and female subgroups. No difference in vomiting episodes was detected.

## 4.0 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

## 4.1 GENDER, RACE, AND AGE for Study F38-26

In order to assess the consistency of the treatment effect of H5 versus H10 across subgroups, this reviewer performed the subgroup analysis for the primary endpoint (percentage of patients achieving successful bowel preparation) using ITT patient population. Since more than 80% of patients are White, no subgroup analysis by race group is performed. Accordingly, the subgroups analyzed for the study are only for Gender (Male and Female) and Age group (age ≤ 65 and age > 65).

### 4.1.1 Gender

Table 4.1.1 presents the results of treatment efficacy comparisons for H5 versus H10 by gender.

**Table 4.1.1 (Reviewer's) Percentage of patients with successful bowel preparation by gender using ITT population**

*Female*

| | H5 % (n/m) | H10 % (n/m) | Percent Diff % (H5 – H10) | 95% Confidence Interval for Percent Diff (H5 – H10) |
|---|---|---|---|---|
| Primary Endpoint[a] | 78.7% (59/75) | 82.4% (70/85) | -3.7% | (-16.0%, 8.6%) |

*Male*

| | H5 % (n/m) | H10 % (n/m) | Percent Diff % (H5 – H10) | 95% Confidence Interval for Percent Diff (H5 – H10) |
|---|---|---|---|---|
| Primary Endpoint | 76.4% (55/72) | 77.0% (47/61) | -0.6% | (-15.1%, 13.8%) |

[a]: Percentage of patients achieving successful bowel preparation;

Table 4.1.1 indicates that for females, the percentage of patients achieving "successful bowel preparation" in the H5 group is numerically 3.0% less than that of the H10 group while for males, the H5 group is numerically 1.0% less than that of the H10 group.

### 4.1.2 Age group (age ≤ 65 and age > 65)

Table 4.1.2 presents the results of treatment efficacy comparisons for H5 versus H10 by age group.

**Table 4.1.2 (Reviewer's) Percentage of patients with successful bowel preparation by age group using ITT population**

Age ≤ 65

| | H5 % (n/m) | H10 % (n/m) | Percent Diff % (H5 – H10) | 95% Confidence Interval for Percent Diff (H5 – H10) |
|---|---|---|---|---|
| Primary Endpoint[s] | 80.9% (89/110) | 86.0% (98/114) | -5.1% | (-14.8%, 4.7%) |

Age > 65

| | H5 % (n/m) | H10 % (n/m) | Percent Diff % (H5 – H10) | 95% Confidence Interval for Percent Diff (H5 – H10) |
|---|---|---|---|---|
| Primary Endpoint[a] | 67.6% (25/37) | 59.4% (19/32) | 8.2% | (-14.6%, 30.9%) |

[a] Percentage of patients achieving successful bowel preparation;

Table 4.1.2 indicates that for patients with ages greater than 65, the percentage of patients achieving "successful bowel preparation" in the H5 group is numerically 8.2% higher than that of the H10 group. However, for patients with ages less than or equal to 65, H5 is 5.1% less than H10.

## 4.2 OTHER SPECIAL/SUBGROUP POPULATIONS - Not applicable

## 5.0 SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues and Collective Evidence

✓ In the protocol, the applicant proposed non-inferiority margin of 15% to assess the efficacy of the study drug H5 (HalfLytely with 5 mg bisacodyl) versus H10 (HalfLytely with 10 mg bisacodyl) using a non-inferiority analysis. However, the applicant did not submit any justification to support the non-inferiority margin of 15%. Since the non-inferiority margin of 15% selected by the applicant was not supported by the well-controlled historical studies conducted under conditions similar to those planned for the new trial as recommended by ICH E10, the non-inferiority margin of 15% is debatable.

Furthermore, since the colonoscopy exam is a risky procedure, from an ethical perspective, in the non-inferiority analysis, the success rate for the bowel preparation of the study drug should be close to that of the active control drug in the sense of not allowing more than 10% reduction in active control treatment level. By this criterion, since the successful bowel preparation rate for H10 is around 80%, the non-inferiority margin should be around 8% (10% of 80%).

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

assessed subjectively. Accordingly, as long as the investigator realized which drug was used by the patient, the assessment on the successful bowel preparation (scored as "good" by investigators) could be biased in favor of the study drug H5.

The ICH E10 Guidance for Industry states that for the comparative trial to be informative concerning relative safety and/or efficacy, the trial needs to be fair; i.e., the conditions of the trial should not inappropriately favor one treatment over the other. Accordingly, in order to avoid the potential for biased assessments in this single blinded trial, the study could have been double blind, where patients in both groups could have been given two tablets without different appearance: H10 giving two 5 mg bisacodyl tablets and H5 giving one 5 mg bisacodyl tablet and one placebo tablet.

To avoid biase in favor of H5, the applicant could have included a 0 mg bisacodyl plus HalfLytely arm (H0) in this trial. This would then have required the applicant to demonstrate superiority of the test arm H5 over H0, which would have been a more valid study design consistent with good statistical principles.

Finally, since no non-inferiority margin was pre-specified for the secondary endpoint "Was cleansing adequate for evaluation", the results from the secondary endpoints can not be validly assessed. Accordingly, these results can not be put in the labeling package kit.

- ✓ From the active controlled arms selected by the applicant for the bowel preparation drugs H20 and H10 studied by previous submitted NDAs, we realize that as long as the study drug (e.g., H20) was approved, then it was used as an active control arm for the next new study drug (e.g., H10). Since the active control arm is changing to the previous study drug, by the insight of the non-inferiority comparison theory, the effect of the newly selected active control arm may be decreased when compared to the previous one. It follows that the non-inferiority of H5 to H10 shown by this study (F38-27) may not be held if H20 was the active controlled arm for the study. Accordingly, in order to preserve the acceptable quality of the non-inferiority analysis, the active controlled arm used for the new bowel preparation drug should not keep changing to the most recently approved drug.

- ✓ The result of this reviewer's primary efficacy endpoint (successful bowel preparation) analysis using data of H5 alone shows that lower bound of the two-sided 95% confidence interval on the success rate of H5 in bowel cleansing quality is around 70.0% using ITT and Per-Protocol patients for Study F38-27. However, due to potential bias in the investigator assessments in favor of the study drug H5, the true success rate of H5 in bowel cleansing quality might be less than 70.0%.

## 5.2 Conclusions and Recommendations

Following the comments made for the non-inferiority analysis, the non-inferiority of HalfLytely with 5 mg bisacodyl (H5) to HalfLytely with 10 mg bisacodyl (H10) is not established.

Consequently the results do not support a labeling claim that the efficacy of H5 is non-inferior to H10 for cleansing of the colon as a preparation for colonoscopy in adults.

However, analysis of the cleansing success rate for HalfLytely 5 mg shows a lower confidence bound of 69.0%. If the medical division deems that a success rate around 70.0% would be much higher than a placebo success rate, then, H5 formulation can be considered effective.

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-21551 | SUPPL-13 | BRAINTREE LABORATORIES INC | HALF LYTELY BISACODYL BOWEL PREP KIT |

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WEN JEN CHEN
07/14/2010

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