CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-881

STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

NDA/Serial Number: 21-881
Drug Name: Moviprep
Indication(s): Bowel cleansing prior to colonoscopy

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Document Reviewed: Volumes 1 to 89 dated June 7, 2005
Review Priority: Standard

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Statistical Keywords: Clinical studies; NDA review.

TABLE OF CONTENTS

1.0 EXECTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 Conclusions and Recommendations

From the statistical perspective, based upon the four remarks, stated in the section of "Statistical Issues and Collective Evidence", given by this reviewer to the justification on the selected non-inferiority margin of 15% provided by the applicant, the non-inferiority margin of 15% selected by the applicant for the two studies is not acceptable. Accordingly, NDA submitted by the applicant does not provide substantial evidence to support that the efficacy of moviprep is non-inferior to that of approved drugs for bowel cleansing prior to colonoscopy [redacted]

However, the lower bound for the two-sided 95% confidence interval on the proportions of bowel cleansing success for moviprep is not less than 0.64, calculated using the applicant's data from the two NDA studies (NRL994-01/2001 and NRL994-02/2001). Using this result as a reference, if the medical division deems that the success rate around 0.60 of moviprep would be higher than that of placebo, then, moviprep can be considered as effective.

1.2 Brief Overview of Clinical Studies

The applicant conducted two randomized, single-blind, active-controlled studies (NRL994-01/2001 and NRL994-02/2001) to assess the efficacy of moviprep for bowel cleansing prior to colonoscopy [redacted].

Both studies were designed as a randomized, active-controlled, single-blind, multi-centre, pivotal phase III trials with two parallel treatment groups, moviprep (NRL994) versus golytely (PEG+E) for Study NRL994-01/2001 with 362 patients enrolled and Nap for Study NRL994-02/2001 with 352 patients enrolled. The primary objective of the study was to demonstrate that the new, low-volume oral gut cleansing solution, NRL994, was no less effective (non-inferior) than the comparators, golytely and Nap, with regard to the overall quality of bowel preparation in hospital in-patients scheduled to receive complete colonoscopy. The applicant proposed that non-inferiority of NRL994 was to be concluded if the rate of successful bowel preparation (overall quality of gut cleansing grade A or B) was not inferior to that of the comparators by more than 15%. The primary efficacy endpoint was the percentage of patients who achieved successful bowel preparation.

1.3 Statistical Issues and Findings

Since the justification for the non-inferiority margin of 15% submitted by the applicant is for both active control arms (golytely and Nap) employed by the two studies (NRL994-01/2001 & NRL994-02/2001), the following comments made by this reviewer on the non-inferiority margin are also for both studies:

- First, instead of following the recommendation of ICH E10 on the margin selections and using the historical studies conducted under the conditions similar to that of the current

trials to identify the smallest sizes of the active control arms (golytely for study NRL994-01/2001 and Nap for study NRL994-02/2001), the 14 references cited by the applicant only provide the efficacy rates (proportion of "excellent" or good") of the two active controlled treatments, golytely & Nap in bowel preparation. No efficacy rates of placebo arm were provided. Then, for each of the 14 studies reported by the 14 articles cited by the applicant, the applicant performs the non-inferiority analysis using the selected margin of 15% to compare the efficacy between golytely and Nap. Based upon the non-inferiority analysis results of 8 studies showed NaP (if used as test) not inferior to golytely (if used as reference) and 8 studies showed golytely (if used as test drug) not inferior to Nap (if used as reference), the applicant concludes that a non-inferior margin as large as 15% used in the present studies is an appropriate and rather restrictive margin for both comparators. Thus, based upon the margin justification provided by the applicant, the non-inferiority margin of 15% for both active controlled treatments (golytely and Nap) was not identified by comparing the effectiveness of the two controlled treatments to that of placebo, as recommended by ICH E10.

In addition, the medical reviewer, Eric Brodsky MD, indicates the assessment criteria for the quality of the gut cleansing employed by the 10 articles submitted by the applicant are different from that used by the two phase III trials (Studies NRL 994-01/2001 & NRL 994-02/2001). In other words, the two phase III trials were not conducted under the conditions similar to that of the historical studies used to support the non-inferiority margin of 15%, as recommended by ICH E10. Consequently, the justification provided by the applicant for the non-inferiority margin of 15% is not statistically persuasive.

- Second, as indicated by the medical reviewer, for Study NRL 994-01/2001, the overall quality of gut cleansing was classified twice (Up and Down) and the poorer of the two assessments was included in the efficacy analysis. In addition, in each assessment, the independent review panel results were the basis for the assessment of the primary endpoint of gut cleansing. In case discrepancy on the rating of gut cleansing occurred, the final rating for the overall gut cleansing was obtained after agreement among the reviewers and investigator was achieved. However, for Study NRL 994-02/2001, only one assessment was performed for the overall gut cleansing quality and the third tape reviewer from the expert panel determined the final grading when discrepancy in terms of preparation success or failure between investigator and videotape reviewer occurred.

  Consequently, the two different assessment procedures on the quality of gut cleansing for the two studies may generate different clinical outcomes. Therefore, it is not statistically sound to use the same non-inferiority margin (15%) for the two studies using two different gut cleansing assessment procedures.
- Third, it is noted that for golytely in Study NRL 994-01/2001, the mode of intake was "split dose" - one dose in the evening before the procedure and one in the morning on the day of the endoscopy procedure- while for Nap in Study NRL 994-02/2001, the mode of intake was "single dose" administered in the evening the day before endoscopy procedure. The medical reviewer indicates that the mode of dose intake (for example, "single dose" versus "split dose") affects the quality of gut cleansing. Yet, more critically, this assertion is also emphasized by the applicant in the response to the justification of margin selection: the rate of effective colon cleansing is dependent on the

mode of intake. Accordingly, the use of same non-inferiority margin of 15% for both active control drugs (golytely versus Nap) is not adequate.

- Finally, strictly speaking, it is implausible that the effectiveness of different drugs (e.g., golytely and Nap) assessed by the same endpoint (gut cleansing) would be similar. Accordingly, it is not statistically convincing to employ the same non-inferiority margin of 15% for both of the active controlled drugs, golytely and Nap.

In conclusion, based upon the above four remarks, the non-inferiority margin of 15% selected by the applicant for the two studies is not supported by the applicant's margin justification and is not acceptable.

Since the two issues "nature of single blinded design" and "defect of non-inferiority analysis criterion" for study 994-01/2001 are congruent to that of study 994-02/2001, the following comments for these two issues are for both studies:

- *Single blinded design*: Although investigators were blinded as to the methods of preparation, since patients knew which drugs were used for their bowel preparations, it would be easy for the investigators to recognize the bowel preparation drug used by patients. Therefore, in reality, the single blinded trial had high potential to be an open label trial for the expert panel. Furthermore, noted by this reviewer, the definitions of "grade C" and "grade B" in bowel cleansing quality are not clear cut and may be assessed subjectively. Accordingly, as long as the members in the expert panel apprehended which drug was used by the patient, the assessment on the successful bowel preparation (scored as "grade A" or "grade B") was likely to be biased in favor of study drug moviprep.
  Due to different appearances shown by the two treatments, moviprep and golytely, it may be difficult for the applicant to conduct a double blinded trial. However, the concerns on the issues of biased efficacy comparisons induced by such trials can not be ignored and the biased conditions induced by the nature of single blinded trial may have been improved if another lower dose arm of moviprep had been included in this trial.
- *Non-inferiority analysis criterion:* One notes that if the outcomes of the bowel preparations for the two treatment groups, moviprep and golytely, are assessed as similar/comparable as possible then the non-inferiority will be claimed for the two drugs. In addition, due to ambiguous definition on the scores "grade B" and "grade C" of the bowel cleansing quality, the bowel preparation quality might not be assessed objectively. Therefore, with only two arms, study drug and comparator, in the trial, it was very likely for the expert panel to assign similar scores to the bowel preparations for the two treatment groups. As long as the expert panel assessed the outcomes of the bowel preparations for the two treatment groups as close as possible, the chance of concluding non-inferiority for the two drugs is greatly increased. However, the non-inferiority of the two treatment groups established by the above assessments may be a biased result. To avert the bias, CFR section 314.126 on adequate and well-controlled studies recommends including additional treatment groups such as dose-comparison control. Thus, as commented by this reviewer above, in order to prevent the potentially biased assessments, the applicant should have included another lower dose arm of moviprep in the trial.

For Study NRL994-01/2001, analysis of the primary endpoint by center indicates that no center was found in the moviprep group to have an abnormally large proportion of patients judged success in gut cleansing. Thus, no center dominates the non-inferiority of moviprep to golytely.

Similarly, for Study NRL 994-02/2001, no center was found in the moviprep group to have abnormally large proportion of patients judged success in gut cleansing or to dominate the non-inferiority of moviprep to Nap.

Finally, for Study NRL994-01/2001, the efficacy analysis on moviprep shows that lower bounds of the two-sided 95% confidence interval on the success rate of bowel cleansing quality are 0.83 and 0.82 respectively for Per-Protocol and ITT patient populations. For Study NRL994-02/2001, the two-sided 95% lower bounds for moviprep are 0.65 and 0.64, respectively for Per-Protocol and ITT patient populations. Since the assessments on the bowel preparations were potentially biased in favor of the test drug moviprep, the lower bound of the 95% two-sided interval for moviprep calculated using the data from more reliable population is expected to be smaller than 0.64. However, using the results of the lower bounds as a reference, if the medical division deems that this success rate of moviprep is higher than that of placebo, then, moviprep can be considered as effective.

2.0 INTRODUCTION

2.1 Overview

With regards to Moviprep, the applicant made the following observations in the study report:

> Polyethylene glycol (PEG) products (including Golytely® and Nulytely®) have been used world-wide for many years for colon cleansing prior to colonoscopy. There effectiveness, safety and tolerability have been established in numerous controlled clinical trials and have been successfully used during daily clinical practice.
>
> However, currently available PEG preparations have the disadvantage of being administered in large quantities, and many patients experience difficulties in ingesting the large volumes of up to 4 liters. Norgine has therefore investigated how to reduce the total volume of the bowel preparation regimen, without modifying the established efficacy and safety profile of PEG based solutions. The search for an atoxic and osmotically active agent that could be used in order to reduce the total amount of fluid ingested identified vitamin C (either ascorbic acid and/or sodium ascorbic) as a potential candidate administered in large doses. This is at least in part due to its limited systematic absorption. The existence of a sodium-dependent and saturable carrier mechanism in small bowel mucosa was shown to lead to an inverse relationship between ingested arid absorbed doses. In order to assess the efficacy (and tolerability) of high doses of vitamin C as part of a bowel cleansing regimen based on PEG, Norgine initiated the current investigational program.

The applicant conducted two randomized, single-blind, active-controlled studies (NRL994-01/2001 and NRL994-02/2001) to assess the efficacy of moviprep for bowel cleansing prior to colonoscopy [redacted].

Both studies were designed as a randomized, active-controlled, single-blind, multi-center, pivotal

phase III trials with two parallel treatment groups, moviprep (NRL994) versus golytely (PEG+E) for Study NRL994-01/2001 and Nap for Study NRL994-02/2001. The primary objective of the study was to demonstrate that the new, low-volume oral gut cleansing solution, NRL994, was no less effective (non-inferiority) than the comparators, golytely and Nap, with regard to the overall quality of bowel preparation in hospital in-patients scheduled to receive complete colonoscopy. The applicant proposed that non-inferiority of NRL994 was to be concluded if the rate of successful bowel preparation (overall quality of gut cleansing grade A or B) was not inferior to that of the comparators by more than 15%. The primary efficacy endpoint was the percentage of patients who achieved successful bowel preparation.

2.2 Data Sources

Documents reviewed include NDA volumes 1 to 89 for Module 5 submitted by the applicant on June 14, 2005. The data used in this reviewer's analysis was submitted by the applicant on August 26, 2005. Later, on November 8, 2005, in the response to this reviewer's information request on the justifications for the selection of non-inferiority margin of 15%, the applicant indicated that they discovered a coding error in the integrated database related to the secondary efficacy variables for Study 02/2001. The applicant re-submitted review copies of the modified sections for chemistry, pharmacology, clinical, and statistical reviewer. In the meantime, the applicant emphasized that although the correction introduced small changes to the numbers, the corrected analysis introduced no change in the original conclusions for either the study (Module 5) or Section 2.7.3 Summary of Clinical Efficacy (Module 2).

3.0 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study NRL994-01/2001 (from June 19, 2002 to December 13, 2002)

Study Design and Endpoints

The study was designed as a randomized, active-controlled, single-blind, multi-centre, pivotal phase III trial with two parallel treatment groups, moviprep (NRL994) versus standard regimen golytely (PEG+E). The primary objective of the study was to demonstrate that the new, low-volume oral gut cleansing solution, NRL994, was no less effective (non-inferiority) than the current standard high volume regimen (PEG+E), with regard to the overall quality of bowel preparation in hospital in-patients scheduled to receive complete colonoscopy. Non-inferiority of NRL994 was to be concluded if the rate of successful bowel preparation (overall quality of gut cleansing grade A or B) was not inferior to that of the comparator by more than 15%.
The study was to last a maximum of 3 days in each given individual. For one or two days prior to their endoscopic intervention (Day-2 or Day-1), eligible patients were asked by the investigator to participate in the trial and were to be randomized to receive moviprep or golytely in 1:1 ratio. Patients enrolled in the study were asked to fill in a questionnaire concerning the acceptability of the preparation. A patient's participation in the study was terminated upon completion of the

intervention by performing a final examination and filling in the study termination page. No interim analysis was to be performed.

Based on the sample size calculation, it was intended to recruit up to 360 in-patients in order to obtain 300 efficacy-evaluable patients. All patients had to be scheduled to undergo complete colonoscopy at up to 15 hospital centers with specialized gastroenterology departments. For the assignment of patients to test or reference treatment during the single-blind treatment period, Dr. _____ had prepared a randomization list with a block size of 4 and passed it on to the Technical Services of Norgine Ltd (Hengoed, UK), responsible for packaging of the investigational drugs. Each patient received one pack of clinical trial material in a shaker containing either 4 sachets moviprep or 4 sachets golytely.

Bowel preparation was performed using equal split doses of either low-volume moviprep (two doses of 1,000 mL each) or high- volume golytely (two doses of 2,000 mL each). The first dose was to be taken in the evening before the procedure, the second dose on the morning of the day of the colonoscopy (i,e., moviprep regimen: 1 L of moviprep solution and 0.5 L water in AM and PM versus golytely regimen: 2 L of golytely solution in AM and PM). The patients allocated to moviprep were asked to drink at least 1L of additional clear liquid in addition to the study drug. In addition, patients were asked to record details of intake of the bowel cleansing solution assigned (eg. timing and volumes of solution and additional fluids taken), to rate the taste of the solution and their satisfaction with the cleansing regimen, and to report any problems with drinking the entire volume. Furthermore the occurrence of pre-defined symptoms and the global tolerability of the solution used were to be reported.

An overview of the investigations carried out and their measurement times are given in the flow chart shown below (Figure 3.1.1.1).

Figure 3.1.1.1 (Applicant's) Flow chart for schedule of assessments

Schedule of assessments	Day –2	Day –1	Day 0	
		before start of bowel preparation	upon completion of bowel prepration	upon completion of colonoscopy
informed consent	X	(X) [1]		
Demographic data	X	(X) [1]		
Check of inclusion / exclusion criteria	X	(X) [1]		
medical history / concomitant medication	X	(X) [1]		
medical examination	X	(X) [1]		
Vital signs, body weight	X	(X) [1]	X	X [3]
Blood sampling (safety lab.)	X	(X) [1]	X [4]	
instructions for use / diary card		hand-out	return	
Standard diet		X	X	
Administration of test or reference solution [2]		X	X	
Registration of procedural details			X	
Degree of gut cleansing (investigator rating)				X
Recording of AEs		⟷	⟷	
End of study participation				X

1: alternative schedule in case the patient was enrolled on the day prior to colonoscopy;
2: first dose in the evening of Day-1 (up to 22:00), second dose in the morning of day0 (from 05:00 onwards)
3: vital signs were to be assessed prior lo and after the colonoscopy, a second measurement of the body weight was to be performed exclusively in case of premature withdrawal (e.g. because of an (S)AE)
4: blood sampling for determination of safety laboratory parameters was to be performed either directly before or within 2 hours after colonoscopy.

The applicant emphasized that due to the fact that the volumes of moviprep and golytely were different, a double-blind design was not possible. Therefore, the investigator responsible for enrolling the patient, handing out the study medication, and dealing with the patient until conduct of the endoscopic procedure remained un-blinded.

No other investigational drugs or drugs known to have a gut cleansing effect (golytely, golytely RSS, laxatives, enemas) were allowed during the entire duration of the study. Patients with regular intake of weak laxatives were not excluded from participation in the trial, but were registered and required to stop intake on the day before colonoscopy.

Colonoscopy was to be performed by an experienced physician and details of the procedure were to be recorded in the CRF. The quality of bowel preparation was to be rated in each of five pre-defined segments (rectum, sigmoid, descending, transverse, and ascending colon), on the basis of a 5-level verbal rating scale (VRS) ranging from 4 (very good) to 0 (very bad). Additionally, each colonoscopy was to be recorded on video tapes in order to allow analysis of overall quality of colon cleansing by the blinded and independent expert panel.

The 5-level VRS 0-4 score scale for each of the five pre-defined segments was defined as follows:
- score 4 (very good): colon empty and clean;

- score 3 (good): presence of clear liquid in the gut;
- score 2 (moderate): brown liquid or semisolid remaining small amounts of stool which can be easily removed or displaced;
- score 1 (bad): semisolid amounts of stool, only partially removable with a risk of incomplete underlying mucosa visualization; and
- score 0 (very bad): semisolid or solid amounts of stool, consequently colonoscopy incomplete or needs to be terminated for predefined areas of the gut (rectum, sigmoid colon, descending colon, transverse colon, ascending colon).

Based on the assessment of the cleansing result (from scores 0 to 4) in each of the five predefined gut segments (for details of the scale used, see below), the overall quality assessment of gut cleansing was classified on a 4-fevel VRS grade (A to D) as follows:

grade A: all colon segments clean, i.e. cleansing result 4 (very good) or 3 (good) in all segments;
grade B: at least one colon segment with residual amounts of brown liquid or semisolid stool which can be easily removed or displaced, i.e. cleansing result 2 (moderate) in at least one segment;
grade C: at least one colon segment with only partially removable stool preventing complete visualization of mucosa, i.e. cleansing result 1 (bad) in at least one segment;
grade D: at least one colon segment which cannot be examined due to the presence of remaining solid stool, i.e. cleansing result 0 (very bad) in at least one segment.

The primary efficacy endpoint was the percentage of patients who achieved effective colonoscopy cleansing. Responders were patients who achieved an "Overall Quality Scale" score of A or B. The efficacy was judged by the consensus of a 3-member gastroenterologist blinded expert panel on the basis of videotapes. Experts assessed efficacy during the introduction of the colonoscope and during the withdrawal of the colonoscope. The poorer of the two assessments was the primary assessment.

The secondary endpoints included the following measurements:

- Classification of the overall quality of gut cleansing - on a 4-level VRS with ranks A, B, C, and D as mentioned for the primary response variable, based on the assessment of the physician performing the endoscopic procedure;
- Mean degree of gut cleansing by averaging all segmental scores in each of the two treatment groups, based on the assessments of the physician performing the endoscopic procedure and by those of a blinded and independent expert panel on the basis of videotapes recorded during colonoscopy (once during introduction of the endoscope and a second time during its withdrawal);
- Global quality of colonic cleansing as assessed on a VAS ranging from 0 (dirty) to 100 mm (perfectly clean) by the physician performing the endoscopic procedure and by a blinded and independent expert panel on the basis of videotapes recorded during colonoscopy, etc.

Finally, the exploratory measurements were as follows:

- Amount of additional clear fluid ingested;

- Time to first bowel movement after start of intake;
- Endpoint of colonoscopy;
- Reason(s) why colonoscopy was performed;
- Injected water, i.e. the amount of fluid placed into the colon during the procedure;
- Residual liquids removed, i.e. amount of fluid aspirated from the intestinal lumen during colonoscopy.

Statistical Methodologies

Based upon the primary objective of this study to demonstrate the gut cleansing effect of moviprep (NRL 994) as no worse than that of the standard regimen golytely (PEG+E) assessed by the primary endpoint, the following two hypotheses (null and alternative) were used by the applicant to address the non-inferiority of moviprep to golytely.

The null hypothesis of clinical inferiority (H_0) in this trial was that the difference between the two treatment groups (movipre - golytely) in terms of the frequency rate of effective gut cleansing is less than or equal to -15 %, i.e., H_0: $\pi_m - \pi_g \leq -15\%$.

The alternative hypothesis of clinical non-inferiority (H_1) in this trial was that the difference between the two treatment groups (movipre – golytely) in terms of the frequency rate of effective gut cleansing is greater than -15 %, i.e., H_1: $\pi_m - \pi_g > -15\%$.

A one-sided 97.5% confidence interval was to be calculated for the treatment difference, resulting in a type I error rate of α=0.025. Non-inferiority of moviprep over golytely (standard regimen) was to be concluded if the lower limit of the one-sided 97.5% confidence interval of the difference in the success rates between the two treatment groups was greater than -15%.

After successful demonstration of non-inferiority, testing for superiority was to be performed. If the lower limit of the one-sided confidence interval of the treatment difference was above zero, then this was to be interpreted as evidence of superiority of moviprep over golytely.

The applicant indicated that the per-protocol (PP) population was considered to be the primary population for the confirmatory analysis. This dataset included all patients who had satisfied all inclusion and none of the exclusion criteria and in whom no major protocol violations occurred during the study period. The intent-to-treat (ITT) population was only analyzed to provide additional evidence. The ITT population comprised the data of all randomized patients who had received at least any amount of the investigational drugs.

The applicant also indicated that missing data occurred at a low frequency. In 16 patients of the moviprep group (8.9%) and 14 patients of the standard regimen group (7.8%), the primary response variable could not be assessed by the blinded expert panel because the respective videotapes had not been recorded. However, the applicant did not specify the method to impute the missing data or how to deal with the missing data.

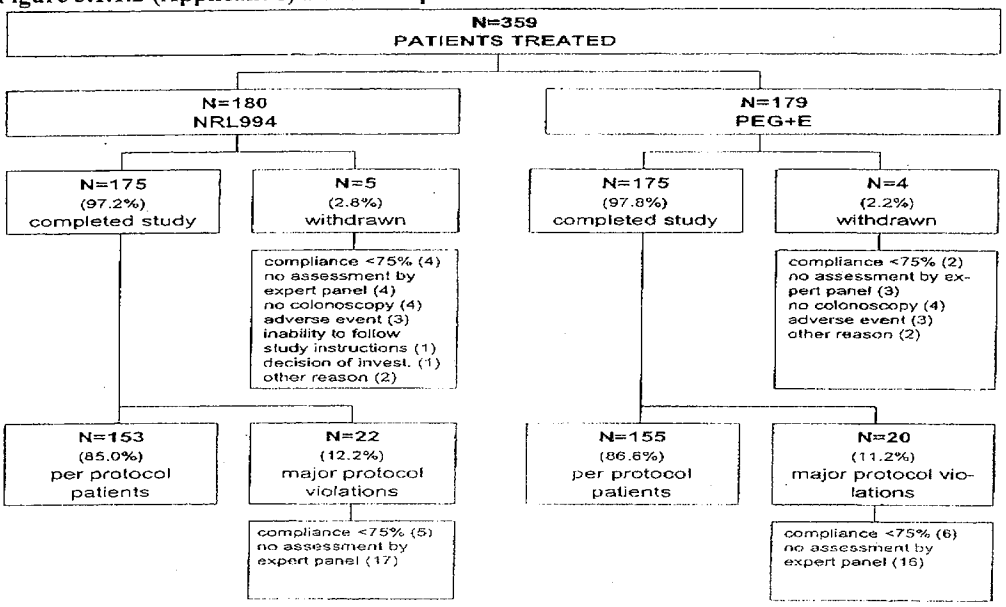
Patient Disposition

This phase III study was carried out from June 19, 2002 (inclusion of first patient) to December 13, 2002 (last visit of last patient). During this period, a total of 362 patients were included in the investigation. Between 8 and 44 patients were recruited in each of the 12 active centers participating.

A total of two patients discontinued the study prior to randomization and without documentation of the reasons for withdrawal. One patient withdrew after random allocation to the standard group, but before treatment started because of a pre-existing allergy to vanilla, the flavor used in the standard regimen formulation. The remaining 359 patients (moviprep: 180 patients; standard: 179 patients) received at least any amount of the investigational products and were therefore part of the safety and intention-to-treat (ITT) populations. Nine patients (5 in the moviprep group and 4 in the standard group) were prematurely withdrawn from the study; in three patients of each treatment group the primary reason was the occurrence of an adverse event. In all but one patient, withdrawal occurred before the colonoscopic procedure. Therefore, no gut cleansing results were available in these patients. The remaining 350 patients (175 patients in each moviprep and standard groups) completed colonoscopy and all visits scheduled in the trial protocol.

Protocol violations were classified to be negligible (minor violation) or relevant (major violation), with only the latter leading to the exclusion of a patient from the per-protocol (PP) population. In 42 patients (moviprep: 22 patients;standard: 20 patients) a major protocol violation had occurred that led to the exclusion from the PP population. In both groups, the most frequently reported reason was the lack of an assessment of the gut cleansing effect by the blinded expert panel, mainly because the video tapes had not been recorded during the procedure either because of an investigator's error or because of technical problems (16 and 14 mentions in moviprep and standard groups, respectively). One patient of the standard group was not assessed because endpoint of the colonoscopy was the stenotic sigmoid. In 5 patients of the moviprep group and 6 patients of the standard group, the compliance has been less than 75%. Thus, the PP analysis data set consisted of 308 patients: 153 in the moviprep group and 155 in the standard group. The disposition of patients is given by Figure 3.1.1.2.

Figure 3.1.1.2 (Applicant's) Patient disposition



Note 1: reason for withdrawal or exclusion from the per protocol population: please note that more than one reason may have been reported in a given patient.

Note2: NRL994 refers to moviprep and PEG+E refers to standard regimen golytely.

Demographics and Baseline Characteristics

The mean age and weight of the patient recruited in the PP population were 58.8± 15.4 years and 75.1 ± 16.4 kg with no relevant between-group differences. In both treatment groups, more than 50% of the patients were aged 60 years or more (moviprep: 52.9%; standard; 60.7%). The moviprep group was well balanced with regard to gender (male to female ratio 1.07). In the standard group, there were slightly more females than males (male to female ratio 0.85); this was particularly pronounced in the age group of > 75 years (male to female ratio 0.42). More than 40% of female patients in both groups were postmenopausal. The applicant indicated that overall, both treatments were well balanced. Table 3.1.1.1 presented demography of patients included in the per-protocol population.

Table 3.1.1.1 (Applicant's) Demography of patients included in the per-protocol population

	NRL994	PEG+E	All Patients
Number	153 (49.7%)	155 (50.3%)	308 (100%)
Male	79 (51.6%)	71 (45.8%)	150 (48.7%)
Female	74 (48.4%)	84 (54.2%)	158 (51.3%)
Age (years):	58.0 ± 14.7 (18 – 83)	59.6 ± 16.0 (19 – 88)	58.8 ± 15.4 (18 – 88)
Age class			
18 ≤ age < 30	5 (3.3%)	8 (5.2%)	13 (4.2%)
30 ≤ age < 45	23 (15.0%)	23 (14.8%)	46 (14.9%)
45 ≤ age < 60	44 (28.8%)	30 (19.4%)	74 (24.0%)
60 ≤ age < 75	58 (37.9%)	66 (42.6%)	124 (40.3%)
75 ≤ age < 85	23 (15.0%)	26 (16.8%)	49 (15.9%)
85 ≤ age	0 (0.0%)	2 (1.3%)	2 (0.6%)
Weight (kg):	75.8 ± 16.3	74.4 ± 16.6	75.1 ± 16.4

Note: Figures represent number of observations (in brackets %) or mean ± SD (in brackets age range for age)

Most patients underwent a brief medical examination, focusing mainly on gastrointestinal disorders where abnormal findings were reported in 23.5% and 20.6% of the patients in the moviprep and standard groups, respectively. With the exception of skin and subcutaneous tissue disorders (i.e. scars), abnormal findings were reported in less than 10% of patients for all other system organ classes. Table 3.1.1.2 presented the medical history of patients included in the per-protocol population (limited to those with incidence of ≥ 3% in the total population).

Table 3.1.1.2 (Applicant's) Medical history of patients included in the per-protocol population

	NRL994	PEG+E	All Patients
Number	153 (49.7%)	155 (50.3%)	308 (100%)
Surgical and medical procedures	57 (37.3%)	67 (43.3%)	124 (40.3%)
Gastrointestinal disorders	48 (31.4%)	45 (29.0%)	93 (30.2%)
Infections and infestations	16 (10.5%)	20 (12.9%)	36 (11.7%)
Neoplasms benign, malignant and unspecified	13 (8.5%	14 (9.0%)	27 (8.8%)
Musculoskeletal and connective tissue disorders	9 (5.9%)	8 (5.2%)	17 (5.5%)
Injury, poisoning and procedural complications	3 (2.0%)	11 (7.1%)	14 (4.5%)
Metabolism and nutrition disorders	8 (5.2%)	6 (3.9%)	14 (4.5%)
Investigations	10 (6.5%)	2 (1.3%)	12 (3.9%)
Vascular disorders	7 (4.6%)	5 (3.2%)	12 (3.9%)
Nervous system disorders	5 (3.3%)	6 (3.9%)	11 (3.6%)
Renal and urinary disorders	7 (4.6%)	4 (2.6%)	11 (3.6%)

Note: Figures represent number of observations (in brackets %).

Applicant's Efficacy Analysis Results and Conclusions

Primary endpoint analysis

The primary efficacy endpoint was the frequency of effective gut cleansing (grade A or B overall quality of gut cleansing) in each of the two treatment groups. The success rate of effective gut cleansing was 88.9% (136 of 153 patients) in the moviprep (NRL 994) group compared with 94.8% (147 of 155 patients) in the golytely (PEG+E) group. This resulted in a rate difference between moviprep and golytely of -5.9%, with a lower limit of the one-sided 97.5% confidence interval of -12.0%. As this value did not smaller than the pre-specified non-inferiority margin of -15%, the applicant concluded that the success rate of effective gut cleansing for moviprep was not inferior to that of golytely (PEG+E) by more than 15% at one-sided α-level of 0.025. Table 3.1.1.3 presented the frequency rate of effective gut cleansing using PP population.

Table 3.1.1.3 (Applicant's) Frequency rate of effective gut cleansing using PP population

	NRL994 (n = 153)	PEG+E (n = 155)	Rate difference
Treatment success »overall quality of gut cleansing«			
Grade A[†]	22 (14.4%)	18 (11.6%)	+2.6%
Grade B[†]	114 (74.5%)	129 (83.2%)	-8.7%
Treatment failure »overall quality of gut cleansing«			
Grade C[†]	15 (9.8%)	7 (4.5%)	+5.3%
Grade D[†]	2 (1.3%)	1 (0.6%)	+0.7%
Success rate grade A + grade B	136 (88.9%)	147 (94.8%)	-5.9% 97.5% CI [-12.0; ∞]

[†] grade A: all colon segments clean (segmental cleansing result 4 or 3); grade B: at least one colon segment with residual amounts of brown liquid or semisolid stool which can be easily removed or displaced (segmental cleansing result 2 in at least one segment); grade C: at least one colon segment with only partially removable stool preventing complete visualization of mucosa (segmental cleansing result 1 in at least one segment); grade D: at least one colon segment (which cannot be examined due to the presence of remaining solid stool (segmental cleansing result 0 in at least one segment).

For the issue of the treatment-by-center interaction, the applicant indicated that the consistency of the treatment effect across centers was qualitatively and quantitatively assessed. In four centers a 100% success rate was achieved in patients of both groups (centers 3, 5, 6, and 11). In four further centers, the success rate was the same at center 2 or in favor of moviprep at centers 7, 9 and 10. In the four remaining centers (1, 4, 12, and 13) the success rate was in favor of golytely and the associated lower limit of the 97.5% one-sided confidence interval less than the pre-specified non-inferiority limit of -15%, being suggestive of inferiority of moviprep over golytely (the standard regimen). Finally, the applicant emphasized that the treatment-by-center interaction was not statistically significant (p=0.189).

For the primary endpoint analysis using the ITT data set, blinded expert panel ratings were preferentially used for the assessment of the frequency rate of effective gut cleansing. If this rating was not available, the colonoscopist rating was used instead. If neither of the two was available, the patient was handled as a treatment failure. Compared with the PP analysis, the success rates of ITT population were slightly lower and calculated to be 86.7% in the moviprep group and 90.5% in the golytely group, resulting in a smaller difference of -3.8%. Since the lower limit of the one-sided 97.5% CI of -10.4% was not less than the pre-specified margin of -15%, the applicant claimed that this analysis supported the conclusion drawn from the PP dataset.

Secondary endpoint analysis

For the secondary efficacy endpoint analysis, the applicant indicated that compared with the blinded expert panel, several secondary efficacy parameters including mean score of all segmental scores, overall use of the gut lavage solution, global quality of colon cleansing were rated more favorably by the colonoscopist. However, no relevant between-group differences were observed in any of these variables, independent of whether they were assessed by the expert panel or the colonoscopist. The overall ease (convenience) to perform the colonoscopy

was also not influenced by the solution used for gut cleansing. Patients consistently preferred moviprep over golytely. All three patient-based parameters (degree of satisfaction, overall acceptability, and global taste evaluation) were significantly in favor of moviprep. In addition, patients in the moviprep group also had fewer problems in drinking the entire volume of the gut cleansing solution and more easily accepted the associated diet compared with their counterparts receiving golytely.

Reviewer's Comments and Analysis

In order to validate the sponsor's efficacy claim, this reviewer first comments on the following two issues: 1) equivalence margin of 15% and 2) assessments of colon cleansing quality. Then, this reviewer performs the following two analyses: 1) primary efficacy analysis by center and 2) efficacy analysis on moviprep.

Reviewer's Comments

1) Issue on the non-inferiority margin

Noted by this reviewer, the applicant specified the non-inferiority margin of 15% for both of the two Studies (RNL 994-01/2001 & RNL 994-02/2001) in the protocols. However, the applicant did not submit the protocols for the agency to review before conducting the two studies. After completing the two studies and the final efficacy analyses, the applicant notified the agency of the existence of the studies and the specified margin in a pre-NDA meeting package (June 28, 2004). In order to comprehend the logic used for the selection of the non-inferiority margin of 15%, this reviewer issued an information letter, dated August 9, 2205, to request the applicant provide the justification for the selection of non-inferiority margin of 15%. The applicant's response (November 8, 2005) to this reviewer's information request with regard to the justification on the selection of non-inferiority margin of 15% is summarized below.

Applicant's response

The applicant indicates that PEG+E (golytely) solutions have been used worldwide for many years for bowel cleansing prior to colonoscopy or colonic surgery. Their effectiveness, safety, and tolerability have been established in numerous controlled clinical trials. Alternative low volume solutions such as Sodium Phosphate (Nap) can induce potentially harmful dehydration as well as biologic changes in certain populations. However, review of literature studies comparing golytely solutions versus Nap solution showed nearly similar efficacy in quality of gut cleansing.

To support the rates of "excellent" or "good" results in gut cleansing in a medium range of 70% of patients for both golytely and Nap, the applicant refers to 14 articles. Table 3.1.1.4 presents the rates of "excellent" or "good" results in gut cleansing reported by the applicant extracted from the 14 articles. The references for these 14 articles are listed in the Appendix A. However, of the 14 referenced articles, only 10 articles (identified by the medical reviewer) were submitted to the agency by the applicant through the NDA submission.

Table 3.1.1.4 (Applicant's) Review of the literature: PEG+E (Golytely) versus Nap solution

	N	Mode of intake	Efficacy Rate	Patient Status	Literature
NaP	118	unknown	55%	Inpatients	Ref. 1
PEG+E	114		58%		
NaP	134	unknown	72%	Outpatients	Ref. 2
PEG+E	126		67%		
NaP	29	unknown	83%	Outpatients	Ref. 3
PEG+E	29		93%		
NaP	93	AM/PM D-1	55%	In+outpatients	Ref. 4
PEG+E	90	4l PM D-1	80%		
NaP	70	AM/PM D-1	86%	In+outpatients	Ref. 5
PEG+E	73	4l PM D-1	91%		
NaP	143	PMD-1 /AM D0	90%	Outpatients	Ref. 6
PEG+E	138	4l PM D-1	68%		
NaP	54	PMD-1 /AM D0	80%	Outpatients	Ref. 7
PEG+E	38	4l PM D-1	66%		
NaP	49	AM/PM D-1	82%	Outpatients	Ref. 8
PEG+E	49	4l PM D-1	82%		
NaP	101	AM/PM D-1	68%	Outpatients	Ref. 9
PEG+E	100	3.8l PM D-1	60%		
NaP	106	AM/PM D-1	89%	Outpatients	Ref. 10
PEG+E	124	4l PM D-1	89%		
NaP	71	AM/PM D-1 or PMD-1 /AM	70%	Unknown	Ref. 11
PEG+E	88	4l PM D-1 or 2l PM D-1, 2 l AM D0	74%		
NaP	54	AM/PM D-1	80%	Inpatients	Ref. 12
PEG+E	48	4l PM D-1	83%		
NaP-I	161	AM/PM D-1	94%	Unknown	Ref. 13
NaP-II	166	PM D-1 /AM D0	82%		
PEG+E	160	4l PM D-1	93%		
NaP (1+2)	106	AM/PM D-1	86%	Unknown	Ref. 14
PEG+E	100	4l PM D-1	82%		

AM: morning; PM: evening; D-1: day before procedure; D0: day of procedure.

In order to address the variations of the efficacy rates for the two gut cleansing solutions (Nap and golytely) across studies reported by literatures, the applicant indicates that the rate of effective colon cleansing is dependent on the mode of intake i.e. "single dose" (complete consumption of dose on the day before the colonoscopy) versus "split dose" (consumption of one half the dose the day before the colonoscopy and the second half the morning of the procedure). Then, the applicant emphasizes that the mode of drug intake influencing the quality of gut cleansing is further supported by Norgine's historical data of three randomized clinical trials developed to evaluate two PEG+E solutions based upon golytely and nulytely formations.

In conclusion, based upon Table 3.1.1.4, without comparing to placebo effect, the applicant claims that effectiveness of PEG+E solutions and Sodium Phosphate (Nap) solutions are well established; comparison of PEG+E gut cleansing solutions (gold standard) with Sodium Phosphate (Nap) solutions showed a high relevant effect in bowel preparation prior to colonoscopy.

As for the justification of the non-inferiority margin, the applicant indicates that effectiveness of gut cleansing varies according to

- the patient's status (inpatients versus outpatients),
- the outcome measures used to define effective colon cleansing,
- the definition of the cut-off between acceptable and non-acceptable cleansing quality, and
- the mode of intake.

Then, differences of response rates between golytely and Nap along with their two-sided 95% confidence limits have been calculated for each of the studies referenced in Table 3.1.1.4. The results are presented by Table 3.1.1.5.

Table 3.1.1.5 (Applicant's) Response rate differences for Nap versus PEG+E and the associated 95% % confidence bounds

Reference	NaP		PEG+E		Difference and 95% confidence limits			Non-inferiority based on 15% level	
	N	Response rate	N	Response rate	NaP-PEG+E	lower	upper	NaP compared to PEG	PEG compared to NaP
1	118	0.55	114	0.55	0.00	-0.13	0.13	yes	yes
2	124	0.72	126	0.67	0.05	-0.06	0.17	yes	no
3	29	0.83	29	0.93	-0.10	-0.27	0.06	no	yes
4	93	0.55	90	0.80	-0.25	-0.38	-0.12	no	yes
5	70	0.86	73	0.91	-0.05	-0.15	0.06	no	yes
6	143	0.90	138	0.68	0.22	0.13	0.31	yes	No
7	34	0.80	38	0.64	0.16	0.04	0.27	yes	No
8	49	0.82	49	0.82	0.00	-0.15	0.15	no	No
9	101	0.68	100	0.60	0.08	-0.05	0.22	yes	no
10	106	0.89	124	0.89	0.00	-0.08	0.08	yes	yes
11	71	0.70	88	0.74	-0.03	-0.17	0.11	no	yes
12	54	0.80	48	0.83	-0.04	-0.19	0.11	no	yes
13	166	0.82	160	0.67	0.15	0.06	0.24	yes	no
14	106	0.86	100	0.82	0.04	-0.06	0.14	yes	yes

Based upon Table 3.1.1.5, the applicant indicates that using pre-specified non-inferiority margin of 15%, of the 14 studies, 8 studies showed NaP (if used as test) not inferior to PEG+E (if used as reference). Similarly, in 8 studies, drug PEG+E (if used as test drug) is not inferior to Nap (if used as reference). In addition, the confidence interval is contained between the range of -15% and +15% in only three of the 14 studies. Based upon the results of the 95% confidence intervals, the applicant declares that as both solutions have established similar efficacy, a non-inferior margin as large as 15% for the present studies is an appropriate and rather restrictive margin for both comparators.

Comments on the applicant's response

Since the justification for the non-inferiority margin of 15% submitted by the applicant is for both active control arms (golytely and Nap) employed by the two studies (NRL994-01/2001 & NRL994-02/2001), the following comments made by this reviewer on the non-inferiority margin are also for both studies.

First, ICH E10, "Guidance for Industry, E10 choice of Control Group and Related Issues in Clinical Trials", indicates that the non-inferiority trials are designed to show that the new drug is not less effective than the active control arm by more than a defined amount, generally called margin. This margin is the degree of inferiority of the test treatment to the control that the trial will attempt to exclude statistically. Theoretically, it is always possible to choose a non-inferiority margin leading to a conclusion of non-inferiority if it is chosen after the data have been inspected. Accordingly, the non-inferiority analysis along with its margin should be pre-specified at the protocol stage before conducting the study

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

As indicated by this reviewer in the beginning of the sub-section "Issue on the non-inferiority margin", the applicant specified the non-inferiority margin of 15% for both Studies NRL 994-01/2001 and NRL 994-02/2001 in the protocols. However, the applicant did not submit the protocols for the agency to review before conducting the two studies. After completing the two studies and the final efficacy analyses, the applicant notified the agency of the existence of the studies and the specified margin in a pre NDA meeting package (June 28, 2004). In order to avoid the conflict between the agency and the applicant on the selected margin, it is imperative that the applicant submit the protocol with the justification for the margin selection to the agency for review before conducting the trials. Based upon the justification for the selection of the non-inferiority margin of 15% provided by the applicant, inevitably, the comments are given below.

From the applicant's response to the justification for the non-inferiority margin of 15%, it is noted that the 14 references cited by the applicant only provide the efficacy rates (proportion of "excellent" or "good") of the two active controlled treatments, golytely and Nap; no efficacy rates of placebo arm were provided. Instead of following the principles recommended by ICH E10 to select the margin, basically, the applicant justifies the 15% margin for golytely by treating golytely as the test drug and Nap as the reference drug. Then, declare that golytely is not inferior to Nap if the upper bound of the two-sided 95% confidence interval of the success rate of Nap minus that of golytely is not larger than 15%. The same justification argument is used to justify the non-inferiority margin of 15% for Nap. Finally, based upon 8 studies separately showed NaP (if used as test) not inferior to PEG+E (if used as reference) and PEG+E (if used as test drug) not inferior to Nap (if used as reference), the applicant concludes that a non-inferior margin as large as 15% for the present studies is an appropriate and rather restrictive margin for both comparators. Thus, based upon the margin justification provided by the applicant, the non-inferiority margin of 15% for both active controlled treatments (golytely and Nap) was not identified by separately, comparing the effectiveness of the two controlled treatments to that of placebo, as recommended by ICH E10.

In addition, the medical reviewer, Eric Brodsky MD, indicates the assessment criteria for the quality of the gut cleansing employed by the 10 articles submitted by the applicant are different from that used by the two phase III trials (Studies NRL 994-01/2001 & NRL 994-02/2001). In other words, the two phase III trials were not conducted under the conditions similar to that of the historical studies used to support the non-inferiority margin of 15%, as recommended by ICH

E10. Consequently, the justification provided by the applicant for the non-inferiority margin of 15% is not statistically persuasive.

Secondly, as indicated by the medical reviewer, for Study NRL 994-01/2001 (German study), the overall quality of gut cleansing was classified twice (Up and Down) and the poorer of the two assessments was included in the efficacy analysis. In addition, in each assessment, the independent review panel results were the basis for the assessment of the primary endpoint of gut cleansing. In case of discrepancy on the rating of gut cleansing occurred, the final rating for the overall gut cleansing was obtained after the agreement among the reviewers and investigator achieved. However, for Study NRL 994-02/2001 (French study), only one assessment was performed for the overall gut cleansing quality and when discrepancy in terms of preparation success or failure between investigator and videotape reviewer occurred, the third tape reviewer from the expert panel determined the final grading.

The two different assessment procedures on the quality of gut cleansing for the two studies may generate different clinical outcomes. Therefore, it is not statistically sound to use the same non-inferiority margin (15%) for both studies.

Thirdly, it is noted that for golytely in Study NRL 994-01/2001, the mode of intake was "split dose" - one dose in the evening before the procedure and one in the morning on the day of endoscopy procedure while for Nap in Study NRL 994-02/2001, the mode of intake was "single dose" administered in the evening the day before endoscopy procedure. The medical reviewer indicates that the mode of dose intake (for example, "single dose" versus "split dose") affects the quality of gut cleansing. Yet, more critically, this assertion is also emphasized by the applicant in the response to the justification of margin selection: the rate of effective colon cleansing is dependent on the mode of intake. Accordingly, the use of same non-inferiority margin of 15% for both active control drugs (golytely versus Nap) is not adequate.

Noted by this reviewer, the success rate of gut cleansing for golytely shown by Study NRL 994-01/2001 is 0.95, while that of Nap shown by Study NRL 994-02/2001 is 0.64. The huge difference (0.31) on the success rates (48% of Nap, i.e., .31/.64) between golytely and Nap supports that the different assessment procedures on the quality of gut cleansing implemented by the two studies and the different modes of drug intake administered in the two studies have great impact on the overall quality of gut cleansing.

Finally, strictly speaking, the effectiveness of the two drugs assessed by certain endpoint is very implausible to be alike; so is the effectiveness of the two drugs (golytely and Nap) on the gut cleansing quality. Consequently, it is not statistically convincing to employ the same non-inferiority margin of 15% for both of the active controlled drugs, golytely and Nap.

In conclusion, based upon the above four remarks, the non-inferiority margin of 15% selected by the applicant for the two studies is not supported by the applicant's margin justification and is not acceptable.

2) Issue on the assessments of colon cleansing quality

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

i) Issue on the single blinded design

As indicated by the applicant, this trial was conducted by single blinded study in which investigators were blinded as to the methods of preparation. However, since patients knew which drugs were used for their bowel preparations, it would be easy for the investigators to recognize the bowel preparation drug used by patients. Therefore, in reality, the single blinded trial had high potential to be an open label trial for the expert panel. Furthermore, the definitions of "grade C" (at least one colon segment with only partially removable stool preventing complete visualization of mucosa) and "grade B" (at least one colon segment with residual amounts of brown liquid or semisolid stool which can be easily removed or displaced) in bowel cleansing quality are not clear cut and may be assessed subjectively. Accordingly, as long as the members in the expert panel comprehended which drug was used by the patient, the assessment on the successful bowel preparation was likely to be biased in favor of study drug moviprep.

In the section of Fairness of comparisons (1.4.3) in E10, it states that for the comparative trial to be informative concerning relative safety and/or efficacy, the trial needs to be fair; i.e., the conditions of the trial should not inappropriately favor one treatment over the other. In order to avoid the potential biased assessments, the sponsor should have included placebo arm or another arm with lower dose of moviprep in this trial. Then, in order for moviprep to be approved, the applicant should have also demonstrated that the success rate of bowel preparations for moviprep was superior to that of placebo or the arm with lower dose of moviprep.

In reality, due to different appearances shown by the two treatments, moviprep and golytely, it may be difficult for the sponsor to conduct a double blinded trial. However, the concerns on the issues induced by such trials can not be ignored and the biased conditions induced by the nature of single blinded trial may have been improved if another lower dose arm of moviprep had been included in this trial.

ii) Issue on the non-inferiority analysis criterion

Based on the efficacy non-inferiority analysis criteria, one notes that if the outcomes of the bowel preparations for the two treatment groups, moviprep and golytely, are assessed as similar/comparable as possible then non-inferiority for the two drugs will be claimed. As indicated in the above sub-section i), due to the ambiguous definition on the "grade B" and "grade C" of the bowel cleansing quality, the bowel preparation quality might not be assessed objectively. Therefore, with only two arms moviprep and golytely in the trial, it was very likely for the expert panel to assign similar scores to the bowel preparations for the two treatment groups. As long as the expert panel assessed the outcomes of the bowel preparations for the two

treatment groups as close as possible, the chance of the non-inferiority for the two drugs is greatly increased. However, the non-inferiority of the two treatment groups established by the above assessments is a biased result. To avert the bias, the section (§ 314.126) of adequate and well-controlled studies in code of federal regulations recommend including additional treatment groups such as dose-comparison control. Thus, as commented by this reviewer in the above sub-section, in order to prevent the potentially biased assessments, the applicant should have included another lower dose arm of moviprep in the trial.

Reviewer's Analysis

1.) Primary efficacy analysis by center

In order to explore whether the non-inferiority of moviprep (NRL994) to golytely (PEG+G) assessed by the primary endpoint (frequency with grade A or B in the overall quality assessment of gut cleansing) was dominated by certain center, this reviewer analyzes the differences in proportions on the primary endpoint by center to compare the efficacy between the two treatments using PP population. The centers used in this analysis are the centers defined by the applicant. Table 3.1.1.6 presents the result.

Table 3.1.1.6 (Reviewer's) Proportion of patient success in the overall gut cleansing assessed by the expert panel by center using PP population

CENTER	MOVIPREP SUCCESS RATE % (N)	GOLYTELY SUCCESS RATE % (N)
Center 1	74 (19)	100 (16)
Center 2	95 (21)	95 (21)
Center 3	100 (14)	100 (18)
Center 4	75 (20)	84 (19)
Center 5	100 (9)	100 (8)
Center 6	100 (10)	100 (9)
Center 7	100 (3)	75 (4)
Center 9	100 (9)	91 (11)
Center 10	100 (12)	92 (12)
Center 11	100 (10)	100 (13)
Center 12	71 (14)	93 (14)
Center 13	83 (12)	100 (10)
Overall results	89 (153)	95 (155)

Table 3.1.1.6 indicates that of the twelve centers, only three centers (7, 9, and 10) for the moviprep group show numerically higher proportions of patients judged success in gut cleansing. However, no center is found in the moviprep group to have abnormally large proportion of patients judged success in gut cleansing or to dominate the non-inferiority of moviprep to golytely.

2) Efficacy analysis on moviprep

As noted by the sub-section of "Issue on the non-inferiority margin", since the justification for the non-inferiority margin of 15% provided by the applicant not statistically persuasive, the non-inferiority claim between the two treatments moviprep and golytely can not be established. In order to determine if the test drug moviprep has efficacy superior to placebo, in this sub-section, this reviewer calculates the two-sided 95% confidence interval on the success rate of moviprep ($\mathbf{P_{moviprep}}$) using both Per-Protocol and ITT patient populations. Table 3.1.1.7 presents the results.

Table 3.1.1.7 (Reviewer's) 95% two-sided confidence intervals on $P_{moviprep}$

	Moviprep		95% Confidence Interval on
Patient Population	No. Success	Success Rate (n/N)	$P_{moviprep}$
Per-Protocol Population	136	0.87 (136/153)	(0.83, 0.94)
Intent-to-Treat Population	140	0.88 (140/153)	(0.82, 0.93)

Table 3.1.1.7 shows the lower bounds for the two-sided 95% confidence intervals on the success rate of bowel cleansing quality are 0.83 and 0.82 respectively for Per-Protocol and ITT patient populations. Since the assessments on the bowel preparations were potentially biased in favor of the test drug moviprep, the lower bound of the 95% two-sided interval for moviprep calculated using the data from more reliable population is expected to be smaller than the one 0.83 or 0.82 presented in Table 3.1.1.7. However, using the results in Table 3.1.1.7 as a reference, if the medical division deems that the success rate of moviprep is higher than that of placebo, then, moviprep can be considered as effective.

3.1.2 Study NRL994-02/2001 (from May 14, 2002 to March 14, 2003)

This was a randomized, multi-center, single-blind (investigator blinded) clinical phase III trial on two parallel treatment groups comparing the efficacy, safety, and acceptability of moviprep (NRL994) versus NaP (OSPS - Oral Sodium Phosphate Solution) solution for colon cleansing prior to colonoscopy. Clinical trial material was provided in a shaker containing 4 sachets for NRL 994 or 2 bottles of 45 ml of NaP (OSPS) solution for each individual patient. The study was performed in 17 specialized hospital endoscopic centers in France. A total of 340 eligible patients (fully complied with inclusion/ exclsion criteria) planned to undergo a colonoscopy (from 8 A.M to 1 P.M.) were to be randomized to either moviprep or NaP solution as colon cleansing. Unlike Study NRL994-01/2001, both bowel cleansing solutions were completely administered the day before the endoscopic procedure (i.e., moviprep regimen: 2 L of moviprep solution and 1 L water only in PM versus NaP regimen: 90 mL of OSPS and 2 L of water only in PM). The flow chart of the study is presented in Table 3.1.2.1.

Table 3.1.2.1 (Applicant's) Flow chart of the study

	Day-30 to -4	Day -1	Day 0
Informed consent	X		
Medical history	X		
Inclusion/exclusion criteria	X		
Clinical examination	X		
Blood sample (12 ml) *	◄	———	► X
Allocation of study treatment £	X		
Instruction leaflet handed to the patient	X		
Study Solution Intake		X	
Nurse filled with the patient the questionnaire prior to colonoscopy **			X
Investigator assess the efficacy of the solution **			X
Recording in CRF Adverse events			X

*: Haematology and clinical chemistry; **: Investigator blinded.

The sample size was chosen on the basis of previously reported studies. Taking into account all the studies comparing NaP solution to 4 liters of PEG+E, efficacy was similar for both drugs with 70% of excellent to good quality bowel preparation. A sample size of 170 patients per treatment group should have at least 80% power to meet the criteria that the absolute value of the lower limit of a two-sided 95% confidence interval for the difference in very good or good preparation between both treatments did not exceed 15%. This calculation assumed that the true good or correct preparation rate of both groups were 70%. Assuming an evaluability rate of at least 85%, it was calculated that approximately 340 patients were to be enrolled in this study with a randomization rate 1: 1. [The method used by the applicant to calculate the sample size was not based upon the equivalence/non-inferiority analysis to compare moviprep versus Nap.] The criteria for the assessments of the efficacy on the overall quality of the colonoscopy solution were similar to that of Study NRL994-01/2001. For detail scores (0 to 4) and grades (A to D) on the overall quality assessments, refer to the section of "Study Design and Endpoints" for Study RLR994-01/2001.

The primary efficacy endpoint was the percentage of patients who achieved effective colonoscopy cleansing. Responders were patients who achieved an "Overall Quality Scale" score of A or B. Efficacy was judged by one blinded expert gastroenterologist (on the basis of videotapes) and the colonoscopist. If the expert and colonoscopist disagreed with the responder status then a second blinded expert would make the final decision.

For the secondary endpoint analysis, the applicant indicated that the following two secondary criteria, not planed in the protocol, were analyzed: the segmental cleansing scores for each colon segment and the mean colon cleansing score which is the average of the different scores of each colon segment.

As to the patient population, the applicant indicated that three different cohorts were planned to be analyzed:

- Intention to treat (ITT): All included patients who took at least ¼ of the study medication were included in this population. This also was the safety population.
- Modified ITT (mITT): All included patients who took at least ¼ of the study medication and

without a major protocol violation and for whom at least one assessment of the quality of the solution was assessed were included in this population.

- Per Protocol (PP): This population includes patients who satisfied the inclusion/exclusion criteria and who subsequently adhered to the protocol and complied to the treatment allocated.

Statistical Methodologies

The primary analysis was based upon the PP population to assess the equivalence between moviprep and Nap solution evaluated according to the expert's assessment on the overall quality of the colonoscopy solution (primary endpoint).

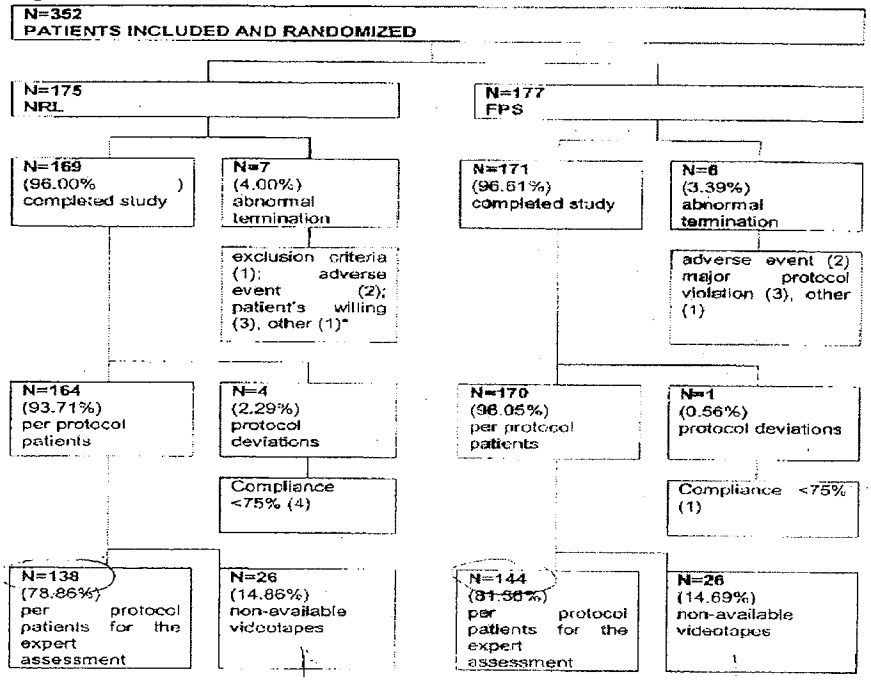
For the equivalence analysis, the applicant indicated that a two-sided 95% confidence interval for the difference in the success rate of bowel cleansing (primary endpoint) assessed by the expert was constructed (NRL994 - OSPS solution) on the basis of the usual normal approximation and the pooled variance estimation for the difference in success rate. The clinical equivalence margin was fixed to 15%. Thus the equivalence was shown if the whole 95% confidence interval lied between -15% and +15%.

Patient Disposition

The applicant indicated that a total of 352 patients were randomized to the two treatment groups of this clinical trial. This size was above the planned number (340) in order to achieve sufficient evaluable patients in the efficacy analysis. Of the 352 patients, 13 randomized patients did not terminate the study normally: eleven patients who were not submitted to the colonoscopy procedure and had not taken any amount of the test preparation were excluded from all analysis (5 for NRL versus 6 for OSPS); one patient who was submitted to colonoscopy procedure but who wasted the test preparation allocated by the randomization and took another commercial solution was excluded from all analyses; one patient who did not have a colonoscopy procedure was analyzed in the ITT population for safety only.

The resulting ITT for safety population is the full set of included patients after exclusion of 12 of them, e.g. 340 patients (169 for NRL versus 171 for OSPS). All the statistical populations constituted for analyses were subsets of this population. The disposition of patients is given by Figure 3.1.2.1.

Figure 3.1.2.1 (Applicant's) Flow chart of disposition of patients



***: the study solution was lost before the day of the intake by the patient and another solution was delivered.**

Figure 3.1.2.1 indicated that thirteen patients (7 in NRL treatment group and 6 in OSPS treatment group) were excluded from all efficacy analyses. In addition, five patients who did not intake "at least 3/4" of the test solution were excluded from the per protocol population. This per protocol population was subdivided in two sub groups: one in which the investigator's advice for each colonoscopy was available and one in which the videotape was available allowing experts' assessment.

Population included in ITT (patients who took at least 1/4 of the study solution) and modified ITT planed (mITT) (patients who took at least 1/2 of the study solution) for the efficacy analyses were in fact identical.

Analyzed populations were summarized by Table 3.1.2.1.

Table 3.1.2.1 (Applicant's) Populations for efficacy analyses

Populations N patients (%)	NRL 994	FPS	TOTAL	p
Randomised	175	177	352	
Excluded from all efficacy analysis	7 (4.00)	6 (3.39)	13 (3.69)	0.984
Efficacy analyses:				
ITT for efficacy (ITT)	168 (96.00)	171 (96.61)	339 (96.31)	0.762
Modified ITT (mITT)	168 (96.00)	171 (96.61)	339 (96.31)	0.762
Per protocol (PP investigators)	164 (93.71)	170 (96.05)	334 (94.89)	0.321
Per protocol (PP experts)	138 (78.86)	144 (81.36)	282 (80.11)	0.557

Note: active control arm FPS shown in the applicant's Table is named OSPS by this reviewer.

Demographics and Baseline Characteristics

The applicant indicated that demographic and other baseline characteristics were evaluated in two different populations: the safety population (all randomized patients n = 352) and the per-protocol patients evaluated by the experts using only 282 patients due to large amount of non-available videotapes (n=52).

The reported demographic and baseline characteristics were gender, age, vital signs, systolic blood pressure, heart rate, at least one baseline abnormal medical condition, medical history at least one abnormal medical condition, at least one abnormal medical condition currently treated, current medications at least one current medication, and at least one ongoing current medication. The applicant indicated that there were no statistically significant differences between groups for the reported demographic and baseline characteristics.

Applicant's Efficacy Analysis Results and Conclusions

Primary endpoint analysis

The applicant indicated that the primary efficacy criterion was a clinical Success/Failure criterion derived from the videotape expert assessment of the degree of cleansing of the five segments of colon (0 to 4 score). This clinical criterion (Success = A or B / failure = C or D) was obtained using an algorithm which should be the same between the investigator and expert assessment. In case of discrepancy between them, the videotape was assessed by a second expert. Table 3.1.2.2 presented the results of bowel cleansing assessed by the expert (PP population).

Table 3.1.2.2 (Applicant's) Bowel cleansing assessed by expert (PP population)

	Moviprep (M) % (n/m)	Nap (N) % (n/m)	Percent Diff % ($P_M - P_N$)	Two-sided 95% Confidence Interval	Margin -δ
Primary Endpoint[a]	73.0% (100/137)	64.3% (92/143)	8.7 %	(-2.2%, 19.5%)	-15%

[a]: Percentage of patients achieving an "Overall Quality Scale" score of A or B.

Based upon Table 3.1.2.2, the applicant indicated that the clinical success rates of the two solutions were 73.0% and 64.3% respectively, for the moviprep group and the Nap group using the expert Per-protocol population. In addition, the two-sided 95% confidence interval for the difference of success rates for treatment moviprep minus treatment Nap was (-2.2%, +19.5%), not included in the interval of (-15%, +15%) formulated by the equivalence margin of 15%. However, the lower bound of the 95% two-sided confidence interval was -2.2%, greater than the negative value of the non-inferiority margin (15%). Therefore, instead of claiming the equivalence of moviprep to Nap, with the non-inferiority margin of 15%, the applicant indicated that the non-inferiority of moviprep to Nap was supported.

Secondary endpoint analysis

As indicated in the section of 2.2 "Data Sources", in the response to this reviewer's information request, the applicant indicated that the coding error was found for the secondary endpoints. Although the correction introduced small changes to the numbers and had no impact on the conclusions made by the applicant in the original NDA submission, the analysis results for the secondary endpoints summarized below were mainly based upon the resubmission on November 8, 2005.

Table 3.1.2.3 presented the results of bowel cleansing assessed by the investigator using PP population.

Table 3.1.2.3 (Applicant's) Bowel cleansing assessed by investigator using PP population

	Moviprep (M) % (n/m)	OSPS (O) % (n/m)	Percent Diff % ($P_M - P_O$)	LL^c	Margin -δ
Primary Endpoint[a]	68.3% (112/164)	71.0% (120/169)	-2.7%	-13.0%	-15%

[a]: Percentage of patients achieving an "Overall Quality Scale" score of A or B;

Based upon Table 3.1.2.3, the applicant indicated that although the same conclusion for non-inferiority was confirmed for the bowel cleansing assessed by investigator using PP population, the observed difference was -2.7% and the lower bound of the two-sided 95% confidence interval of the difference on the success rates of NRL minus OSPS was -13.0% close to the negative value of the non-inferiority margin (-15%).
In addition, the applicant indicated that the non-inferiority for the primary expert clinical criterion was confirmed for the mITT and ITT population with, approximately, the same difference in favor of the mpviprep solution: + 8.44 % (MITT) and + 7.9% (ITT), respectively with two-sided 95% lower bounds -2.33% and -1.9%.

Based upon the above efficacy results, the applicant concluded that whatever the population analyzed, the lower confidence bounds of the difference of success rates between the two treatment groups were very similar. They demonstrated that moviprep was "at least non-inferiority" to Nap'.

For the colon segment cleansing assessments (0 to 4), the applicant indicated that in the moviprep group, the more frequent score was 3 for the five colonic regions except for the ascending colon, caecum and rectum. However, in the Nap group, the predominant scores were 2 and 4 respectively. There was a significantly higher proportion of "3" in the moviprep group and a significantly higher proportion of "4" score in the Nap group.

For the mean colon cleansing score, the applicant indicated that using PP population, mean scores calculated on the basis of the ratings assigned by expert panel ranged between 2.8 and 3.2 for each of the first four gut segments (rectum, sigmoid colon, descending colon, and transvers colon), with no relevant between-group differences. Ascending colon was rated higher in the moviprep group (2.3 versus 1.9). The mITT population showed similar results. The applicant further addressed that there was more frequent classification "4" in the Nap group (contrary to "3" more frequent in the moviprep group).

For the overall quality of the preparation (A = very good preparation, B = good preparation, C= poor preparation and D = bad preparation), the applicant indicated that according to the experts' assessments, the proportion of very good preparation (A) was higher in the moviprep group, 46%, versus 27% in the Nap group. The proportion of B, C and D solutions was consistently higher in the OSPS group. The investigator assessment gave similar profiles but differences between treatment groups were lower, and the proportion of A grade in the moviprep group was much lower.

Finally for the overall quality of cleansing assessed by the investigator with the VAS (0 = excellent, 100 = very bad), the applicant indicated that the quality of bowel cleansing using the VAS was always higher in the moviprep group, the difference between treatment group ranging from + 6.88% to + 7.12% in the different analyses.

Reviewer's Comments and Analysis

In order to validate the sponsor's efficacy claim, this reviewer first comments on the following two issues: 1) equivalence margin of 15% and 2) assessments of colon cleansing quality. Then, this reviewer performs the following two analyses: 1) primary efficacy analysis by center and 2) efficacy analysis on moviprep.

Reviewer's Comments

1) Issue on the equivalence margin

Refer to the comments on the issue of the non-inferiority margin given in the section of "Reviewer's Comments" for Study NRL 994-01/2001.

2) Assessments of colon cleansing quality

Refer to the comments on the two issues (nature of single blinded design and defect of non-

inferiority analysis criterion) of the colon cleansing quality to comments made in the section of the "Reviewer's Comments" for Study NRL994-01/2001.

Reviewer's Analysis

1.) Primary efficacy analysis by center

In order to explore whether the non-inferiority of moviprep (NRL994) to Nap (OSPS) assessed by the primary endpoint (frequency with grade A or B in the overall quality assessment of gut cleansing) was dominated by certain centers, this reviewer analyzes the differences in proportions on the primary endpoint to compare the efficacy between the two treatments using PP population. The centers used in this analysis are the centers defined by the applicant. Table 3.1.2.4 presents the result.

Table 3.1.2.4 (Reviewer's) Proportion of patient success in the overall gut cleansing assessed by the expert panel by center using PP population

CENTER	MOVIPREP SUCCESS RATE % (N)	NAP SUCCESS RATE % (N)
Center 1	83 (6)	100 (6)
Center 2	80 (5)	57 (7)
Center 4	80 (10)	50 (12)
Center 5	100 (7)	50 (6)
Center 6	64 (11)	67 (12)
Center 8	65 (17)	59 (17)
Center 10	60 (10)	78 (9)
Center 11	25 (4)	63 (8)
Center 12	93 (14)	85 (13)
Center 13	81 (16)	53 (17)
Center 14	64 (11)	73 (11)
Center 15	80 (5)	67 (3)
Center 16	65 (17)	57 (21)
Center 17	50 (2)	50 (2)
Center 19	100 (2)	100 (1)
Overall results	73 (137)	64 (145)

Table 3.1.2.4 indicates that of the fifteen centers, eight centers (2, 4, 5, 8, 12, 13, 15, and 16) for the moviprep group show numerically higher proportions of patients judged success in gut cleansing than that in the Nap group. No center is found for the moviprep group to have unusually high proportion of patients judged success in gut cleansing and dominates the non-inferiority of moviprep to Nap.

2) Efficacy analysis on moviprep

Similar to study NRL 994-01/2001, due to the justification for the non-inferiority margin of 15% provided by the applicant not statistically persuasive, the non-inferiority claim between the two treatments moviprep and Nap can not be established. In order to determine if the test drug moviprep has efficacy superior to placebo, in this sub-section, this reviewer performs the two-sided 95% confidence interval on the success rate of moviprep using both Per-Protocol and ITT patient populations. Table 3.1.2.5 presents the results.

Table 3.1.2.5 (Reviewer's) 95% two-sided confidence intervals on $P_{moviprep}$

	Moviprep		95% Confidence Interval on
Patient Population	No. Success	Success Rate (n/N)	$P_{moviprep}$
Per-Protocol Population	100	0.73 (100/137)	(0.65, 0.80)
Intent-to-Treat Population	101	0.73 (101/137)	(0.64, 0.80)

Table 3.1.2.5 shows the lower bounds for the two-sided 95% confidence intervals on the success rate of bowel cleansing quality are 0.65 and 0.64 respectively for Per-Protocol and ITT patient populations. Since as noted by this reviewer, the assessments on the bowel preparations were potentially biased in favor of the test drug moviprep, the lower bound of the 95% two-sided interval for moviprep calculated using the data from more reliable population is expected to be smaller than the one 0.65 or 0.64 presented in Table 3.1.2.5. However, using the results in Table 3.1.2.5 as a reference, if the medical division deems that the success rate of moviprep is higher than that of placebo, then, moviprep can be considered as effective.

3.2 Evaluation of Safety

3.2.1 Study NRL994-01/2001

The applicant indicated that treatments with moviprep and golytely were generally well tolerated. No serious adverse events were observed. Overall the number of patients experiencing adverse events and the quality and frequency of AEs were comparable between the two treatment groups though they were somewhat more frequent in the golytely group. Most of the AEs were considered to be treatment-related and consisted of symptoms known to be associated with the intake of gut cleansing solutions in this patient population (malaise, nausea, vomiting, and abdominal pain). With one exception, all were of mild to moderate intensity. Severe abdominal pain was reported in one patient; the event resolving within a few hours without further treatment, and the patient was able to almost complete the intake of moviprep as scheduled (1,800 of 2,000 mL). Occurrence of an AE was the main reason why 7 patients in the moviprep group and 6 patients in the golytely group ingested less than 75% of the scheduled amount of the study medication and were excluded from the PP population.

Nausea and abdominal pain were significantly less frequently observed in the moviprep group compared with the golytely group. In the global tolerability assessment, patients significantly favored moviprep over golytely by assigning very good and good ratings more frequently.

Finally, there was no indication of relevant treatment-related average or individual shifts in the laboratory safety tests; almost all clinically relevant abnormal values were observed prior to treatment.

3.2.2 Study NRL994-02/2001

The applicant indicated that the incidence rates of patient having at least one adverse event were low in each treatment group. However there was a very significantly higher proportion of patient presenting at least one adverse event in the Nap group (15.0% with n=25 versus 4.0% with n=7 in the moviprep group). In addition, there were 3 patients having at least one serious adverse event in the Nap group versus 0 in the moviprep group. Table 3.2.2.1 summarizes the results of the adverse event analysis.

Table 3.2.2.1 (Applicant's) Results of the adverse event analysis

At least one adverse events (N, % of patients *)	NRL N (%)	FPS N (%)	P-value for Chi-Square
➢ Seriousness			
Serious	0 (0.00)	3 (1.75)	0.084
Non serious	7 (4.14)	22 (13.66)	0.084
➢ Relation to the study drug			
Non-related	3 (1.77) *	7 (4.09)	0.206
Related	5 (2.96) *	19 (11.11)	0.003
➢ Severity			
Mild	1 (0.59)	16 (9.36)	0.000
Moderate	6 (3.55)	6 (3.51)	0.983
Severe	0 (0.00)	3 (1.75)	0.084
At least one AE	7 (4.14)	25 (14.62)	0.001
All patients	169	171	

*: The patient approach "at least one adverse event" of each level category, the frequencies are not necessarily additive because some patients actually hove more than one adverse events with different attribute.

4.0 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 GENDER, RACE, AND AGE

In order to assess the consistency of the treatment effect of moviprep versus golytely/Nap across subgroups, this reviewer performed the subgroup analysis by non-inferiority margin approach for the primary endpoint (percentage of patients achieving an "Overall Quality Scale" score of A or B) using per-protocol patient population. Since the applicant did not submit data regarding race, the subgroups analyzed for Studies NRL 994-01/2001 and NRL 994-02/2001 are Gender (Male and Female) and Age group (age $\leq$ 65 and age > 65).

4.1.1 Study NRL 994-01/2001

i) Gender

Table 4.1.1.1 presents the results of treatment efficacy comparisons for moviprep versus golytely by gender.

Table 4.1.1.1 (Reviewer's) Results of the non-inferiority margin analysis using per-protocol population

Female

	Moviprep (M) % (n/m)	Golytely (G) % (n/m)	Percent Diff % ($P_M - P_G$)	LL[c]	Margin -δ
Primary Endpoint[a]	92% (68/74)	96% (81/84)	-4.0%	-12.0%	-15%

Male

	Moviprep (M) % (n/m)	Golytely (G) % (n/m)	Percent Diff % ($P_M - P_G$)	LL	Margin -δ
Primary Endpoint	86 % (68/79)	93% (66/71)	-6.9%	-17.0%	-15%

[a]: Percentage of patients achieving an "Overall Quality Scale" score of A or B:

[c]: 97.5% one-sided lower limit for the event rate difference of $P_M - P_G$.

Table 4.1.1.1 indicates that the percentages of patients achieving an "Overall Quality Scale" score of A or B (success rate of gut cleansing) in the moviprep group are numerically less than those of the golytely group for both males and females. However, for females, the lower limit of the one-sided 97.5% lower confidence interval on the proportion difference of the success rate of gut cleansing for moviprep minus golytely is -12%, greater than the negative value of the non-inferiority margin (-15%). As a result, for females, the effect of cleansing gut assessed by the primary endpoint for moviprep is not inferior to that of golytely by more than 15%.

ii) Age group (age ≤ 65 and age > 65)

Table 4.1.1.2 presents the results of treatment efficacy comparisons for moviprep versus golytely by age group.

Table 4.1.1.2 (Reviewer's) Results of the non-inferiority margin analysis using per-protocol population

Age > 65

	Moviprep (M) % (n/m)	Golytely (G) % (n/m)	Percent Diff % ($P_M - P_G$)	LL[c]	Margin -δ
Primary Endpoint[a]	84% (41/49)	92% (59/64)	-8.0%	-21.0%	-15%

Age ≤ 65

	Moviprep (M) % (n/m)	Golytely (G) % (n/m)	Percent Diff % ($P_M - P_G$)	LL	Margin -δ
Primary Endpoint	91% (95/104)	97% (88/91)	-6.0%	-12.0%	-15%

[a]: Percentage of patients achieving an "Overall Quality Scale" score of A or B:

[c]: 97.5% one-sided lower limit for the event rate difference of $P_M - P_G$.

Table 4.1.1.2 indicates that the percentages of patients achieving an "Overall Quality Scale" score of A or B (success rate of gut cleansing) in the moviprep group are numerically less than those of the golytely group for both of the junior and senior groups. However, for the younger group, the lower limit of the one-sided 97.5% lower confidence interval on the proportion difference of the success rate of gut cleansing for moviprep minus golytely is -12.0%, greater than the negative value of the non-inferiority margin (-15%). As a result, for the younger group, the effect of cleansing gut assessed by the primary endpoint for moviprep is not inferior to that of golytely by more than 15%.

4.1.2 Study NRL 994-02/2001

i) Gender

Table 4.1.2.1 presents the results of treatment efficacy comparisons for moviprep versus Nap by gender.

Table 4.1.2.1 (Reviewer's) Results of the non-inferiority margin analysis using per-protocol population

Female

	Moviprep (M) % (n/m)	Nap (N) % (n/m)	Percent Diff % ($P_M - P_N$)	LL	Margin -δ
Primary Endpoint	69.0% (44/64)	74.0% (51/69)	-5.0%	-21.0%	-15%

Male

	Moviprep (M) % (n/m)	Nap (N) % (n/m)	Percent Diff % ($P_M - P_N$)	LL[c]	Margin -δ
Primary Endpoint[a]	77.0% (56/73)	55.0% (42/76)	22.0%	7.0%	-15%

[a]: Percentage of patients achieving an "Overall Quality Scale" score of A or B;
[c]: 97.5% one-sided lower limit for the event rate difference of $P_M - P_N$.

Table 4.1.2.1 indicates that for males, the lower limit of the one-sided 97.5% lower confidence interval on the proportion difference of the success rate of gut cleansing for moviprep minus Nap is 7.0%, greater than zero. As a result, the effect of cleansing gut assessed by the primary endpoint for moviprep is superior to that of Nap for males.

For females, however, the percentage of patients achieving an "Overall Quality Scale" score of A or B (success rate of gut cleansing) in the moviprep group is numerically less than that of the Nap group. In addition, the limit of the one-sided 97.5% lower confidence interval on the proportion difference of the success rate of gut cleansing for moviprep minus Nap is -21.0%, less than the negative value of the non-inferiority margin (-15%). Accordingly, for females, the effect of cleansing gut assessed by the primary endpoint for moviprep is inferior to that Nap by more than 15%.

ii) Age group (age ≤ 65 and age > 65)

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

Table 4.1.2.2 (Reviewer's) Results of the non-inferiority margin analysis using per-protocol population

Age > 65

	Moviprep (M) % (n/m)	Nap (N) % (n/m)	Percent Diff % ($P_M - P_N$)	LL[c]	Margin -δ
Primary Endpoint[a]	78.0% (18/23)	65.0% (17/26)	13.0%	-12.0%	-15%

Age ≤ 65

	Moviprep (M) % (n/m)	Nap (N) % (n/m)	Percent Diff % ($P_M - P_N$)	LL	Margin -δ
Primary Endpoint	72.0 % (82/144)	64.0% (76/119)	8.0%	-4.0%	-15%

[a]: Percentage of patients achieving an "Overall Quality Scale" score of A or B;
[c]: 97.5% one-sided lower limit for the event rate difference of $P_M - P_N$.

Table 4.1.2.2 indicates that the percentages of patients achieving an "Overall Quality Scale" score of A or B (success rate of gut cleansing) in the moviprep group are numerically higher than those of the Nap group for both of age groups. In addition, for both age groups, the lower limit of the one-sided 97.5% lower confidence interval on the proportion difference of the success rate of gut cleansing for moviprep minus Nap are respectively, -4% and -12%, greater than the negative value of the non-inferiority margin (-15%). Therefore, for both age groups the effects of cleansing gut assessed by the primary endpoint are not inferior to that of Nap by more than 15%.

4.2 OTHER SPECIAL/SUBGROUP POPULATIONS - Not applicable

5.0 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Since the justification for the non-inferiority margin of 15% submitted by the applicant is for both active control arms (golytely and Nap) employed by the two studies (NRL994-01/2001 & NRL994-02/2001), the following comments made by this reviewer on the non-inferiority margin are also for both studies:

- First, instead of following the recommendation of ICH E10 on the margin selections and using the historical studies conducted under the conditions similar to that of the current trials to identify the smallest sizes of the active control arms (golytely for study NRL994-01/2001 and Nap for study NRL994-02/2001), the 14 references cited by the applicant only provide the efficacy rates (proportion of "excellent" or good") of the two active controlled treatments, golytely & Nap in bowel preparation. No efficacy rates of placebo arm were provided. Then, for each of the 14 studies reported by the 14 articles cited by the applicant, the applicant performs the non-inferiority analysis using the selected margin of 15% to compare the efficacy between golytely and Nap. Based upon the non-inferiority analysis results of 8 studies showed NaP (if used as test) not inferior to golytely (if used as reference) and 8 studies showed golytely (if used as test drug) not inferior to Nap (if used as reference), the applicant concludes that a non-inferior margin as large as 15% used in the present studies is an appropriate and rather restrictive margin for both comparators. Thus, based upon the margin justification provided by the

applicant, the non-inferiority margin of 15% for both active controlled treatments (golytely and Nap) was not identified by comparing the effectiveness of the two controlled treatments to that of placebo, as recommended by ICH E10.

In addition, the medical reviewer, Eric Brodsky MD, indicates the assessment criteria for the quality of the gut cleansing employed by the 10 articles submitted by the applicant are different from that used by the two phase III trials (Studies NRL 994-01/2001 & NRL 994-02/2001). In other words, the two phase III trials were not conducted under the conditions similar to that of the historical studies used to support the non-inferiority margin of 15%, as recommended by ICH E10. Consequently, the justification provided by the applicant for the non-inferiority margin of 15% is not statistically persuasive.

- Second, as indicated by the medical reviewer, for Study NRL 994-01/2001, the overall quality of gut cleansing was classified twice (Up and Down) and the poorer of the two assessments was included in the efficacy analysis. In addition, in each assessment, the independent review panel results were the basis for the assessment of the primary endpoint of gut cleansing. In case discrepancy on the rating of gut cleansing occurred, the final rating for the overall gut cleansing was obtained after agreement among the reviewers and investigator was achieved. However, for Study NRL 994-02/2001, only one assessment was performed for the overall gut cleansing quality and the third tape reviewer from the expert panel determined the final grading when discrepancy in terms of preparation success or failure between investigator and videotape reviewer occurred.

  Consequently, the two different assessment procedures on the quality of gut cleansing for the two studies may generate different clinical outcomes. Therefore, it is not statistically sound to use the same non-inferiority margin (15%) for the two studies using two different gut cleansing assessment procedures.
- Third, it is noted that for golytely in Study NRL 994-01/2001, the mode of intake was "split dose" - one dose in the evening before the procedure and one in the morning on the day of the endoscopy procedure- while for Nap in Study NRL 994-02/2001, the mode of intake was "single dose" administered in the evening the day before endoscopy procedure. The medical reviewer indicates that the mode of dose intake (for example, "single dose" versus "split dose") affects the quality of gut cleansing. Yet, more critically, this assertion is also emphasized by the applicant in the response to the justification of margin selection: the rate of effective colon cleansing is dependent on the mode of intake. Accordingly, the use of same non-inferiority margin of 15% for both active control drugs (golytely versus Nap) is not adequate.
- Finally, strictly speaking, it is implausible that the effectiveness of different drugs (e.g., golytely and Nap) assessed by the same endpoint (gut cleansing) would be similar. Accordingly, it is not statistically convincing to employ the same non-inferiority margin of 15% for both of the active controlled drugs, golytely and Nap.

In conclusion, based upon the above four remarks, the non-inferiority margin of 15% selected by the applicant for the two studies is not supported by the applicant's margin justification and is not acceptable.

Since the two issues "nature of single blinded design" and "defect of non-inferiority analysis criterion" for study 994-01/2001 are congruent to that of study 994-02/2001, the following comments for these two issues are for both studies:

- *Single blinded design*: Although investigators were blinded as to the methods of preparation, since patients knew which drugs were used for their bowel preparations, it would be easy for the investigators to recognize the bowel preparation drug used by patients. Therefore, in reality, the single blinded trial had high potential to be an open label trial for the expert panel. Furthermore, noted by this reviewer, the definitions of "grade C" and "grade B" in bowel cleansing quality are not clear cut and may be assessed subjectively. Accordingly, as long as the members in the expert panel apprehended which drug was used by the patient, the assessment on the successful bowel preparation (scored as "grade A" or "grade B") was likely to be biased in favor of study drug moviprep.
  Due to different appearances shown by the two treatments, moviprep and golytely, it may be difficult for the applicant to conduct a double blinded trial. However, the concerns on the issues of biased efficacy comparisons induced by such trials can not be ignored and the biased conditions induced by the nature of single blinded trial may have been improved if another lower dose arm of moviprep had been included in this trial.
- *Non-inferiority analysis criterion:* One notes that if the outcomes of the bowel preparations for the two treatment groups, moviprep and golytely, are assessed as similar/comparable as possible then the non-inferiority will be claimed for the two drugs. In addition, due to ambiguous definition on the scores "grade B" and "grade C" of the bowel cleansing quality, the bowel preparation quality might not be assessed objectively. Therefore, with only two arms, study drug and comparator, in the trial, it was very likely for the expert panel to assign similar scores to the bowel preparations for the two treatment groups. As long as the expert panel assessed the outcomes of the bowel preparations for the two treatment groups as close as possible, the chance of concluding non-inferiority for the two drugs is greatly increased. However, the non-inferiority of the two treatment groups established by the above assessments may be a biased result. To avert the bias, CFR section 314.126 on adequate and well-controlled studies recommends including additional treatment groups such as dose-comparison control. Thus, as commented by this reviewer above, in order to prevent the potentially biased assessments, the applicant should have included another lower dose arm of moviprep in the trial.

For Study NRL994-01/2001, analysis of the primary endpoint by center indicates that no center was found in the moviprep group to have an abnormally large proportion of patients judged success in gut cleansing. Thus, no center dominates the non-inferiority of moviprep to golytely.

Similarly, for Study NRL 994-02/2001, no center was found in the moviprep group to have abnormally large proportion of patients judged success in gut cleansing or to dominate the non-inferiority of moviprep to Nap.

Finally, for Study NRL994-01/2001, the efficacy analysis on moviprep shows that lower bounds of the two-sided 95% confidence interval on the success rate of bowel cleansing quality are 0.83

and 0.82 respectively for Per-Protocol and ITT patient populations. For Study NRL994-02/2001, the two-sided 95% lower bounds for moviprep are 0.65 and 0.64, respectively for Per-Protocol and ITT patient populations. Since the assessments on the bowel preparations were potentially biased in favor of the test drug moviprep, the lower bound of the 95% two-sided interval for moviprep calculated using the data from more reliable population is expected to be smaller than 0.64. However, using the results of the lower bounds as a reference, if the medical division deems that this success rate of moviprep is higher than that of placebo, then, moviprep can be considered as effective.

5.2 Conclusions and Recommendations

From the statistical perspective, based upon the four remarks, stated in the section of "Statistical Issues and Collective Evidence", given by this reviewer to the justification on the selected non-inferiority margin of 15% provided by the applicant, the non-inferiority margin of 15% selected by the applicant for the two studies is not acceptable. Accordingly, NDA submitted by the applicant does not provide substantial evidence to support that the efficacy of moviprep is non-inferior to that of approved drugs for bowel cleansing prior to colonoscopy, intestinal surgery and barium enema X-ray examination.

However, the lower bound for the two-sided 95% confidence interval on the proportions of bowel cleansing success for moviprep is not less than 0.64, calculated using the applicant's data from the two NDA studies (NRL994-01/2001 and NRL994-02/2001). Using this result as a reference, if the medical division deems that the success rate around 0.60 of moviprep would be higher than that of placebo, then, moviprep can be considered as effective.

6.0 APPENDIX A

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