CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209381Orig1s000

STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/SN #:	209,381 / SN 11, 17, 27
Related IND #:	120089
Drug Name:	Plenvu (NER1006 Powder)
Indication(s):	Cleansing of the Colon in Preparation for Colonoscopy in Adults
Applicant:	Norgine BV
Dates: Submission date PDUFA V	 April 13, 2017 March 5, 2018
Review Priority:	Standard
Biometrics Division:	Division of Biometrics 3
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EDR Locations:	EDR: \\CDSESUB1\evsprod\NDA209381\209381.enx SharePoint: NDA 209381 Plenvu- Norgine 4.13.2017
Keywords: NDA review, clinical study	

Table of Contents

1 EXECUTIVE SUMMARY

The Sponsor is developing NER1006 for cleansing of the colon in preparation for colonoscopy in adults. They submitted IND 120089 for NER1006 to FDA on December 18, 2013. An end-of-phase 2 (EoP2) meeting was held on April 16, 2014 to gain FDA guidance on the ongoing developmental program and proposed Phase 3 studies. In addition, a pre-NDA meeting was held on February 2 of 2016.

The sponsor has submitted the results of two, Phase 3, multicenter, randomized, parallel-group studies to support the efficacy of NER1006 Powder for the indication of cleansing of the colon in preparation for colonoscopy in adults.

The statistical reviewer evaluated the totality of evidence and confirmed the Sponsor's results. The reviewer concluded that the efficacy results of the two studies showed statistical non-inferiority of NER1006 to the comparators for the indication of cleansing of the colon in preparation for colonoscopy (the primary efficacy endpoint of "Overall Bowel Cleansing") in adults.

2 INTRODUCTION

(Parts of the descriptions in this section are extracted from the sponsor's clinical study report)

2.1 Overview and Background

Colonoscopy enables visual inspection of the entire large bowel from the distal rectum to the cecum via a flexible fiber-optic tube with a camera at its end called a colonoscope. In order to perform colonoscopy or colonic surgery effectively, it is necessary to empty the contents of the colon and cleanse the bowel.

NER1006 is a Powder for Oral Solution (hereafter referred to as NER1006). The Sponsor used NER1006 as the investigational product (IP) in this Phase 3 study in a 2-day split dosing regimen. NER1006 is supplied as two formulations; one formulation "evening dose" and the second formulation is the "morning dose". Both these doses are reconstituted with water (up to 16 fl. oz. [approximately 500 mL]).

The sponsor has submitted two Phase-3, multicenter, randomized, parallel-group studies (Study NOCT and Study MORA).

A brief description of the Phase 3 efficacy studies is shown in Tables 1A and 1B.

Table 1A: Study NOCT

Study Design	A multicenter, randomized, parallel group, phase 3 study comparing the bowel cleansing efficacy, safety and tolerability of ner1006 (a low volume bowel cleansing solution) vs. a trisulfate bowel cleansing solution using a 2-day split-dosing regimen in adults in 12 US sites.
2 Co-Primary Efficacy Endpoints	• The overall bowel cleansing success rate using the HCS, wherein success corresponded to grades A and B, and failure corresponded to grades C and D. • The "Excellent plus Good" cleansing rate in the colon ascendens using the segmental cleansing scoring system of the HCS, wherein the ordinal score of 4 corresponded to "Excellent" cleansing and score of 3 corresponded to "Good" cleansing.
Number of Subjects	Total: 621 NER1006: 310 Trisulfate: 311
Number of Site/ Country	12/ USA

Table 1B: Study MORA

Study Design	A multicenter, randomized, parallel group, phase 3 study comparing the bowel cleansing efficacy, safety and tolerability of ner1006 (a low volume bowel cleansing solution) versus moviprep® using a 2-day split-dosing and 1-day morning split-dosing regimens in adults in 29 sites across the European Union
2 Co-Primary Efficacy Endpoints	• The overall bowel cleansing success rate using the HCS, wherein success corresponded to grades A and B, and failure corresponded to grades C and D. • The "Excellent plus Good" cleansing rate in the colon ascendens using the segmental cleansing scoring system of the HCS, wherein the ordinal score of 4 corresponded to "Excellent" cleansing and score of 3 corresponded to "Good" cleansing.
Number of Subjects	Total: 849 NER1006 (2-day): 283 NER1006 (1-day): 283 Moviprep (2-day): 283
Number of Sites/ Countries	29 Sites in Belgium, France, Germany, Italy, Poland, Spain and United Kingdom

The Sponsor had planned two co-primary efficacy endpoints for their clinical trials. At the EoP2 as well as the Pre-NDA meeting, we conveyed our concerns regarding the selected endpoints and aspects of the study design that might impact the ability of the phase 3 trials to support approval and product labeling for the 2-day split dosing and 1-day morning split dosing regimens.

FDA's Concerns regarding the Second Alternative Primary (colon ascendens):
At the Pre-NDA meeting dated February 2, 2016) it was reiterated by the agency that the alternate primary endpoint of "excellent plus good cleansing in the colon ascendens" (b) (4) on this endpoint, FDA would need to see replication or a highly persuasive statistical result.

Moreover, as documented in the Sponsor's meeting minutes (SN0008), the Sponsor acknowledges that if overall assessment (designated as Alternative Primary Endpoint 1) does not show noninferiority (or superiority), then the Agency would not deem the studies sufficient for NDA approval from a clinical perspective.

Additionally, a statistical assessment of the relationship between overall cleansing and cleansing in the ascending colon using the HCS has been conducted using data from the OPT Phase II study. The assessment demonstrated the correlation between the two alternative primary

endpoints to be very high for the NER1006 arms of the study. Therefore, the probability of disparate outcomes in the Phase III studies, and specifically of achieving non-inferiority in the ascending colon and not achieving noninferiority overall, is deemed to be very low. It should be noted that correlated efficacy endpoints are not acceptable (b) (4). For the reasons listed above, we do not accept the second co-primary efficacy endpoint of colon ascendens and will present the results for this endpoint only for exploratory purposes.

2.2 Data Sources

In this submission, the statistical reviewer reviewed the applicant's clinical study reports, datasets, clinical summaries, and proposed labeling. The submission was submitted in eCTD format and was entirely electronic. Both SDTM and analysis datasets (ADaM) were submitted. The applicant supplied all data electronically as SAS transport files which can be found in the CDER electronic document room. The datasets that contains the primary endpoints in both studies are: ADEFF2.XPT which were located at: EDR: \\CDSESUB1\evsprod\NDA209381\209381.enx

2.3 Data and Analysis Quality

The integrity of the data was acceptable for the efficacy analyses.

3 STATISTICAL EVALUATION

The objectives, efficacy endpoints, analysis sets as well as the primary analyses for both studies NOCT and MORA were the same. Therefore, for brevity reasons, we described them in this section. The detailed efficacy analyses and results for each study are reported separately. The protocols were finalized on June 25, 2015 (Version 7.0). The statistical analyses included in the clinical study reports followed the pre-specified protocol.

3.1 Both Studies

3.1.1 Study Objectives

To evaluate the overall bowel cleansing efficacy and the "Excellent plus Good" cleansing rate in the colon ascendens of NER1006 compared to a comparator, graded according to the Harefield Cleansing Scale (HCS) in patients undergoing screening, surveillance, or diagnostic colonoscopy.

3.1.2 Primary and Secondary Endpoints

The primary efficacy endpoints:

1. The overall bowel cleansing success rate using the HCS, wherein success corresponded to grades A and B, and failure corresponded to grades C and D.

2. The "Excellent plus Good" cleansing rate in the colon ascendens using the segmental cleansing scoring system of the HCS, wherein the ordinal score of 4 corresponded to "Excellent" cleansing and score of 3 corresponded to "Good" cleansing.

Based on meeting minutes for the End of Phase (EoP) 2, dated July of 2014 Page 21of 71the Sponsor stated that: "As documented in the meeting minutes (SN0008), the Sponsor acknowledges that if overall assessment (designated as Alternative Primary Endpoint 1) does not show noninferiority (or superiority), then the Agency would not deem the studies sufficient for NDA approval from a clinical perspective." Additionally, a statistical assessment of the relationship between overall cleansing and cleansing in the ascending colon using the HCS has been conducted using data from the OPT Phase II study. The assessment demonstrated the correlation between the two alternative primary endpoints to be very high for the NER1006 arms of the study. Therefore, the probability of disparate outcomes in the Phase III studies, and specifically, of achieving non- inferiority in the ascending colon and not achieving noninferiority overall is deemed to be very low.

The secondary efficacy endpoints:

1. Adenoma Detection Rate (ADR) as defined by the proportion of patients with at least one adenoma in the colon ascendens as confirmed by a pathologist

2. ADR as defined by the proportion of patients with at least one adenoma in the overall colon as confirmed by a pathologist

3. Polyp Detection Rate (PDR) as defined by the proportion of patients with at least one polyp in the colon ascendens, as confirmed by the colonoscopist

4. PDR as defined by the proportion of patients with at least one polyp in the overall colon as confirmed by the colonoscopist

3.1.3 Analysis Population

Modified Full Analysis Set (mFAS) was the primary analysis population and included all randomized patients with the exception of any patient who (i) was randomized but subsequently failed to meet entry criteria and (ii) in whom it was confirmed (from their patient diary) that the same patient did not receive any study drug. Patients in this analysis set were summarized according to the treatment to which they were randomly assigned. Patients who did not have their eligibility confirmed based on the entry criteria were included in the mFAS, regardless of whether they received any study drug.

3.1.4 Analysis of the Primary Efficacy Endpoints and Statistical Methodology

The hypotheses for the two alternative primary endpoints measured in this study were:

• The overall bowel cleansing success rate of NER1006 is non-inferior to that of comparator using the HCS, wherein success corresponded to grades A and B, and failure corresponded to grades C and D.

• The "Excellent plus Good" cleansing rate in the colon ascendens of NER1006 is non-inferior to that of comparator using the segmental cleansing scoring system of the HCS, wherein the ordinal

score of 4 corresponded to "Excellent" cleansing and score of 3 corresponded to "Good" cleansing.

The hypothesis for each alternative primary endpoint was to demonstrate non-inferiority of NER1006 to the comparator using a non-inferiority margin of 10% (i.e. for overall bowel cleansing, a difference in success rates of no greater than 10% in favor of the comparator and, for the colon ascendens cleansing, a difference in "Excellent plus Good" cleansing rates of no greater than 10% in favor of the comparator). If non-inferiority was met for at least one of the primary endpoints, the sponsor planned to assess superiority.

Reviewer's Remark: The Sponsor used mFAS as the primary population for all efficacy analyses which consequently, made the sample size smaller and therefore, for calculating response rate, the denominator was smaller and hence higher success rates. In this review, the statistical reviewer, first, replicated the Sponsor's results and then, in order to verify the robustness of the results we analyzed the data based on the full analysis set (FAS) that included all randomized subjects, where the missing values were considered as non-responders.

Primary Efficacy Analysis Approach
For both alternative primary endpoints, the Sponsor reports the number and percentage of patients with successful cleansing. The confidence interval (CI) for the difference between bowel preparation cleansing rates was determined using PROC FREQ (using exact Clopper-Pearson confidence limits) in SAS and p-values generated using Fisher's exact test. This reviewer used a simple χ^2, assuming normal distribution for all analyses.

Multiple testing procedures
The sequential hierarchical testing algorithms specified by the sponsor for studies MORA and NOCT do not have equivalent representation as closed testing procedures and do not control overall type I error rate at 0.05 significance level. For study MORA, type I error is inflated, for example, because sponsor's procedure generates multiple testing sequences after non-inferiority for NER1006 2-Day is established. As specified in the SAP, the testing proceeds with 5% alpha to test simultaneously superiority of NER1006 2-Day and non-inferiority of NER1006 1-Day dose. Also, Hochberg procedure applied to the testing of the alternative primary endpoints is non-separable (i.e. alpha exhaustive). Hence, subsequent hierarchical testing is possible only if both alternative primary endpoints demonstrate efficacy.

3.2 Study NOCT

3.2.1 Study Design

A total of 12 sites in the United States participated in Study NER1006-01/2014 (NOCT). The study is a Phase-3, multicenter, randomized, colonoscopist-blinded study in male and female patients aged 18 to 85 years (inclusive) who were undergoing a screening, surveillance, or diagnostic colonoscopy. The duration of study for each patient was a maximum of 47 days

(including the screening period). The final protocol (Version 7.0) was submitted on June 25, 2015.

The patients were responsible for preparing the study drugs by themselves for administration. NER1006 was administered in a 2-day evening/morning split-dosing regimen.

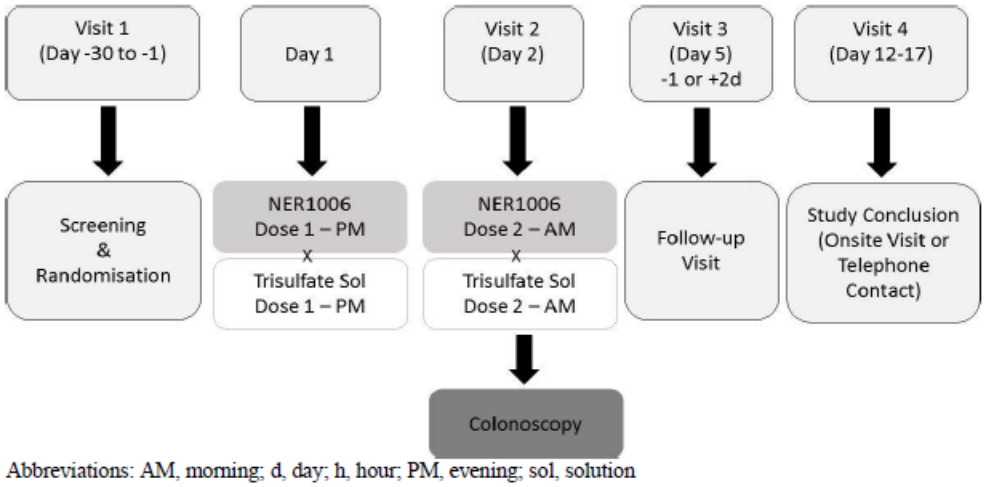
Patients were randomly assigned in a 1:1 ratio to a 2-day split-dosing regimen of either NER1006 or Trisulfate Solution. Patients self-administered their allocated study drug in accordance with the assigned regimen of a 2-day split-dosing regimen of either NER1006 or Trisulfate Solution.

For this split-dosing regimen study, the procedure was advised to be a morning or early afternoon colonoscopy after the patient had completed the intake of the morning dose and required additional water/clear fluid, and had been transferred to the study site. Scheduled evaluations and assessments were to be completed prior to the colonoscopy procedure. The blinded colonoscopist conducted the colonoscopy. A colonoscopy was regarded as complete when the ileo-cecal valve was visualized. If the colonoscopy was incomplete (i.e. the ileo-cecal valve was not visualized), the anatomical position of the end of the scope at the time of termination of the procedure was to be documented. Segmental cleansing was to be assessed initially by the blinded colonoscopist at the study site using the HCS. The HCS grade was automatically computed from the scores entered in the electronic case report form (eCRF). Video recordings of each colonoscopy were then sent to a central facility. A central colonoscopist (first reader) performed an independent assessment of the segmental cleansing using the HCS. As before, the HCS grade was automatically computed from the scores entered in the eCRF.

If the two assessments of overall HCS bowel cleansing efficacy success or failure matched, the first reader's results were to be used for the primary and secondary endpoint analysis. If the two assessments differed, a second central colonoscopist (second reader) viewed the video recording and performed an independent assessment of the segmental cleansing using the HCS, and the results of this assessment were to be used for the primary and secondary endpoint analysis. The central readers were blinded to the previous assessments of colon cleansing.

The overall and segmental polyp count and PDR were determined by the site colonoscopist. The overall and segmental adenoma count and ADR were determined from the examination results of lesion biopsies performed post-colonoscopy by a pathologist. In each case, these assessments were regarded as the final counts and rates to be included in the eCRF and statistical analysis. The pathologist also recorded the number of polyps identified by histology as carcinomas.
The assessment of bowel cleansing efficacy using the BBPS was performed by the first and if applicable, second central reader (in accordance with the independent assessment to be used for the primary endpoint analysis).

Figure 1: Study Schedule (Study NOCT)



Abbreviations: AM, morning; d, day; h, hour; PM, evening; sol, solution

Source: Sponsor's Study Report, Page 28 of 483

3.2.2 Controlling for Multiplicity of Endpoints

The sponsor pre-specified the following multiple testing procedure in Study NOCT:
To assess the alternative primary endpoints for non-inferiority, the Sponsor used the Hochberg procedure as follows:
• If the lower 1-sided 97.5% confidence limits (CLs) for both alternative primary endpoints excluded a 10% or greater difference in favor of Trisulfate Solution, then non-inferiority was concluded for both endpoints.
• If, however, one of the alternative primary endpoints had a lower 1-sided 97.5% CL that did not exclude a 10% difference in favor of Trisulfate Solution, then non-inferiority for the other alternative primary endpoint was only to be declared if the lower 1-sided 98.75% CL for that alternative primary endpoint excluded a 10% or greater difference in favor of Trisulfate Solution.
With respect to the assessment of superiority, the following closed test procedure was used:

• If both alternative primary endpoints demonstrated non-inferiority:
- and both showed a significant advantage for NER1006 relative to Trisulfate Solution with 1-sided P values <0.025, then NER1006 was to be declared superior for both alternative primary endpoints
- and one had a 1-sided P value ≥0.025, then the other alternative primary endpoint, to be declared superior, must have achieved a 1-sided P value <0.0125 o and both had a 1-sided P value ≥0.025, then superiority could not be declared for either endpoint

• If only one alternative primary endpoint demonstrated non-inferiority in terms of the 1-sided 98.75% CL excluding a 10% difference in favor of Trisulfate Solution, then, to be declared superior, the non-inferior alternative primary endpoint was also to have achieved a 1-sided P value <0.0125.

• If both alternative primary endpoints failed to show non-inferiority, then both endpoints were deemed inferior and formal superiority testing of these endpoints was stopped.

If either of the alternative primary endpoints showed non-inferiority, then the four key secondary endpoints were to be evaluated hierarchically in the order pre-specified. If non-inferiority was not met for either of the alternative primary endpoints, then the four key secondary endpoints were to be summarized descriptively. P values were to be determined; however, the results were not to be interpreted as showing formal significance.

If either of the alternative primary endpoints showed non-inferiority, then the four key secondary endpoints were to be evaluated hierarchically in the order pre-specified. For the first key secondary endpoint, if the 1-sided 97.5% CL for difference in the proportion of events in NER1006 compared to Trisulfate Solution excluded a 10% or greater difference in favor of Trisulfate Solution, then non-inferiority was concluded.

Further, if the difference in the proportion of events in NER1006 compared to Trisulfate Solution yielded a 1-sided P value <0.025, superiority was concluded. Formal testing was to proceed to the next key secondary endpoint in the hierarchy in the same fashion only if the preceding key secondary endpoint had at least met non-inferiority.

If non-inferiority was not met for either of the alternative primary endpoints, then the four key secondary endpoints were to be summarized descriptively. P values were determined; however, the results of such determinations were not interpreted as showing formal significance.
If non-inferiority was met for either of the alternative primary endpoints and the hierarchical testing was carried out, but non-inferiority was not met for one of the key secondary endpoints, then the remaining key secondary endpoints were to be summarized descriptively.

The prospective use of the Hochberg procedure to control type I error meant that if either alternative primary endpoint was met the study would be a success.

Reviewer's Remark: The multiple testing procedure proposed by the sponsor does not provide strong control of type I error rate, see comments earlier in this review.

3.2.3 Analyses and Results for Study NOCT

Disposition of Subjects:
A total of 621 patients (full analysis set) were randomly assigned to receive study drug (310 patients in the NER1006 treatment group and 311 patients in the Trisulfate Solution treatment group).

Table 2: Disposition of Patients (Study NOCT)

	Trisulfate Solution (N=311) n (%)	NER1006 (N=310) n (%)
Total number of patients		
Randomized	311 (100.0)	310 (100.0)
Completed study	261 (83.9)	255 (82.3)
Discontinued study	50 (16.1)	55 (17.7)
Primary reason for discontinuation from study		
Adverse event	1 (0.3)	1 (0.3)
Non-compliant	1 (0.3)	2 (0.6)
Lack of efficacy	1 (0.3)	0
Lost to follow-up	2 (0.6)	4 (1.3)
Withdrawal of patient	17 (5.5)	15 (4.8)
Other	28 (9.0)	33 (10.6)

Source: Sponsor's Study Report, Page 64 of 483

A total of 255 (82.3%) patients in the NER1006 treatment group and 261 (83.9%) patients in the Trisulfate Solution treatment group completed the study. Fifty-five (17.7%) patients discontinued the study in the NER1006 treatment group and the most frequently reported reasons for discontinuation were other reasons (33 [10.6%] patients) and withdrawal of patient (15 [4.8%] patients). Fifty (16.1%) patients discontinued the study in the Trisulfate Solution treatment group with other reasons (28 [9.0%] patients) and withdrawal of patient (17 [5.5%] patients) being the most frequently reported reasons for discontinuation. Table 2 summarizes these results. The 'Other' reasons in both treatment groups primarily included patients meeting the exclusion criterion of GFR <60 mL/min: 21 of 33 patients in the NER1006 treatment group and 16 of 28 patients in the Trisulfate Solution treatment group. One patient (0.3%) each in the NER1006 and Trisulfate Solution treatment groups discontinued the study due to an AE. Two patients (0.6%) in the NER1006 treatment group and one patient (0.3%) in the Trisulfate Solution treatment group discontinued the study as they were considered to be noncompliant based on investigator's assessment at the end of study.

The main efficacy analysis was performed on the mFAS that comprised 276 (89.0%) patients in the NER1006 treatment group and 280 (90.0%) patients in the Trisulfate Solution treatment group.

Demographics and Baseline Characteristics:
Table 3 shows the demographics and baseline characteristics of subjects in Study NOCT. Overall, demographic characteristics of subjects appeared to be balanced between the two treatment arms.

Table 3: Demographics and Baseline Characteristics (Study NOCT)

	Trisulfate Solution (N=311)	NER1006 (N=310)
Age (years)		
n	311	310
Mean (SD)	57.3 (10.56)	57.7 (10.36)
Median	58.0	58.0
Minimum, maximum	18, 81	22, 86
Age group (years), n (%)		
≤65	248 (79.7)	249 (80.3)
>65	63 (20.3)	61 (19.7)
Sex, n (%)		
Male	169 (54.3)	158 (51.0)
Female	142 (45.7)	152 (49.0)
Race, n (%)		
White or Caucasian	252 (81.0)	258 (83.2)
Black	37 (11.9)	45 (14.5)
Asian	17 (5.5)	7 (2.3)
American Indian or Alaska native	1 (0.3)	0
Native Hawaiian or Other Pacific Islander	1 (0.3)	0
Other	3 (1.0)	0
Ethnicity, n (%)		
Hispanic or Latino	40 (12.9)	19 (6.1)
Not Hispanic or Latino	271 (87.1)	291 (93.9)
Height (cm)		
n	311	310
Mean (SD)	170.34 (10.687)	169.98 (10.156)
Median	170.20	170.00
Minimum, maximum	142.2, 203.0	142.2, 198.1
Weight (kg)		
n	311	310
Mean (SD)	86.51 (19.172)	85.91 (18.020)
Median	85.90	84.65
Minimum, maximum	42.9, 143.8	46.6, 154.2

Source: Sponsor's Study Report, Page 71 of 483

The mean (SD) age of patients was 57.7 (10.36) years in the NER1006 treatment group and 57.3 (10.56) years in the Trisulfate Solution treatment group. There were similar percentages of patients ≤65 years of age in both the treatment groups: 249 [80.3%] patients in the NER1006 treatment group and 248 [79.7%] patients in the Trisulfate Solution treatment group. A similar percentage of male patients (51.0% in the NER1006 treatment group and 54.3% in the Trisulfate Solution treatment group) compared with female patients (49.0% in the NER1006 treatment group and 45.7% in the Trisulfate Solution treatment group) were observed in the two treatment groups with slightly more males than females. The majority of patients were white or Caucasian (258 [83.2%] patients in the NER1006 treatment group and 252 [81%] patients in the Trisulfate Solution treatment group). The mean (SD) weight of patients was 85.91 (18.02) kg in the NER1006 treatment group and 86.51 (19.17) kg in the Trisulfate Solution treatment group.

Analysis of the Primary Efficacy Endpoints:
Tables 4A and 4B show the results of the primary endpoint, Overall Harefield Cleansing Scale, by the Sponsor and the reviewer for Study NOCT, respectively. The Sponsor used the mFAS population and this reviewer used all randomized subjects.

Table 4A: Sponsor's Analysis of Efficacy (Response Rates) – NOCT Study

	Trisulfate Solution (N=280)	NER1006 (N=276)
Harefield Cleansing Scale, n (%)		
Successful[a]	238 (85.0)	235 (85.1)
Failure	42 (15.0)	41 (14.9)
Difference in Harefield Cleansing Scale success rate[b]		0.14
97.5% 1-sided lower confidence limit		–8.15
98.75% 1-sided lower confidence limit		–9.33
P value[c]		0.528

[a] Grades A and B were classified as successful cleansing and grades C and D were classified as failures.
[b] Difference was calculated as NER1006 success rate – Trisulfate Solution success rate. Rate was defined as the number of patients with successful cleansing divided by the number of patients in the modified full analysis set converted to a percentage.
[c] 1-sided *P* value was obtained from Fisher's exact test. The comparison was with the difference in rate between NER1006 and Trisulfate Solution versus a hypothesized difference of zero.

Source: Sponsor's Clinical Study Report Page 73 of 483

Based on Sponsor's findings, with regard to the alternative primary endpoint of bowel cleansing efficacy in the *overall colon*, 235 (85.1%) patients in the NER1006 treatment group as compared with 238 (85.0%) patients in the Trisulfate Solution treatment group achieved successful bowel cleansing. Non-inferiority of NER1006 to Trisulfate Solution was proven with treatment difference of +0.14%and 97.5% 1-sided lower CL of –8.15%. Superiority of NER1006 to Trisulfate Solution was not demonstrated statistically (1-sided P value 0.528).

Table 4B: Reviewer's Analysis of Efficacy (Response Rates) – NOCT Study

Primary Endpoint*	NER1006 2-Day	Trisulfate 2_Day	Difference 95% CI
Overall Colon			
Reviewer (n=621)	235/310 (75.8%)	238/311 (76.5%)	-0.7% (-7.4%, 6.0%)

Alternative Primary 1 Overall Harefield Cleansing Scale Yes/No
Sponsor used mFAS; the reviewer used all randomized subjects
The NI margin was set to 10%
$\chi 2$ test (Proc Freq in SAS, normal distribution)

Based on the statistical reviewer's analyses, regarding the primary endpoint of bowel cleansing efficacy in the overall colon, 235 (75.8%) patients in the NER1006 treatment group as compared with 238 (76.5%) patients in the Trisulfate Solution treatment group achieved successful bowel cleansing. Non-Inferiority of NER1006 to Trisulfate was shown with the difference of -0.7% and 95% CI of (-7.4% to 6%), using the Fisher's exact test.

With regard to the primary endpoint of cleansing rate in Ascending Colon, "Excellent plus Good" cleansing was achieved in 99 (31.9%) patients in the NER1006 treatment group as compared with 82 (26.4%) patients in the Trisulfate Solution treatment group. Non-inferiority of

NER1006 to Trisulfate Solution was shown with a difference of 5.6% and 95% CI of (-1.6%, 12.7%), using Fisher's exact test. Superiority of NER1006 to Trisulfate Solution was not demonstrated.

Table 4C shows the results of the second primary endpoint (Harefield Cleansing Scale in the Colon Ascendens) for Study NOCT using mFAS population.

Table 4C: Sponsor's Analysis of Efficacy for the Second Primary Endpoint (Harefield Cleansing Scale in the Colon Ascendens) (mFAS)– NOCT Study

	Trisulfate Solution (N=280)	NER1006 (N=276)
Harefield Cleansing Scale, n (%)		
Excellent plus good[a]	82 (29.3)	99 (35.9)
Adequate plus failure	198 (70.7)	177 (64.1)
Difference in Harefield Cleansing Scale excellent plus good rate[b]		6.58
97.5% 1-sided lower confidence limit		−1.69
98.75% 1-sided lower confidence limit		−2.88
P value[c]		0.059

[a] Score of 4 corresponded to excellent cleansing, score of 3 to good cleansing, score of 2 to adequate cleansing, and scores of 1 and 0 to failure in cleansing.

[b] Difference was calculated as NER1006 excellent plus good rate – Trisulfate Solution excellent plus good rate. Rate was defined as the number of patients with excellent plus good cleansing divided by the number of patients in the modified full analysis set converted to a percentage.

[c] 1-sided *P* value was obtained from Fisher's exact test. The comparison was with the difference in rate between NER1006 and Trisulfate Solution versus a hypothesized difference of zero.

With regard to the second co-primary, cleansing rate in the colon ascendens, "Excellent plus Good" cleansing was achieved in 99 (35.9%) patients in the NER1006 treatment group as compared with 82 (29.3%) patients in the Trisulfate Solution treatment group. Non-inferiority of NER1006 to Trisulfate Solution was proven (treatment effect +6.58%, 97.5% 1-sided lower CL –1.69%). Superiority of NER1006 to Trisulfate Solution was not demonstrated statistically (1-sided P value 0.059).

Analysis of the Secondary Efficacy Endpoints:
Since superiority was not demonstrated for the primary endpoints, the formal hierarchical testing of the key secondary endpoints is stopped.
Also, non-inferiority was not shown for the first key secondary endpoint, the adenoma detection rate (ADR) in the colon ascendens, since the lower bound of 95% CI is below 10%; therefore, as indicated by the sponsor, the remaining efficacy data are discussed descriptively.

Table 5A: Adenoma Detection Rate in Colon Ascendens and Overall Colon (mFAS)

	Trisulfate Solution (N=280)		NER1006 (N=276)	
	Colon Ascendens	Overall Colon	Colon Ascendens	Overall Colon
Number of adenomas, n (%)				
0	232 (82.9)	182 (65.0)	237 (85.9)	183 (66.3)
1	34 (12.1)	56 (20.0)	29 (10.5)	45 (16.3)
2	11 (3.9)	17 (6.1)	8 (2.9)	21 (7.6)
>2	3 (1.1)	25 (8.9)	2 (0.7)	27 (9.8)
ADR[a]	17.14	35.00	14.13	33.70
Difference in ADR (95% 2-sided CI)			−3.01 (−11.36, 5.28)	−1.30
P value[b]			0.863	0.660
Number of carcinomas, n (%)				
0		280 (100.0)		276 (100.0)
1		0		0
2		0		0
>2		0		0

Abbreviations: ADR, adenoma detection rate; CI, confidence interval

[a] ADR was defined as the number of patients with at least one adenoma divided by the number of patients in the modified full analysis set.

[b] 1-sided *P* value was obtained from Fisher's exact test. The comparison was with the difference in rate between NER1006 and Trisulfate Solution versus a hypothesized difference of zero.

Source: Sponsor's Study Report, Page 79 of 483

The results for ADR in colon ascendens and overall colon are shown in Tables 5A which show the number of subjects with a specific number of lesions in each treatment arm.

Table 5B shows the Sponsor's results of polyp detection rate in colon ascendens and overall colon based on mFAS population.

Table 5B: Polyp Detection Rate in Colon Ascendens and Overall Colon (mFAS)

	Trisulfate Solution (N=280)		NER1006 (N=276)	
	Colon Ascendens	Overall Colon	Colon Ascendens	Overall Colon
Number of polyps, n (%)				
0	213 (76.1)	144 (51.4)	225 (81.5)	150 (54.3)
1	51 (18.2)	70 (25.0)	36 (13.0)	61 (22.1)
2	11 (3.9)	26 (9.3)	11 (4.0)	24 (8.7)
>2	5 (1.8)	40 (14.3)	4 (1.4)	41 (14.9)
PDR[a]	23.93	48.57	18.48	45.65
Difference in PDR			−5.45	−2.92
P value[b]			0.953	0.781

Abbreviations: PDR, polyp detection rate; CI, confidence interval

[a] PDR was defined as the number of patients with at least one polyp divided by the number of patients in the modified full analysis set.

[b] 1-sided *P* value was obtained from Fisher's exact test. The comparison was with the difference in rate between NER1006 and Trisulfate Solution versus a hypothesized difference of zero.

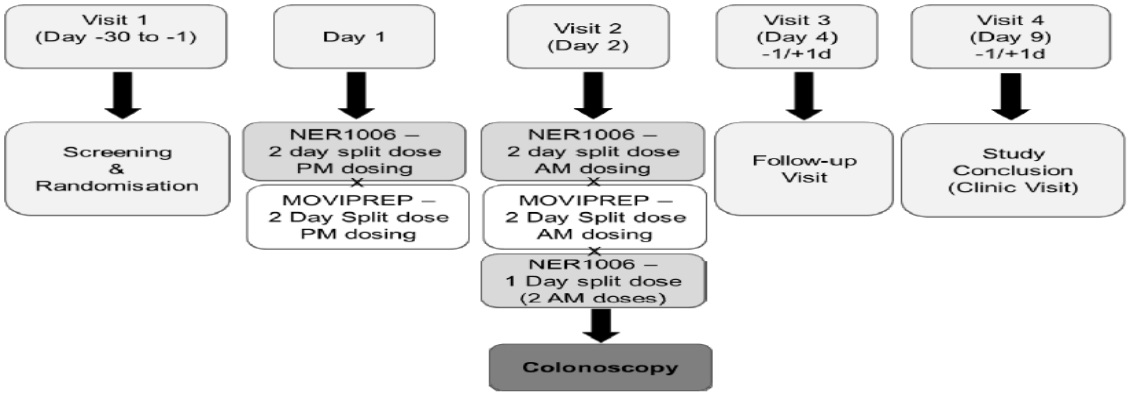
Source: Sponsor's Study Report Page 80 of 483

3.3 Study MORA

3.3.1 Study Design

A total of 29 Sites in Belgium, France, Germany, Italy, Poland, Spain and United Kingdom participated in this study. This was a multicenter, randomized, colonoscopist-blinded study in male and female patients aged 18 to 85 years (inclusive) who were undergoing a screening, surveillance, or diagnostic colonoscopy. Patients were randomly assigned in a 1:1:1 ratio to 2-Day Split-dosing NER1006: 2-Day Split-Dosing MOVIPREP: 1-Day Morning Split-Dosing NER1006. Patients self-administered their allocated study drug in accordance with their assigned regimen. For patients in the NER1006 and MOVIPREP 2-Day Split-Dosing groups, the colonoscopy procedure was advised to be in the morning or early afternoon after the patient had completed the intake of both doses of the study drug and additional clear fluid, and had been transferred to the study site. For the NER1006 1-Day Morning Split-Dosing group, the colonoscopy procedure was advised to be in the early afternoon after the patient had completed the intake of both doses of the study drug and additional clear fluid, and had been transferred to the study site. Scheduled evaluations and assessments were to be completed prior to the colonoscopy procedure. The blinded colonoscopist conducted the colonoscopy.

Figure 2: The Study Schedule Schematic (Study MORA)



Abbreviation: AM, morning; d, day; PM, evening
Source: Sponsor's Study Report, Page 8 of 620

3.3.2 Controlling for Multiplicity of Endpoints and Treatment Arms

The method using to control for the two co-primary endpoints were similar to that of Study NOCT. To accommodate the comparison of two NER1006 regimens, a hierarchical testing approach was used, whereby NER1006 2-Day was assessed first and, if successful, then NER1006 1-Day was evaluated. Statistical assessment of superiority was performed if non-inferiority was met for at least one of the alternative primary endpoints for NER1006 2-Day or, additionally, for NER1006 1-Day. The prospective use of the Hochberg procedure to control type I error meant that if either alternative primary endpoint was met the study would be a success.

If either of the alternative primary endpoints showed non-inferiority, then the four key secondary endpoints were to be evaluated hierarchically in the order pre-specified.

Reviewer's Remark: Multiple testing proposed by the sponsor does not control type I error rate. In particular, in this case, key secondary endpoints for comparison of NER1006 2-Day with active comparator, and primary endpoint for comparison of NER1006 1-Day with active comparator can't be assessed unless superiority of NER1006 2-Day established in both primary endpoints.

3.3.3 Analysis and Results for Study MORA

An interactive web response system (IWRS) was used for the randomization. Biostatistics generated the randomization schedule for IWRS, which links sequential patient randomization numbers to treatment codes. The randomization was not stratified and the site colonoscopist and central reader(s) were blinded. The randomization numbers were blocked, and within each block the same numbers of patients were allocated to each treatment group.

Disposition of Subjects:
An overall 850 patients were planned to be randomly assigned to study drug. A total of 849 patients (full analysis set) were randomized to receive study drug (283 patients in each treatment arms. Table 6 summarizes the disposition of the subjects by treatment group.

Table 6: Disposition of Patients - Study MORA

	MOVIPREP (N=283) n (%)	NER1006 2-Day Split-Dosing (N=283) n (%)	NER1006 1-Day Morning Split-Dosing (N=283) n (%)
Total number of patients			
Randomized	283 (100.0)	283 (100.0)	283 (100.0)
Completed	259 (91.5)	260 (91.9)	262 (92.6)
Discontinued	24 (8.5)	23 (8.1)	21 (7.4)
Primary reason for discontinuation from study			
Adverse event	1 (0.4)	0	0
Non-compliant	2 (0.7)	1 (0.4)	1 (0.4)
Lost to follow up	0	1 (0.4)	1 (0.4)
Non-compliance with study drug	1 (0.4)	0	0
Withdrawal of patient	10 (3.5)	12 (4.2)	11 (3.9)
Other	10 (3.5)	9 (3.2)	8 (2.8)

Source: Sponsor's MORA Clinical Study Report, Page 71 of 620

A total of 260 (91.9%) patients in the NER1006 2-Day Split-Dosing treatment group, 262 (92.6%) patients in the NER1006 1-Day Morning Split-Dosing treatment group, and 259 (91.5%) patients in the MOVIPREP treatment group completed the study. Twenty-three (8.1%) patients discontinued the study in the NER1006 2-Day Split-Dosing treatment group, and the most frequently reported reasons for discontinuation were withdrawal of patient (12 [4.2%] patients) and other reasons (9 [3.2%] patients). Twenty-one (7.4%) patients discontinued the study in the NER1006 1-Day Morning Split-Dosing treatment group, and the most frequently reported reasons

for discontinuation were withdrawal of patient (11 [3.9%] patients) and other reasons (8 [2.8%] patients). Twenty-four (8.5%) patients discontinued the study in the MOVIPREP treatment group with withdrawal of patient and other reasons (each with 10 [3.5%] patients) being the most frequently reported reasons for discontinuation. The 'Other' reasons in the three treatment groups primarily included meeting exclusion criteria, screening failure, and ECG abnormalities. Two patients (0.7%) in the MOVIPREP treatment group and 1 patient (0.4%) each in the NER1006 2-Day Split-Dosing and NER1006 1-Day Morning Split-Dosing treatment groups discontinued from the study as they were considered to be non-compliant to study procedures based on the investigator's assessment at the end of the study. Similarly, 1 patient (0.4%) each in the NER1006 2-Day Split-Dosing and NER1006 1-Day Morning Split-Dosing treatment groups was discontinued due to lost to follow-up. One patient (0.4%) in the MOVIPREP treatment group discontinued the study due to an AE.

Demographics and Baseline Characteristics:
Overall, demographic characteristics appeared to be balanced among the three treatment groups. Table 7 summarizes these results.

Table 7: Demographics and Baseline Characteristics

	MOVIPREP (N=283)	NER1006 2-Day Split-Dosing (N=283)	NER1006 1-Day Morning Split-Dosing (N=283)
Age (years)			
n	283	283	283
Mean (SD)	54.3 (12.48)	56.3 (12.03)	54.9 (13.21)
Median	56.0	57.0	57.0
Minimum, maximum	22, 84	18, 81	20, 79
Age group (years), n (%)			
≤65	235 (83.0)	209 (73.9)	219 (77.4)
>65	48 (17.0)	74 (26.1)	64 (22.6)
Sex, n (%)			
Male	144 (50.9)	120 (42.4)	131 (46.3)
Female	139 (49.1)	163 (57.6)	152 (53.7)
Race, n (%)			
White or Caucasian	280 (98.9)	275 (97.2)	279 (98.6)
Black	1 (0.4)	6 (2.1)	3 (1.1)
Asian	2 (0.7)	0	0
American Indian or Alaska native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Other	0	2 (0.7)	1 (0.4)
Ethnicity, n (%)			
Hispanic or Latino	82 (29.0)	89 (31.4)	71 (25.1)
Not Hispanic or Latino	201 (71.0)	194 (68.6)	212 (74.9)
Height (cm)			
n	280	281	283
Mean (SD)	169.16 (9.154)	167.74 (9.455)	168.65 (8.878)
Median	169.00	168.00	168.00
Minimum, maximum	150.0, 195.0	148.0, 198.0	150.0, 191.0
Weight (kg)			
n	280	281	282
Mean (SD)	75.80 (14.993)	77.19 (16.383)	77.21 (15.755)
Median	74.00	75.00	75.75
Minimum, maximum	44.0, 138.0	43.0, 144.0	42.0, 151.0

Note: As per the eCRF, Hispanic or Latino was defined as any person of Spanish, Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of their race.
Source: Sponsor's Study Report, Page 80 of 620

The mean (SD) age of patients was 56.3 (12.03) years in the NER1006 2-Day Split-Dosing treatment group, 54.9 (13.21) years in the NER1006 1-Day Morning Split-Dosing treatment group, and 54.3 (12.48) years in the MOVIPREP treatment group. There were a greater percentage of patients ≤65 years of age in the MOVIPREP treatment group (235 [83.0%] patients) compared with the NER1006 1-Day Morning Split-Dosing treatment group (219 [77.4%] patients) and NER1006 2-Day Split-Dosing treatment group (209 [73.9%] patients). There were greater percentages of female patients in the NER1006 2-Day Split-Dosing treatment group (163 [57.6%] patients) and NER1006 1-Day Morning Split-Dosing treatment group (152 [53.7%]

patients) compared with percentage of male patients (120 [42.4%] patients and 131 [46.3%] patients, respectively). A similar percentage of male (144 [50.9%]) patients and female (139 [49.1%]) patients were observed in the MOVIPREP treatment group. The majority of patients were white or Caucasian (275 [97.2%] patients in the NER1006 2-Day Split-Dosing treatment group, 279 [98.6%] patients in the NER1006 1-Day Morning Split-Dosing treatment group, 280 [98.9%] patients in the MOVIPREP treatment group). The mean (SD) weight of patients was similar in all treatment groups (77.19 [16.383] kg in the NER1006 2-Day Split-Dosing treatment group, 77.21 [15.755] kg in the NER1006 1-Day Morning Split-Dosing treatment group, and 75.80 [14.993] kg in the MOVIPREP treatment group).

Analysis of the Primary Efficacy Endpoints:
Tables 8A, 8B, and 8C show the results of both alternative primary endpoints for Study MORA based on the Sponsor's and the reviewer's analyses, respectively. The Sponsor used the mFAS population and this reviewer used all randomized subjects.

Table 8A: Sponsor's Analysis of the First Primary Efficacy Endpoint (Response Rates in the Overall Colon) – Study MORA

	MOVIPREP (N=272)	NER1006 2-Day Split-Dosing (N=275)	NER1006 1-Day Morning Split-Dosing (N=275)
Harefield Cleansing Scale, n (%)			
Successful[a]	238 (87.5)	253 (92.0)	245 (89.1)
Failure	34 (12.5)	22 (8.0)	30 (10.9)
Difference in Harefield Cleansing Scale success rate[b]		4.50	1.59
97.5% 1-sided lower confidence limit		−4.00	−6.91
98.75% 1-sided lower confidence limit		−5.20	−8.10
P value[c]		0.055	0.328

[a] Grades A and B were classified as successful cleansing, and grades C and D were classified as failures.
[b] Difference was calculated as NER1006 success rate – MOVIPREP success rate. Rate was defined as the number of patients with successful cleansing divided by the number of patients in the modified full analysis set converted to a percentage.
[c] 1-sided *P* value was obtained from Fisher's exact test. The comparison was with the difference in rate between NER1006 and MOVIPREP versus a hypothesized difference of zero.

Source: Sponsor's Clinical Study Report Table 11-4, Page 83 0f 620

Based on the Sponsor's findings, with regard to the alternative primary endpoint of bowel cleansing efficacy in the overall colon, 253 (92.0%) patients in the NER1006 2-Day Split-Dosing treatment group and 245 (89.1%) patients in the NER1006 1-Day Morning Split-Dosing treatment group as compared with 238 (87.5%) patients in the MOVIPREP treatment group achieved successful bowel cleansing. Non-inferiority of NER1006 2-Day Split-Dosing treatment to the MOVIPREP treatment was established with treatment effect +4.50%, and 97.5% 1-sided lower CL –4.00%. Superiority of NER1006 2 Day Split Dosing treatment to the MOVIPREP treatment was not demonstrated statistically (1-sided P value 0.055). Non-inferiority of NER1006 1-Day Morning Split-Dosing treatment to the MOVIPREP treatment was also proven (treatment effect

+1.59%, 97.5% 1-sided lower CL –6.91%). Superiority of NER1006 1-Day Morning Split-Dosing treatment to the MOVIPREP treatment was not demonstrated statistically (1-sided P value 0.328), therefore, non-inferiority of 2-Day dose can't be tested.

Table 8B: Reviewer's Analysis of Efficacy (Response Rates) – Study MORA

Primary Endpoint*	NER1006 2 Day (n=283)	NER1006 1 Day (n=283)	Moviprep 2 Day (n=283)	Difference 95% CI
First: Overall Colon	253 (89.4%)	245 (86.6%)	238 (84.1%)	1 vs. 3** 5.3% (0.3%, 10.9%)
				2 vs. 3 2.5% (-3.4%, 8.3%)
				1 vs. 2** 2.8% (-2.5%, 8.2%)
Second: Ascending Colon	87 (30.7%)	93 (32.9%)	41 (14.5%)	1 vs. 3 16.3% (9.5%, 23.0%) P<0.001
				2 vs. 3 18.4% (11.5%, 25.2%) P<0.001
				1 vs. 2 -2.1% (-9.8%, 5.6%)

*Alternative Primary 1 Overall Harefield Cleansing Scale Yes/No
Alternative Primary 2 Harefield Cleansing Scale in the Colon Ascendens was analyzed only for exploratory purposes.
**1= NER1006 2 day -- 2= NER1006 1 day -- 3= Moviprep 2 day
The NI margin was set to 10%, $\chi 2$ test (Proc Freq in SAS, normal distribution)
All randomized subjects
Source: Reviewer

Our results for both primary efficacy endpoints were consistent with the Sponsor's results.

Table 8C shows the results of the second primary efficacy endpoint, Harefield Cleansing Scale in the Colon Ascendens, for Study MORA in the mFAS population.

Table 8C: Sponsor's Analysis of the Second Primary Efficacy Endpoint (Response Rates based on Harefield Cleansing Scale in the Colon Ascendens) (mFAS) - Study MORA

	MOVIPREP (N=272)	NER1006 2-Day Split-Dosing (N=275)	NER1006 1-Day Morning Split-Dosing (N=275)
Harefield Cleansing Scale, n (%)			
Excellent plus good[a]	41 (15.1)	87 (31.6)	93 (33.8)
Adequate plus failure	231 (84.9)	188 (68.4)	182 (66.2)
Difference in Harefield Cleansing Scale "Excellent plus Good" rate[b]		16.56	18.74
97.5% 1-sided lower confidence limit		8.11	10.32
98.75% 1-sided lower confidence limit		6.91	9.12
P value[c]		<0.001	<0.001

[a] Score of 4 corresponded to excellent cleansing, score of 3 to good cleansing, score of 2 to adequate cleansing, and scores of 1 and 0 to failure in cleansing.
[b] Difference was calculated as NER1006 excellent plus good rate – MOVIPREP excellent plus good rate. Rate was defined as the number of patients with excellent plus good cleansing divided by the number of patients in the modified full analysis set converted to a percentage.
[c] 1-sided *P* value was obtained from Fisher's exact test. The comparison was with the difference in rate between NER1006 and MOVIPREP versus a hypothesized difference of zero.

With regard to the cleansing rate in the colon ascendens, "Excellent plus Good" cleansing was achieved in 87 (31.6%) patients in the NER1006 2-Day Split-Dosing treatment group and 93 (33.8%) patients in the NER1006 1-Day Morning Split-Dosing treatment group as compared with 41 (15.1%) patients in the MOVIPREP treatment group. Superiority of cleansing in the colon ascendens was demonstrated statistically for NER1006 2-Day Split-Dosing treatment (treatment effect +16.56%, 97.5% 1-sided lower CL 8.11%, 1-sided P value <0.001). Similarly, superiority of cleansing in the colon ascendens was also demonstrated statistically for NER1006 1-Day Morning Split-Dosing treatment (treatment effect +18.74%, 97.5% 1-sided lower CL 10.32%, 1-sided P value <0.001).

Analysis of the Key Secondary Endpoints:
The Sponsor pre-specified four secondary endpoints:

1. 1st Secondary Adenoma Detection Rate (ADR) in Colon Ascendens
2. 2nd Secondary Overall ADR
3. 3rd Secondary Polyp Detection Rate (PDR) in Colon Ascendens
4. 4th Secondary Overall PDR

Since superiority was not demonstrated for both primary endpoints, the formal hierarchical testing of the key secondary endpoints is stopped and the remaining efficacy data are discussed descriptively. For all key secondary endpoints, in the sponsor's analysis, the denominator was based on mFAS. The difference in ADR or PDR was calculated as NER1006 rate − MOVIPREP rate. This reviewer used all randomized subjects for the analyses.

Tables 9A, 9B, 9C show the results of the secondary endpoints for Study MORA by the Sponsor.

Table 9A: Adenoma Detection Rate in Colon Ascendens and Overall Colon (Modified Full Analysis Set)

	MOVIPREP (N=272)		NER1006 2-Day Split-Dosing (N=275)		NER1006 1-Day Morning Split-Dosing (N=275)	
	Colon Ascendens	Overall Colon	Colon Ascendens	Overall Colon	Colon Ascendens	Overall Colon
Number of adenomas, n (%)						
0	250 (91.9)	199 (73.2)	243 (88.4)	202 (73.5)	243 (88.4)	199 (72.4)
1	13 (4.8)	44 (16.2)	21 (7.6)	38 (13.8)	22 (8.0)	43 (15.6)
2	5 (1.8)	15 (5.5)	7 (2.5)	16 (5.8)	7 (2.5)	19 (6.9)
>2	4 (1.5)	14 (5.1)	4 (1.5)	19 (6.9)	3 (1.1)	14 (5.1)
ADR[a]	8.09	26.84	11.64	26.55	11.64	27.64
Difference in ADR[b] (95% 2-sided CI)			3.55 (–4.80, 12.00)	–0.29 (–8.74, 8.02)	3.55 (–4.80, 12.00)	0.80 (–7.65, 9.11)
***P* value[c]**			0.106	0.569	0.106	0.455
Number of carcinomas, n (%)						
0		271 (99.6)		271 (98.5)		273 (99.3)
1		1 (0.4)		4 (1.5)		2 (0.7)
2		0		0		0
>2		0		0		0

Abbreviations: ADR, adenoma detection rate; CI, confidence interval.

[a] ADR was defined as the number of patients with at least one adenoma in the colon ascendens divided by the number of patients in the modified full analysis set.

[b] Difference was calculated as NER1006 rate – MOVIPREP rate.

[c] *P* value was obtained from Fisher's exact test. The comparison was with the difference in rate between NER1006 and MOVIPREP versus a hypothesized difference of zero.

Source: Sponsor's Study Report Page 90 of 620

Table 9B: Polyp Detection Rate in Colon Ascendens and Overall Colon (Modified Full Analysis Set)

	MOVIPREP (N=272)		NER1006 2-Day Split-Dosing (N=275)		NER1006 1-Day Morning Split-Dosing (N=275)	
	Colon Ascendens	Overall Colon	Colon Ascendens	Overall Colon	Colon Ascendens	Overall Colon
Number of polyps, n (%)						
0	228 (83.8)	151 (55.5)	211 (76.7)	154 (56.0)	224 (81.5)	151 (54.9)
1	28 (10.3)	52 (19.1)	42 (15.3)	55 (20.0)	31 (11.3)	51 (18.5)
2	9 (3.3)	29 (10.7)	15 (5.5)	21 (7.6)	12 (4.4)	32 (11.6)
>2	7 (2.6)	40 (14.7)	7 (2.5)	45 (16.4)	8 (2.9)	41 (14.9)
PDR[a]	16.18	44.49	23.27	44.00	18.55	45.09
Difference in PDR[b] (95% 2-sided CI)			7.10 (–1.41, 15.47)	–0.49 (–8.85, 8.00)	2.37 (–6.12, 10.82)	0.61 (–7.78, 9.09)
***P* value[c]**			0.024	0.579	0.268	0.478

Abbreviations: PDR, polyp detection rate; CI, confidence interval.

[a] PDR was defined as the number of patients with at least one polyp divided by the number of patients in the modified full analysis set.

[b] Difference was calculated as NER1006 rate – MOVIPREP rate.

[c] 1-sided *P* value was obtained from Fisher's exact test. The comparison was with the difference in rate between NER1006 and MOVIPREP versus a hypothesized difference of zero.

Source: Sponsor's Study Report Page 89 of 620

Table 9D: Reviewer's results for Secondary Endpoints for Study MORA (All Randomized Subjects)

Secondary Endpoints:	NER1006 2 Day (n=283)	NER1006 1 Day (n=283)	Moviprep 2 Day (n=283)	Difference 95% CI
	1 or More Lesions Found			
ADR in Colon Ascendens	32 (11.3%)	32 (11.3%)	22 (7.8%)	1 vs. 3 & 2 vs. 3**: 3.5% (-1.3%, 8.4%)
Overall ADR	73 (25.8%)	76 (26.9%)	73 (25.8%)	1 vs. 3: 0% (-7%, 7%)
				2 vs. 3: 0.1% (-6%, 8%)
PDR in Colon Ascendens	64 (22.6%)	51 (18.0%)	44 (15.6%)	1 vs. 3: 7% (0.6%, 13.5%)
				2 vs. 3: 2.5% (-3.7%, 8.6%)
Overall PDR	121 (42.8%)	124 (43.8%)	121 (42.8%)	1 vs. 3: 0% (-8%, 8%) 2 vs. 3: 1% (-7%, 9%)

*1= NER1006 2 day -- 2= NER1006 1 day -- 3= Moviprep 2 day
** The proportions for Arm 1 and Arm 2 were identical
Source: Reviewer. 95% CIs were calculated using normal approximation

Based on the reviewer's analysis, adenomas were detected in the colon ascendens in 32 (11.3%) patients in each of the NER1006 treatment groups as compared with 22 (7.8%) patients in the MOVIPREP treatment group; and in the overall colon in 73 (25.8%) patients in the NER1006 2-Day Split Dosing treatment group, 76 (27.64%) patients in the NER1006 1-Day Morning Split Dosing treatment group, and 73 (26.84%) patients in the MOVIPREP treatment group. Polyps were detected in the colon ascendens in 64 (23.27%) patients in the NER1006 2-Day Split Dosing treatment group and 51 (18.0%) patients in the NER1006 1-Day Morning Split Dosing treatment group as compared with 44 (16.18%) patients in the MOVIPREP treatment group; and in the overall colon in 121 (42.8%) patients in the NER1006 2-Day Split Dosing treatment group, 124 (43.8%) patients in the NER1006 1-Day Morning Split Dosing treatment group, and 121 (42.8%) patients in the MOVIPREP treatment group.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Subgroup Analysis of the Primary Efficacy Endpoint (the overall bowel cleansing success rate)

Tables 9 through 13 show the reviewer's subgroup summary results for the primary efficacy endpoint of "Overall Bowel Cleansing" by gender, age category and country in each study.

4.1.1 Analysis by Gender

Table 10: Analysis by Gender - Study NOCT

Gender	NER1006 2-Day	Trisulfate 2-Day
Females	118/152 (77.6%)	103/142 (72.5%)
Males	117/158 (74.1%)	135/169 (79.9%)

Source: Reviewer

Table 11: Analysis by Gender - Study MORA

Gender	NER1006 2-Day	NER1006 1-Day	Moviprep 2-Day
Females	149/163 (91.4%)	134/152 (88.2%)	110/139 (79.1%)
Males	104/120 (86.7%)	111/131 (84.7%)	128/144 (88.9%)

Source: Reviewer

In general, the response rates in NER 1006 2-Day and NER 1006 1-Day arms were numerically similar than those in active comparator arms in Male and Female subgroups, in both studies (Tables 10 and 11).

4.1.2 Analysis by Age Category

The age category was 65 years and younger vs. older than 65 years. The summary of the response rates is presented in Tables 12 and 13.

Table 12: Analysis by Age Category - Study NOCT

Age Category	NER1006 2-Day	Trisulfate 2-Day
≤ 65	192/249 (77.1%)	197/248 (79.4%)
> 65	43/61 (70.5%)	41/63 (65.1%)

Source: Reviewer

Table 13: Analysis by Age Category - Study MORA

Age Category	NER1006 2-Day	NER1006 1-Day	Moviprep 2-Day
≤ 65	184/209 (88.0%)	191/219 (87.2%)	198/235 (84.3%)
> 65	69/74 (93.2%)	54/64 (84.4%)	40/48 (83.3%)

Source: Reviewer

Overall, the response rates in NER 1006 2-Day and NER 1006 1-Day arms were numerically similar to those in active comparator arms in the age subgroups, in both studies.

4.1.3 Analysis by Country

Study NOCT was conducted in the US.

Table 14 shows the results of the analyses by country for Study MORA.

Table 14: Analysis by Country - Study MORA

Country	NER1006 2-Day	NER1006 1-Day	Moviprep 2-Day
Belgium	29/32 (90.6%)	25/39 (64.1%)	32/39 (82.1%)
Germany	31/34 (91.2%)	37/40 (92.5%)	40/45 (88.9%)
Spain	62/71 (87.3%)	53/59 (89.8%)	56/62 (90.3%)
France	9/12 (75.0%)	6/7 (85.7%)	10/13 (76.9%)
United Kingdom	12/12 (100.0%)	10/16 (62.5%)	5/8 (62.5%)
Italy	15/17 (88.2%)	12/13 (92.3%)	14/19 (73.7%)
Poland	95/105 (90.5%)	102/109 (93.6%)	81/97 (83.5%)

Source: Reviewer

In general, in most of the countries, NER1006 2-Day and NER1006 1-Day showed similar response rates to the response rate of Moviprep 2-Day. Only in Great Britain NER1006 2-Day showed substantially higher response rates compared to the Moviprep 2 day -. However, the sample size in the United Kingdom was small (e.g. Moviprep 2-Day arm had only 8 subjects).

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

The statistical reviewer evaluated the totality of evidence and confirmed the Sponsor's results. The reviewer concluded that the efficacy results of the two studies showed statistical non-inferiority of NER1006 to the comparators for the indication of cleansing of the colon in preparation for colonoscopy (the primary efficacy endpoint of "Overall Bowel Cleansing") in adults.

6 APPENDIX

During the protocol review, at the IND stage, the Agency had issues regarding the statistical analysis plan (SAP) and conveyed these concerns to the Sponsor. Some of our concerns are listed below:

On December 19, 2014
Reviewer's Comment:
Your proposed closed test procedure for multiplicity adjustment regarding non-inferiority testing followed by superiority testing cannot properly control the study-wise type I error under one-sided 2.5% in a strong sense. Hochberg procedure does not hold a separable property that can render some leftover alpha for the next step if any of the hypotheses within the current step fail to be rejected. Moreover, it is unclear how Hochberg procedure could be used on the confidence intervals instead of p-values. Please revise the multiple comparison adjustment method or analytically prove that the study-wise type I error is controlled in a strong sense with your current proposal.

Sponsor's Response:
The Sponsor acknowledges the Agency's comment; however, Norgine believes the proposed closed test procedure appropriately controls the overall Type I error for the following reasons: The use of confidence intervals to assess non-inferiority is directly exchangeable with a 1-sided p-value testing at the $\alpha/2$ level. The confidence interval used to assess non-inferiority (NI) in terms of the lower confidence limit [$100(1-\alpha/2)\%$] for the estimated difference between test and reference products (excluding the predefined margin, $-\Delta$) is directly exchangeable whether the estimated difference between test and reference products is less than the predefined margin, $-\Delta$, (as opposed to less than zero). Therefore, it is possible to use p-value based closed test procedures, like Hochberg to control Type I error even in a non-inferiority setting when the goal is to limit the fraction of false non-inferiority claims to 2.5% or less.

Reviewer's Comment:
You should provide justification of your proposed 10% non-inferiority margin based on historical data. For more details on the study design and non-inferiority margin of a non-inferiority study, please refer to the draft FDA guidance entitled, "Guidance for Industry: Non-Inferiority Clinical Trials," located at the following web address:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM202140.pdf.

Sponsor's Response:
A10% non-inferiority (NI) margin has been proposed between NER1006 and the active comparators for the three Phase II studies (MORA, DAYB and NOCT) based on statistical reason and clinical conclusions from previous studies. Comparative clinical studies of relevant bowel preparation products provide a significant clinical precedence to support the use of a 10% NI margin. The NI margin selected for other relevant approved bowel preparation products was 15%;

therefore, the 10% NI margin selected for the NER1006 Phase III studies is considered relatively conservative and clinically realistic.

Question 6a:
Does the Agency agree that Norgine's strategy for the conduct and the design of the Phase 3 clinical study program (i.e. with studies #1 and #2 as described above, using a trisulfate based bowel preparation and MOVIPREP® as the respective comparator products) will generate data that could support the two dosing regimens, split-dosing (evening/morning) and morning-only dosing?

FDA Response:
Because you have provided only protocol synopses, we cannot provide definitive comments regarding all study design elements. However, we do not agree with your proposed co-primary endpoint model using both an overall success rate and mean change in the HCS for ascending colon. You have not defined what constitutes a successful bowel cleansing based on the HCS within the synopses. Given that the efficacy of the active comparators in your proposed non-inferiority trials was demonstrated using different scales, you will need to justify the use of HCS to establish non-inferiority.

The Sponsor further stated that they are very comfortable that the use of a Hochberg procedure, as laid out in the synopses, provides strong and appropriate control of the overall alpha level. The Sponsor explained that success is only declared if either (i) both endpoints meet non-inferiority (or superiority) at the 0.025 level or (ii) if one p value is greater than 0.025, the other must achieve less than 0.0125. In this manner, an overall Type I error of 0.025 1-sided is maintained. The Sponsor clarified that they chose the Hochberg procedure due to its simplicity, conservative nature and confers readily transparent overall Type I error control.

Dr. Griebel stated that the issue is clinical and not statistical. The Agency indicated that while, technically, there would be a possibility that the product could fail non-inferiority overall and yet meet non-inferiority or better in HCS for the ascending colon, if this was to occur, it would not be sufficient for approval as, from the Agency's perspective, the product would need to be at least non-inferior overall.

Page 21of 71:
As documented in the Sponsor's meeting minutes (SN0008), the Sponsor acknowledges that if overall assessment (designated as Alternative Primary Endpoint 1) does not show noninferiority (or superiority), then the Agency would not deem the studies sufficient for NDA approval from a clinical perspective. Additionally, a statistical assessment of the relationship between overall cleansing and cleansing in the ascending colon using the HCS has been conducted using data from the OPT Phase II study. The assessment demonstrated the correlation between the two alternative primary endpoints to be very high for the NER1006 arms of the study. Therefore, the probability of disparate outcomes in the Phase III studies,

and specifically, of achieving non-inferiority in the ascending colon and not achieving noninferiority overall (as in Scenario 3), is deemed to be very low.

From the Pre-NDA meeting dated December 29, 2015:

- A key consideration regarding the persuasiveness of the data to support noninferiority is whether the scoring was performed during advancement or withdrawal of the scope. As communicated in the Advice Letter, dated September 15, 2014, we expressed concerns that any bowel cleaning that occurred during advancement of the scope would not be captured in the primary efficacy data since the proposed scoring was to be performed during withdrawal of the scope. Any cleaning during advancement of the scope would result in a bias toward noninferiority; therefore, assessment of bowel cleansing after irrigation with the scope is not acceptable to support a successful bowel cleansing endpoint. Furthermore, the Moviprep label states that grading of the colon cleanse occurred twice (during introduction and withdrawal of the colonoscope) and the poorer of the two assessments was used in the primary efficacy analysis. As stated previously, it
- may be difficult to establish noninferiority between NER1006 and the comparator if the scoring method used in the phase 3 trials differs from the scoring used in the trials that supported product labeling for the comparator.

- The endpoint of "Excellent plus Good cleansing rate in the colon ascendens" (b) (4) is important to visualize the mucosa along the entire colon during colonoscopy, as communicated in the EOP2 meeting minutes, dated May 6, 2014. While the data may support individual subjects who met the criteria for success on both overall cleansing and excellent plus good in the ascending colon, the comparator products are not indicated for cleansing in the ascending colon; therefore, demonstrating non-inferiority to a product(s) that is not approved for this specific indication (b) (4) However, we would consider this endpoint further if superiority were demonstrated over the comparator.

- The split-dose regimen of Moviprep during the MORA study is not consistent with the administration instructions in the Moviprep label.

Results of Non-Inferiority and Superiority Testing for Alternative -- Study NOCT Primary and Key Secondary Endpoints (Modified Full Analysis Set)

Type of Endpoint	Endpoint	Non-Inferiority Met	Superiority Met
Alternative Primary 1	Overall Harefield Cleansing Scale	Yes	No
Alternative Primary 2	Harefield Cleansing Scale in the Colon Ascendens	Yes	No
1st Secondary	ADR in Colon Ascendens	No	N/A
2nd Secondary	Overall ADR	N/A	N/A
3rd Secondary	PDR in Colon Ascendens	N/A	N/A
4th Secondary	Overall PDR	N/A	N/A

Abbreviations: ADR, adenoma detection rate; N/A, not applicable; PDR, polyp detection rate

Source: Sponsor's Study Report Page 80 of 483

Results of Non-Inferiority and Superiority Testing for Alternative – Study MORA Primary and Key Secondary Endpoints (Modified Full Analysis Set)

Type of Endpoint	Endpoint	Non-Inferiority Met	Superiority Met
Comparison: MOVIPREP and NER1006 2-Day Split-Dosing			
Alternative Primary 1	Overall Harefield Cleansing Scale	Yes	No
Alternative Primary 2	Harefield Cleansing Scale in the Colon Ascendens	Yes	Yes
1st Secondary	ADR in Colon Ascendens	Yes	No
2nd Secondary	Overall ADR	Yes	No
3rd Secondary	PDR in Colon Ascendens	Yes	Yes
4th Secondary	Overall PDR	Yes	No
Comparison: MOVIPREP and NER1006 1-Day Morning Split-Dosing			
Alternative Primary 1	Overall Harefield Cleansing Scale	Yes	No
Alternative Primary 2	Harefield Cleansing Scale in the Colon Ascendens	Yes	Yes
1st Secondary	ADR in Colon Ascendens	Yes	No
2nd Secondary	Overall ADR	Yes	No
3rd Secondary	PDR in Colon Ascendens	Yes	No
4th Secondary	Overall PDR	Yes	No

Abbreviations: ADR, adenoma detection rate; PDR, polyp detection rate.

Source: Sponsor's Study Report Page 91 of 620

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/s/

SHAHLA S FARR
03/07/2018

GEORGE KORDZAKHIA
03/07/2018

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/SN #:	NDA 209381 / SN 11, 17, 27
Drug Name:	PLENVU (NER1006)
Indication(s):	Bowel preparation prior to colonoscopy
Safety Issue(s):	Orthostatic change, hypotension, sodium, urea, alanine transaminase, creatinine, chloride, potassium
Applicant:	Norgine, B.V.
Date(s):	Receipt of Application: April 13, 2017 Consult Request: May 2, 2017 Day 74 Letter: June 26, 2017 Mid-cycle Review Meeting: September 15, 2017 Wrap –up Meeting: February 22, 2018 Primary Reviews Due: March 2, 2018 Action Date: April 13, 2018 PDUFA Goal Date: May 13, 2018 Completion Date: March 2, 2018
Review Priority:	Standard
Biometrics Division:	Division of Biometrics VII (DBVII)
Statistical Reviewer:	Thanh Van Tran, Ph.D.
Concurring Reviewers:	Clara Y. Kim, Ph.D., Team Leader; Mark Levenson, Ph.D., Division Director
Medical Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Clinical Team:	Sandhya Apparaju, Ph.D.; Tara Altepeter, M.D.
Project Manager:	Lawrence Allen

Keywords: bowel preparation, colonoscopy, shift analysis, difference in mean change, electrolytes, orthostatic, hypotension

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

Norgine B.V. submitted New Drug Application (NDA) 209381 on April 13, 2017 for Plenvu (NER1006), a powder for oral solution to cleanse the colon in preparation for colonoscopy. Acute use at high dosages of a laxative for colon cleansing may result in water and electrolyte imbalances that can be unsafe. The primary disturbance is dehydration followed by sodium overload or depletion, potassium (K) overload or depletion, and chloride (CL) depletion.

This safety review focuses on hypotension (systolic blood pressure < 90 mmHg), orthostatic changes (>20 mmHg), and extreme laboratory parameters for sodium, chloride (CL), alanine transaminase (ALT), urea, creatinine (CREAT), and potassium (K) at scheduled visit 1 (prior to drug administration and colonoscopy), visit 2 (day of colonoscopy), visit 3 (follow-up visit 4 days after the colonoscopy), and visit 4 (follow-up visit 9 days after the colonoscopy). We present comparisons of laboratory and blood pressure parameters between treatments arms to detect extreme values and their persistence after colonoscopy, termed shift analysis and persistence analysis, respectively.

The three studies (NOCT, MORA, DAYB) analyzed in this review are multi-center, randomized, active-controlled, phase III trials designed to study the efficacy, safety, and tolerability of NER1006 versus a comparator. The studies recruited male and female patients 18-85 years who had an indication for screening, surveillance, or diagnostic colonoscopy. The study objectives, endpoints, patient population, eligibility criteria, study visit conduct, procedures, and assessment are similar across studies with minor variations in exclusion criteria. The safety analysis population includes 527 subjects in NOCT study (265 Trisulfate, 262 NER1006 2 day split dosing), 793 subjects in MORA study (262 MOVIPREP, 269 NER1006 1 day split dosing, 262 NER1006 2 day split dosing) and 471 subjects in the DAYB study (238 SP+MS, 233 NER1006 1 day split dosing). For NOCT study and DAYB study, there are no notable imbalances in the demographic characteristics between treatment arms. For MORA study, subject demographic characteristics are generally balanced with the possible exception for the percentage of males (MOVIPREP 52%, NER1006 1 day split dosing 46%, NER1006 2 day split dosing 41%). Laboratory parameters are generally balanced across treatment arms in each study at baseline (visit 1).

The greatest mean absolute change from visit 1 typically occurs at visit 2 for many laboratory parameters. NER1006 has a greater mean absolute change than the comparator at visit 2 for sodium, ALT, and CL in NOCT study; sodium and CL in MORA study; and ALT for DAYB study.

NER1006 has greater percentages of extreme values than the comparator at visit 2 for CL in all studies, for sodium in NOCT and MORA study, and for ALT in NOCT and DAYB study. In contrast to the sponsor's conclusion that extreme shift values for sodium move back towards normal at visits 3 and 4, our analysis of MORA study shows an increase in the percentage of patients with abnormal sodium at visit 4 (NER1006 2 day split dosing 15% (visit 2), 0% (visit 3), 5% (visit 4)). Additionally, percentages of extreme urea values increase from visit 2 to visits 3 and 4 (NOCT NER1006 2 day split dosing 2%, 4%, 5%; DAYB NER1006 1 day split dosing 3%, 5%, 6%). The persistence analysis examining subjects who have extreme laboratory values

at visit 2 and continue to have extreme laboratory values at visit 3 produced low counts of subjects with extreme values that precluded conclusive inference.

For all 3 studies, the percentage of subjects with hypotension (orthostatic or supine systolic blood pressure < 90 mmHg) are less than or equal to 1%, and there is no indication of a difference between treatment arms. Although percentages of orthostatic change > 20 mmHg are small (≤ 6%) across all studies and there are no differences between treatment arms, NER1006 arms consistently have greater ranges of orthostatic change than the comparator at visit 2. These ranges can be as wide as [21, 49] mmHg in NER1006 2 day split dosing arm of the NOCT study. High orthostatic changes are suggestive of significant intravascular volume loss and dehydration.

A major limitation of laboratory parameter analyses is the percentage of subjects with data at visit 1 and a subsequent visit decreases with follow-up time and can be as low as 61% in DAYB study SP+MS treatment arm. Missing data may affect the reliability and generalizability of the estimates for difference in mean change and shift analyses at later visits. Additionally, low counts of laboratory values in the shift and persistence analyses may be insufficient to satisfy the normal approximation in the computation of confidence intervals. Interpretation of differences between treatment arms in the shift and persistence analyses should be conservative. Finally, the studies are not powered for formal hypothesis testing of the safety endpoints considered in this review. Therefore, results should not be considered confirmatory, but as supportive evidence if the same trend persists in multiple studies. We performed many comparisons without adjustment for type I error resulting in a conservative analysis of safety outcomes, i.e., the probability is higher for concluding a safety signal.

This review focuses on comparisons of laboratory and blood pressure parameters between treatments arms to detect extreme values and their persistence after colonoscopy. We have two potential safety concerns. Firstly, NER1006 arms have greater percentages of more extreme sodium (42%), ALT (10%), and CL (26%) values at visit 2 than the comparator. In contrast to the sponsor's conclusion that all extreme shift values for sodium move back towards normal at visits 3 and 4, our findings for sodium and urea may indicate otherwise, at times the percentage of extreme values increase during visits 3 and 4. Secondly, across all studies, NER1006 arms consistently have greater ranges of orthostatic change at visit 2 than the comparator that can be as wide as [21, 49] mmHg.

2 INTRODUCTION

Norgine B.V. submitted New Drug Application (NDA) 209381 on April 13, 2017 for Plenvu (NER1006), a powder for oral solution to cleanse the colon in preparation for colonoscopy. Acute use at high dosages of a laxative for colon cleansing may result in water and electrolyte imbalances that can be unsafe. The Division of Gastroenterology and Inborn Errors Products (DGIEP) consulted Division of Biometrics VII for a safety review of the submission's clinical trial data.

This safety review analyzes hypotension, orthostatic changes, and extreme laboratory parameters for sodium, chloride (CL), alanine transaminase (ALT), urea, creatinine (CREAT), and potassium (K). We focus on comparisons of laboratory and blood pressure parameters between treatments arms to detect extreme values and their persistence after colonoscopy. Unless otherwise stated, all tables and figures belong to our independent analysis of the sponsor's submitted data. Table 1 lists all submitted phase III randomized trials, each containing an active comparator drug, that support this review.

Table 1: Studies included in safety review.

Study Name	Active Comparator Drug	Treatment Period	Study Arms and Sample Size
NER1006-01/2014 (NOCT)	Trisulfate bowel cleaning solution SUPREP	2 days	Trisulfate: 280 NER1006 2 day split dosing: 276
NER1006-02/2014 (MORA)	MOVIPREP	1 or 2 days	MOVIPREP: 272 NER1006 1 day split dosing: 275 NER1006 2 day split dosing: 275
NER1006-03/2014 (DAYB)	sodium picosulfate + magnesium salt CITRAFLEET (SP+MS)	1 day	SP+MS: 251 NER1006 1 day split dosing: 250

Source: Norgine, B.V.'s Module 2.7.3: Clinical Summary - Summary of Clinical Efficacy

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

2.1 Data Sources

The sponsor's NDA application submission can be accessed through the following link: \\CDSESUB1\evsprod\NDA209381\0009. The submitted data are in Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) standards. This review analyzed ADaM data and crosschecked with SDTM data to verify the validity of ADaM data. We also referenced study report Module 2.7.4 Clinical Summary - Summary of Clinical Safety and the sponsor's response, dated August 15, 2017, to information request.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The submitted ADaM data were adequately annotated and organized for data analysis. We were unable to replicate the sponsor's sample size numbers for shift analysis using the description provided in Module 2.7.4 Clinical Summary Tables 2.7.4-26 and 2.7.4-27 because of insufficient details on how the safety analysis set was constructed. The sponsor's response, dated August 15, 2017, to an information request provided clarification on how subjects were selected for the safety analysis, which we applied and were still unable to replicate the sponsor's sample size numbers. The discrepancies are sponsor's N=263 vs. our N=262 for MOVIPREP arm; sponsor's N=241 vs. our N= 238 for SP+MS arm; sponsor's N=235 vs. our N=233 NER1006 1 day split dosing arm.

In addition, the sponsor's derived analysis variable *visitnum* indicated that subjects had laboratory or blood pressure measured before colonoscopy at scheduled visit 2 but included subjects whose measurement times (date and time) are either missing or occurred after colonoscopy started. In NOCT study, the safety analysis sample sizes decreased by at most 15 for any laboratory or blood pressure parameter after excluding subjects whose measurement times are either missing or occurred after colonoscopy started. In MORA and DAYB, the safety analysis sample sizes decreased by at most 4. In Section 3.3.4.3, we present a sensitivity analysis assessing the effect of excluding subjects whose measurement times are either missing or occurred after colonoscopy started.

3.2 Analysis Population

The safety analysis population includes all randomized subjects who received treatment at least once. As stated in the response to information request dated August 15, 2017, the sponsor further restricted the safety analysis population to patients with (a) statistical analysis plan pre-specified laboratory parameters (all lab parameters considered in this review), (b) scheduled visits 1, 2, 3, or 4, and (c) one data record per visit. We applied the same restrictions in our analyses.

3.3 Evaluation of Safety

Unless otherwise stated, all tables and figures belong to our independent analysis of the sponsor's submitted data.

3.3.1 Study Design and Endpoints

The three studies are multi-center, randomized, active-controlled, phase III trials designed to study the efficacy, safety, and tolerability of NER1006 versus a comparator on different dosing regimens summarized in Table 2. The studies recruited male and female patients, 18-85 years old, who had an in indication for screening, surveillance, or diagnostic colonoscopy. The inclusion criteria were the same across studies, and the exclusion criteria were mostly similar across studies with few minor differences. Patients were randomized to NER1006 or the comparator and had the following visit schedule:

Visit 1: screening and randomization
Visit 2: day of colonoscopy
Visit 3: follow-up visit 1-3 days after the colonoscopy
Visit 4: follow-up visit (mandatory clinic visit) 6-8 days after the colonoscopy

Refer to Figure 1 for a summary of the study timeline. Including the screening period, the study duration was at most 40 days. Patients self-administered the treatment according to the dosing regimen and were advised to have their colonoscopy conducted in the morning or early afternoon after the completion of doses.

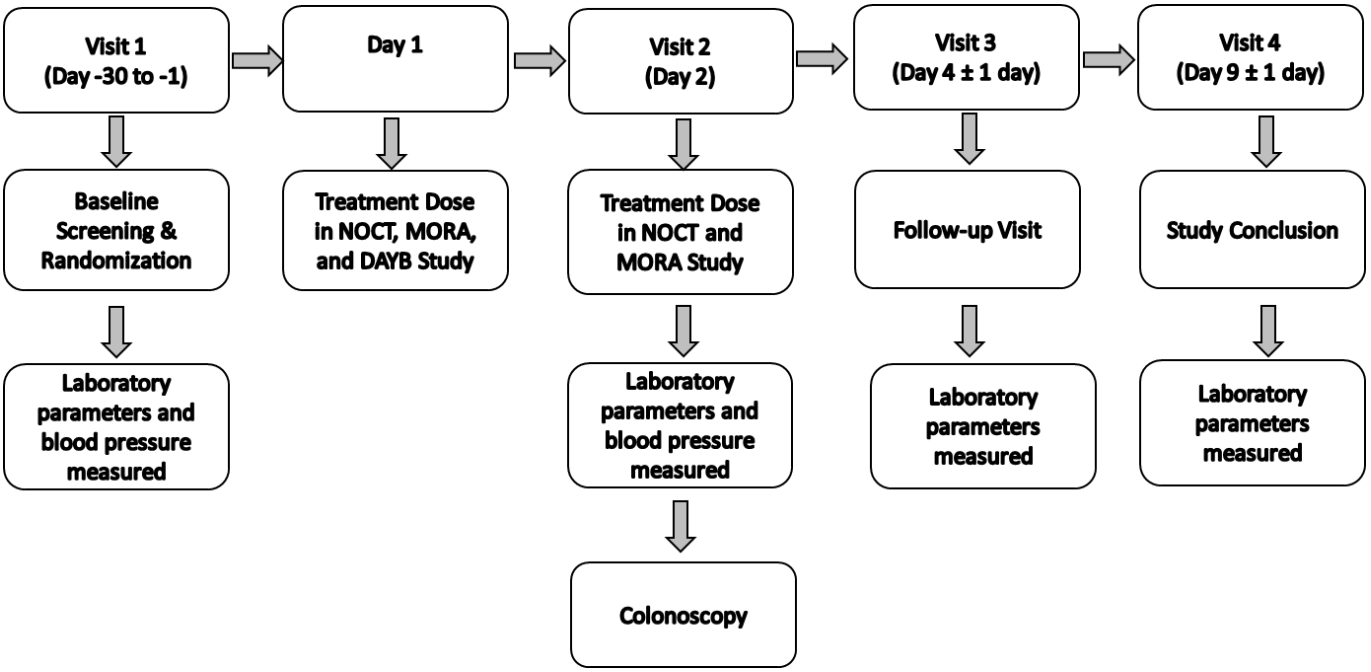
The safety endpoints are laboratory parameters sodium, CL, ALT, urea, CREAT, and K measured at scheduled visits 1-4. Blood pressure endpoints include systolic blood pressure < 90 mmHg and orthostatic change >20 mmHg at visits 1 and 2.

Table 2. NER1006 and comparator dosing regimens.

Treatment	**Phase III study**		
	NOCT	**MORA**	**DAYB**
NER1006:			
2-day split dosing NER1006	NER1006 2 day split dosing	NER1006 2 day split dosing	
1-day split dosing NER1006 (day of colonoscopy)		NER1006 1 day morning split dosing	
1-day split dosing NER1006 (day before colonoscopy)			NER1006 day before only dosing
Control:			
2-day split dosing Control	Trisulfate 2 day split dosing	MOVIPREP 2 day split dosing	
1-day split dosing Control (day before colonoscopy)			SP + MS day before only dosing

Source: Norgine, B.V.'s Analysis Data Reviewer's Guide, Table 1, page 5.

Figure 1. Study timeline indicating the occurrence of treatment, colonoscopy, and the collection of laboratory measurements and vital statistics.



3.3.2 Statistical Methods

The analyses methods were chosen based on a previous safety review of Picoprep, another bowel preparation solutions for colonoscopy, and in consultation with DGIEP. For laboratory values, the following analyses were conducted:

a. Mean Analysis:

- Mean laboratory value and its 95% confidence interval (CI) at visits 1-4.
- Difference in mean change (DMC) from visit 1 and 95% CI for visits 2-4. The comparisons are NER1006 vs. Trisulfate, NER1006 vs. MOVIPREP, and NER1006 vs. SP+MS. To calculate DMC for a given visit post-colonoscopy, the mean absolute change from visit 1 is calculated for each arm and then the difference between each arm is calculated (treatment-control). At visit 1, we calculate the difference in laboratory means between treatment arms.
- Plots of mean absolute change from visit 1 for visits 2-4 by treatment arms.

b. Shift Analysis: Fraction and percentage of laboratory values outside the normal reference range at visits 2-4 among subjects who are normal at visit 1. Risk differences (RD) for NER1006 vs. Trisulfate, NER1006 vs. MOVIPREP, and NER1006 vs. SP+MS and 95% Wald CIs are computed at visits 2-4. RD is calculated as the percentage difference between treatment arms (treatment-control).

For laboratory parameters sodium and K, we are interested in values outside the normal reference ranges. For laboratory parameters CL, ALT, urea, and CREAT, we are interested in values above the normal reference range. Appendix Table 4 shows normal reference ranges, which differ by study site; not all study sites were reported.

c. Persistence Analysis: Fraction and percentage of subjects who are normal at visit 1, have extreme laboratory values at visit 2, and continue to have extreme values at visit 3. RD for NER1006 vs. Trisulfate, NER1006 vs. MOVIPREP, and NER1006 vs. SP+MS and 95% Wald CIs are computed at visit 3. RD is the percentage difference between treatment arms.

For blood pressure, the following analyses were conducted:

a. Hypotension Analysis: Fraction and percentage of subjects with systolic blood pressure < 90 mmHg, an indication of hypotension, at visits1-2. A difference in percentage of extreme values for NER1006 vs. Trisulfate, NER1006 vs. MOVIPREP, and NER1006 vs. SP+MS is assessed using Fisher's exact test.

b. Orthostatic Change Analysis: The fraction and percentage of subjects with a decrease at visit 2 in systolic and separately, diastolic blood pressure >20 mmHg from supine position to standing position, i.e., supine blood pressure – standing blood pressure > 20 mmHg. High orthostatic changes are suggestive of significant intravascular volume loss and dehydration. A difference in percentage of orthostatic change > 20 mmHg for NER1006 vs. Trisulfate, NER1006 vs. MOVIPREP, and NER1006 vs. SP+MS is assessed using Fisher's exact test.

c. Histograms of subjects with systolic and separately, diastolic orthostatic changes > 20 mmHg.

We did not test for a linear trend in extreme laboratory values from visits 1-4, but provided qualitative assessments. For blood pressure, we performed many comparisons without adjustment for type I error resulting in a conservative analysis of safety outcomes, i.e., the probability is higher for concluding a safety signal. For both laboratory and blood pressure values, we did not formally investigate the magnitude of extremeness, but focused on its dichotomous characterization.

The analyses methods described thus far used the sponsor's derived analysis variable *visitnum*, an indicator for the visit that laboratory and blood pressure parameters were measured. We repeated the above analyses methods using time variables, which contain date and time, to exclude any laboratory and blood pressure parameters that occurred after colonoscopy started at visit 2. The results are presented as sensitivity analysis in Section 3.3.4.3.

3.3.3 Subject Disposition, Demographic and Baseline Characteristics

The number of randomized patients are 556 subjects in NOCT study (280 Trisulfate, 276 NER1006 2 day split dosing), 822 subjects in MORA study (272 MOVIPREP, 275 NER1006 1

day split dosing, 275 NER1006 2 day split dosing), and 501 subjects in the DAYB study (251 SP+MS, 250 NER1006 1 day split dosing). Among randomized patients, the remaining patients included in this safety review are 527 subjects in NOCT study (265 Trisulfate, 262 NER1006 2 day split dosing), 793 subjects in MORA study (262 MOVIPREP, 269 NER1006 1 day split dosing, 262 NER1006 2 day split dosing), and 471 subjects in the DAYB study (238 SP+MS, 233 NER1006 1 day split dosing).

The number of subjects with laboratory data at visit 1 and a subsequent visit decreases with follow-up time (sample size columns in Appendix Tables 1-3). The percentage of subjects with data at visit 1 and a subsequent visit may be as low as 77% for treatment arms in NOCT study (NER2 202/262), 73% for treatment arms in MORA study (NER2 191/262), and 61% for treatment arms in DAYB study (SP+MS 142/233). Missing data may affect the reliability and generalizability of the estimates for difference in mean change and shift analyses at later visits. Missing data occurs less frequently in blood pressure data; the percentage of subjects with data at visit 2 in a treatment arm may be as low as 99% (261/262) in NOCT, 85% (224/262) in MORA, and 98% (233/238) in DAYB.

Baseline (visit 1) demographic characteristics by treatment arm are presented in Tables 3-5. Medical history is summarized by selected system organ class (SOC). We consider the absence of an SOC equivalent to not having an SOC. A subject may have different medical conditions under the same SOC, but is counted only once in Tables 3-5. The total number of subjects by arm in MORA and DAYB studies is different compared to the sponsor's study report Module 2.7.4 Tabled 2.7.4-26 and 2.7.4-27 because we applied all the restrictions to the safety analysis population as described in Section 3.2.

For NOCT study and DAYB study, there is no notable imbalance in the demographic characteristics between arms. For MORA study, subject demographic characteristics are generally balanced with the possible exception for the percentage of males (MOVIPREP 52%, NER1006 1 day split dosing 46%, NER1006 2 day split dosing 41%).

Table 3. Study NOCT: Visit 1 demographic characteristics by treatment arm.

	Trisulfate (*N*=265) *n* (%)	NER2 (*N*=262) *n* (%)
Sex		
Male	150 (57)	135 (52)
Age		
Age >= 55	163 (62)	168 (64)
Age mean(sd)	56.9 (10.3)	57.5 (10.3)
Race		
White	219 (83)	221 (84)
Black	25 (9)	34 (13)
Other	21 (8)	7 (3)

Medical History		
Cardiac disorders	22 (8)	17 (6)
Gastrointestinal disorders	184 (69)	185 (71)
Metabolism and nutrition disorders	134 (51)	119 (45)
Endocrine disorders	42 (16)	47 (18)
Nervous system disorders	76 (29)	63 (24)
Renal and urinary disorders	42 (16)	40 (15)

NER2=NER1006 2 day split dosing
N = number of patients included in the safety analysis
n = number of subjects with indicated characteristic

Table 4. Study MORA: Visit 1 demographic characteristics by treatment arm.

	MOVIPREP (*N*=262) *n* (%)	NER1 (*N*=269) *n* (%)	NER2 (*N*=262) *n* (%)
Sex			
Male	136 (52)	124 (46)	108 (41)
Age			
Age >= 55	149 (57)	169 (63)	166 (63)
Age mean (sd)	54.2 (12.7)	54.9 (13.2)	56.6 (11.8)
Race			
White	259 (99)	266 (99)	256 (98)
Black	1 (0)	3 (1)	5 (2)
Other	2 (0)	0 (0)	1 (0)
Medical History			
Cardiac disorders	8 (3)	18 (7)	10 (4)
Gastrointestinal disorders	83 (32)	96 (36)	90 (34)
Metabolism and nutrition disorders	59 (23)	72 (27)	62 (24)
Endocrine disorders	33 (13)	32 (12)	29 (11)
Nervous system disorders	15 (6)	19 (7)	14 (5)
Renal and urinary disorders	10 (4)	15 (6)	10 (4)

NER1=NER1006 1 day split dosing, NER2=NER1006 2 day split dosing
N = number of patients included in the safety analysis
n = number of subjects with indicated characteristic

Table 5. Study DAYB: Visit 1 demographic characteristics by treatment arm.

	SP+MS (*N*=238) *n* (%)	NER1 (*N*=233) *n* (%)
Gender		
Male	76 (32)	85 (36)
Age		
Age >= 55	115 (48)	120 (52)
Age mean(sd)	52.1 (12.9)	54.2 (11.6)
Race		
White	236 (99)	232 (100)
Black	1 (0)	0 (0)
Other	1 (0)	1 (0)
Medical History		
Cardiac disorders	19 (8)	21 (9)
Gastrointestinal disorders	90 (38)	97 (42)
Metabolism and nutrition disorders	53 (22)	45 (19)
Endocrine disorders	31 (13)	20 (9)
Nervous system disorders	18 (8)	15 (6)
Renal and urinary disorders	9 (4)	8 (3)

NER1=NER1006 1 day split dosing
N = number of patients included in the safety analysis
n = number of subjects with indicated characteristic

3.3.4 Results

3.3.4.1 Laboratory Values

3.3.4.1.1 Baseline Analysis

The number of subjects *n* with laboratory values outside the normal reference range among all subjects *N* in a treatment arm for a given laboratory parameter at visit 1 is given in Tables 6-8. Sodium in study MORA and urea in study DAYB may be imbalanced in the percentage of subjects who are outside the normal reference range. Otherwise, laboratory values at visit 1 appear balanced across treatment arms in each study.

Table 6. Study NOCT: Fraction and percentage (*n/N* (%)) of laboratory values outside the normal reference range at visit 1 by lab parameter and treatment arm.

	Trisulfate	NER2
	n/N (p)	*n/N* (*p*)
SODIUM (mmol/L)	16/263 (6)	14/259 (5)
UREA (mmol/L)	17/261 (7)	13/257 (5)
ALT (IU/L)	30/263 (11)	20/257 (8)
CREAT (umol/L)	5/262 (2)	9/258 (3)
CL(mmol/L)	8/263 (3)	9/259 (3)
K (mmol/L)	4/263 (2)	5/259 (2)

NER2=NER1006 2 day split dosing
N = number of patients at visit 1 with data present
n = number of subjects abnormal at visit 1

Table 7. Study MORA: Fraction and percentage (*n/N* (%)) of laboratory values outside the normal reference range at visit 1 by lab parameter and treatment arm.

	MOVIPREP	NER1	NER2
	n/N (%)	*n/N* (%)	*n/N* (%)
SODIUM	3/254 (1)	6/262 (2)	9/257 (4)
UREA	10/256 (4)	18/263 (7)	13/255 (5)
ALT	25/255 (10)	26/262 (10)	26/259 (10)
CREAT	15/256 (6)	12/263 (5)	17/259 (7)
CL	13/254 (5)	17/263 (6)	10/259 (4)
K	8/254 (3)	13/262 (5)	12/257 (5)

NER1=NER1006 1 day split dosing, NER2=NER1006 2 day split dosing
N = number of patients at visit 1 with data present
n = number of subjects abnormal at visit 1

Table 8. Study DAYB: Fraction and percentage (*n/N* (%)) of laboratory values outside the normal reference range at visit 1 by lab parameter and treatment arm.

	SP+MS	NER1
	n/N (%)	*n/N* (%)
SODIUM	13/238 (5)	12/230 (5)
UREA	16/238 (7)	7/232 (3)
ALT	19/238 (8)	24/231 (10)
CREAT	7/238 (3)	6/232 (3)
CL	7/238 (3)	7/231 (3)
K	3/238 (1)	6/230 (3)

NER1=NER1006 1 day split dosing
N = number of patients at visit 1 with data present
n = number of subjects abnormal at visit 1

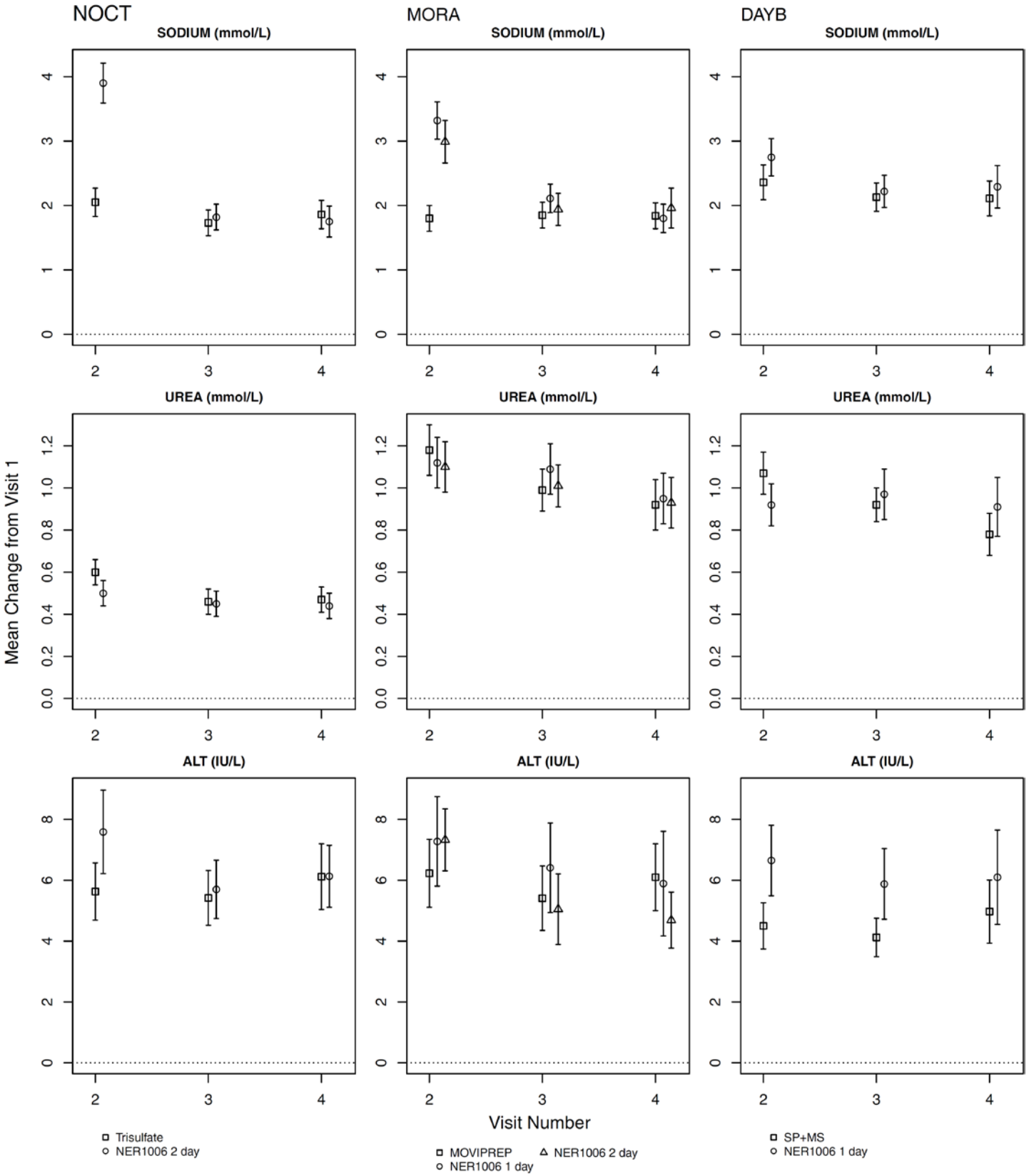
3.3.4.1.2 Mean Analysis

The greatest mean absolute change from visit 1 typically occurs at visit 2 for many laboratory parameters (Figures 2-3). In the NER1006 arm of NOCT study, mean absolute change for sodium, urea, CREAT, CL, and K appears to decrease towards zero. In the NER1006 arms of MORA study, mean absolute change for sodium, urea, ALT, CL, and K appears to decrease towards zero.

Appendix Table 1 indicates that for NOCT study, NER1006 2 day split dosing has a greater mean absolute change from visit 1 to visit 2 than Trisulfate for sodium (DMC 1.85; CI (1.48, 2.22)), ALT (DMC 1.96; CI (0.31, 3.61)), and CL (DMC 2.30; CI (1.89, 2.71)). For MORA study (Appendix Table 2), both NER1006 arms have greater mean changes from visit 1 to visit 2 than MOVIPREP for sodium (NER1006 1 day split dosing: DMC 1.52; CI (1.17, 1.87); NER1006 2 day split dosing: DMC 1.19; CI (0.80, 1.58)) and CL (NER1006 1 day split dosing: DMC 1.98, CI (1.61, 2.35); NER1006 2 day split dosing: DMC 1.92, CI (1.06, 2.78)). For DAYB study (Appendix Table 3), NER1006 1 day split dosing has a greater mean change than SP+MS arm for ALT at visit 2 (DMC 2.15; CI (0.78, 3.52)) and visit 3 (DMC 1.76; CI (0.45, 3.07)). The above differences in mean absolute change between comparator and NER1006 mostly occur at visit 2 as depicted in Figures 2-3.

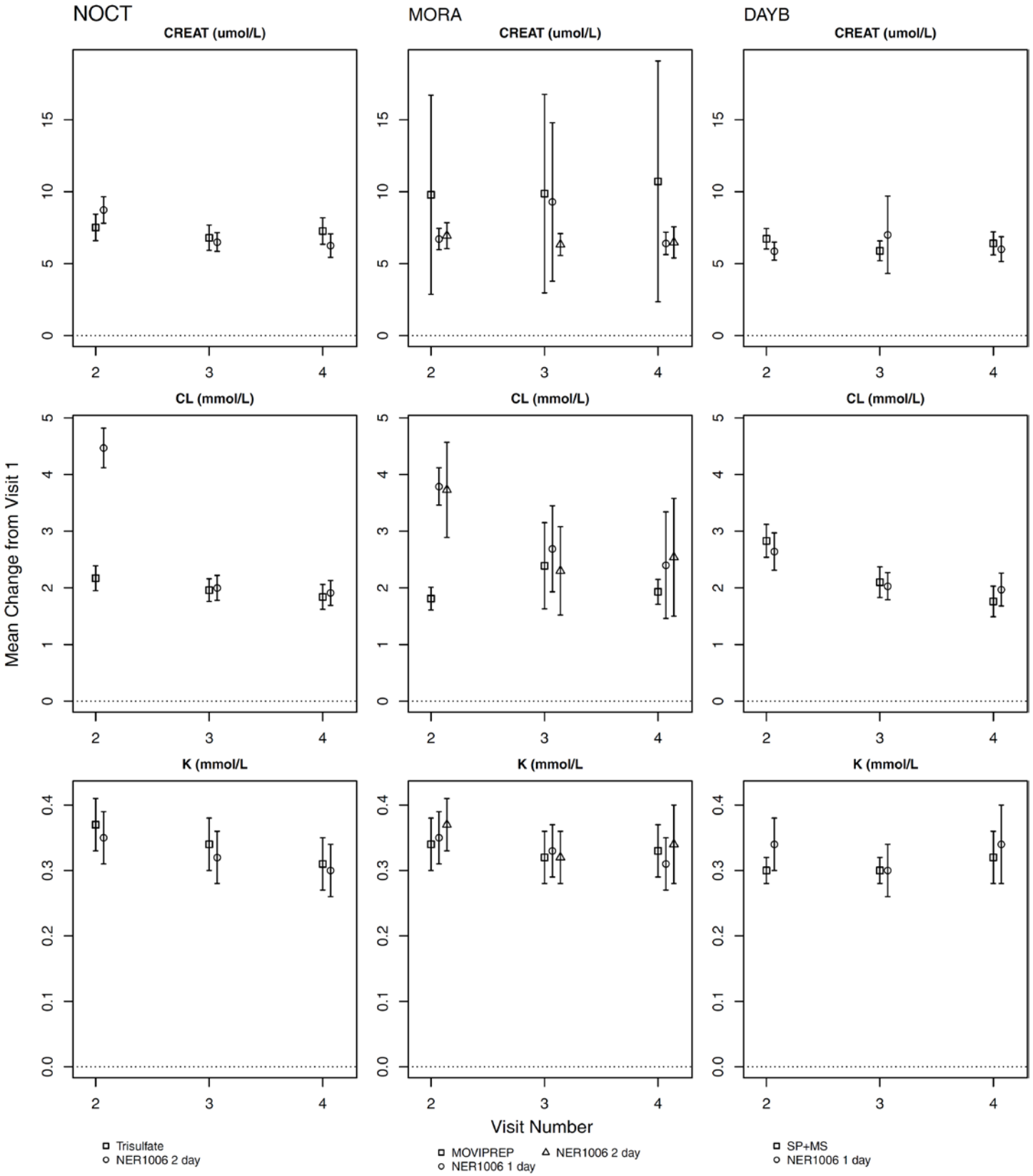
Unique subject identification number NER100603-(b) (6) is excluded from the mean analysis of CREAT in study DAYB, visit 2, arm SP+MS due to exceptionally high value of 3889.60 umol/L considering the normal reference range at the site is (53.04, 97.24) umol/L.

Figure 2. Mean absolute change from visit 1 for visits 2-4 by treatment arm, laboratory parameter, and study.



ALT= alanine transaminase

Figure 3. Mean absolute change from visit 1 for visits 2-4 by treatment arm, laboratory parameter, and study.



CREAT=creatinine, CL=chloride, K=potassium

3.3.4.1.3 Shift Analysis

In a shift analysis, we consider subjects who have normal baseline values at visit 1 and have extreme values at visit 2, 3, or 4. By comparing to visit 1, a shift analysis evaluates the presence of extreme laboratory values during post-colonoscopy visits. The number of subjects *n* with laboratory values outside the normal reference range at a post-colonoscopy visit among subjects *N* that are normal at visit 1 is given in Tables 9-11.

The shift analysis results are different from the sponsor's Module 2.7.4 Tables 2.7.4-26 and 2.7.4-27 due to different laboratory range values and number of subjects considered. The sponsor used the number of subjects with normal baseline values at visit 1 as the denominator for all time points. We used the number of subjects who have normal baseline values at visit 1 and have data at the visit of interest as the denominator to accurately attribute changes to those subjects. Also, we conducted analyses for additional laboratory parameters urea and CREAT. Also, the sponsor stated fixed laboratory normal ranges for the shift analysis, whereas we allowed laboratory ranges to change with study site.

For NOCT study, NER1006 2 day split dosing has greater percentages of extreme values than Trisulfate for all laboratory parameters except K. The difference is seen in either visit 2 or visit 3 (Table 9). For MORA study (Table 10), NER1006 1 and 2 day split dosing arms have greater percentages of extreme values than MOVIPREP at visit 2 for sodium (NER1006 1 day split dosing: RD 18, CI (12, 24); NER1006 2 day split dosing: RD 13, CI (9, 17)) and CL (NER1006 1 day split dosing: RD 23, CI (17, 29); NER1006 2 day split dosing: RD 17, CI (11, 23)). NER1006 1 day split dosing has a greater percentage of extreme values than NER1006 2 day split dosing for sodium at visit 3. For DAYB study (Table 11), the NER1006 arm has a greater percentage of extreme values than SP+MS at visit 2 for ALT (RD 7; CI (3, 11)) and CL (RD 11; CI (7, 15)).

In contrast to the sponsor's conclusion that NER1006 extreme shift values for sodium move back towards normal at visits 3 and 4, i.e., shift percentages approach 0%, in MORA study there is an increase in the percentage of patients with abnormal sodium at visit 4 (Table 10: NER1006 2 day split dosing 15%, 0%, 5%). Additionally, percentages of extreme urea values increase from visit 2 to visits 3 and 4 (Table 9: NER1006 2 day split dosing 2%, 4%, 5%; Table 11: NER1006 1 day split dosing 3%, 5%, 6%).

Table 9. Study NOCT: Fraction and percentage (*n/N* (%)) of laboratory values outside the normal reference range among subjects who are normal at visit 1 by visit and treatment arm. Also shown is the risk differences (RD) and 95% confidence interval (CI) between treatment arms.

	Trisulfate *n/N* (%)	NER2 *n/N* (%)	RD (CI)
SODIUM Visit 2	14/246 (6)	103/246 (42)	36 (30,42)
SODIUM Visit 3	7/239 (3)	11/243 (5)	2 (-2,6)
SODIUM Visit 4	10/205 (5)	6/193 (3)	-2 (-6,2)
UREA Visit 2	2/240 (1)	5/243 (2)	1 (-1,3)
UREA Visit 3	2/232 (1)	10/239 (4)	3 (1,5)
UREA Visit 4	11/196 (6)	9/192 (5)	-1 (-5,3)
ALT Visit 2	7/232 (3)	23/238 (10)	7 (3,11)
ALT Visit 3	4/227 (2)	8/233 (3)	1 (-1,3)
ALT Visit 4	5/190 (3)	5/186 (3)	0 (-4,4)
CREAT Visit 2	8/248 (3)	18/244 (7)	4 (0,8)
CREAT Visit 3	7/240 (3)	3/241 (1)	-2 (-4,0)
CREAT Visit 4	10/205 (5)	5/194 (3)	-2 (-6,2)
CL Visit 2	4/237 (2)	54/229 (24)	22 (16,28)
CL Visit 3	3/229 (1)	8/226 (4)	3 (1,5)
CL Visit 4	3/194 (2)	9/178 (5)	3 (-1,7)
K Visit 2	11/255 (4)	7/253 (3)	-1 (-5,3)
K Visit 3	4/251 (2)	6/251 (2)	0 (-2,2)
K Visit 4	4/214 (2)	3/202 (1)	-1 (-3,1)

NER2=NER1006 2 day split dosing
N = number of subjects normal at visit 1 with data at indicated visit
n = number of subjects normal at visit 1 and abnormal at the indicated visit

Table 10. Study MORA: Fraction and percentage (*n/N* (%)) of laboratory values outside the normal reference range among subjects who are normal at visit 1 by visit and treatment arm. Also shown is the risk differences (RD) and 95% confidence interval (CI) between treatment arms.

	MOVIPREP *n/N* (%)	NER1 *n/N* (%)	NER2 *n/N* (%)	NER1- MOVIPREP RD (CI)	NER2-MOVIPREP RD (CI)	NER2-NER1 RD (CI)
SODIUM Visit 2	5/246 (2)	48/246 (20)	35/235 (15)	18 (12,24)	13 (9,17)	-5 (-11,1)
SODIUM Visit 3	7/251 (3)	10/252 (4)	1/243 (0)	1 (-3,5)	-3 (-5,-1)	-4 (-6,-2)
SODIUM Visit 4	3/203 (1)	5/207 (2)	10/190 (5)	1 (-1,3)	4 (0,8)	3 (-1,7)
UREA Visit 2	4/237 (2)	8/231 (3)	9/232 (4)	1 (-1,3)	2 (-2,6)	1 (-3,5)
UREA Visit 3	8/238 (3)	10/233 (4)	8/235 (3)	1 (-3,5)	0 (-4,4)	-1 (-5,3)
UREA Visit 4	6/194 (3)	7/190 (4)	7/183 (4)	1 (-3,5)	1 (-3,5)	0 (-4,4)
ALT Visit 2	13/226 (6)	20/224 (9)	24/226 (11)	3 (-1,7)	5 (-1,11)	2 (-4,8)
ALT Visit 3	7/228 (3)	12/231 (5)	7/231 (3)	2 (-2,6)	0 (-4,4)	-2 (-6,2)
ALT Visit 4	4/187 (2)	3/189 (2)	6/177 (3)	0 (-2,2)	1 (-3,5)	1 (-3,5)
CREAT Visit 2	4/233 (2)	11/235 (5)	5/222 (2)	3 (-1,7)	0 (-2,2)	-3 (-7,1)
CREAT Visit 3	3/234 (1)	6/238 (3)	4/226 (2)	2 (0,4)	1 (-1,3)	-1 (-3,1)
CREAT Visit 4	8/191 (4)	4/194 (2)	4/182 (2)	-2 (-6,2)	-2 (-6,2)	0 (-2,2)
CL Visit 2	6/224 (3)	58/225 (26)	45/226 (20)	23 (17,29)	17 (11,23)	-6 (-14,2)
CL Visit 3	9/228 (4)	9/230 (4)	8/233 (3)	0 (-4,4)	-1 (-5,3)	-1 (-5,3)
CL Visit 4	4/184 (2)	4/190 (2)	4/178 (2)	0 (-2,2)	0 (-2,2)	0 (-2,2)
K Visit 2	13/238 (5)	7/238 (3)	8/232 (3)	-2 (-6,2)	-2 (-6,2)	0 (-4,4)
K Visit 3	12/245 (5)	9/245 (4)	8/242 (3)	-1 (-5,3)	-2 (-6,2)	-1 (-5,3)
K Visit 4	7/198 (4)	9/202 (4)	8/187 (4)	0 (-4,4)	0 (-4,4)	0 (-4,4)

NER1=NER1006 1 day split dosing, NER2=NER1006 2 day split dosing
N = number of subjects normal at visit 1 with data at indicated visit
n = number of subjects normal at visit 1 and abnormal at the indicated visit

Table 11. Study DAYB: Fraction and percentage (*n/N* (%)) of laboratory values outside the normal reference range among subjects who are normal at visit 1 by visit and treatment arm. Also shown is the risk differences (RD) and 95% confidence interval (CI) between treatment arms.

	SP+MS *n/N* (%)	NER1 *n/N* (%)	RD (CI)
SODIUM Visit 2	18/216 (8)	15/216 (7)	-1 (-7,5)
SODIUM Visit 3	11/224 (5)	14/217 (6)	1 (-3,5)
SODIUM Visit 4	10/136 (7)	6/134 (4)	-3 (-9,3)
UREA Visit 2	3/209 (1)	6/218 (3)	2 (0,4)
UREA Visit 3	8/214 (4)	11/217 (5)	1 (-3,5)
UREA Visit 4	4/130 (3)	8/136 (6)	3 (-3,9)
ALT Visit 2	4/212 (2)	19/205 (9)	7 (3,11)
ALT Visit 3	3/217 (1)	9/205 (4)	3 (-1,7)
ALT Visit 4	1/134 (1)	5/123 (4)	3 (-1,7)
CREAT Visit 2	6/220 (3)	3/217 (1)	-2 (-4,0)
CREAT Visit 3	4/226 (2)	5/217 (2)	0 (-2,2)
CREAT Visit 4	3/136 (2)	3/132 (2)	0 (-4,4)
CL Visit 2	0/220 (0)	24/217 (11)	11 (7,15)
CL Visit 3	7/227 (3)	6/218 (3)	0 (-4,4)
CL Visit 4	3/140 (2)	2/136 (1)	-1 (-3,1)
K Visit 2	2/226 (1)	7/221 (3)	2 (0,4)
K Visit 3	8/233 (3)	7/223 (3)	0 (-4,4)
K Visit 4	6/144 (4)	6/138 (4)	0 (-4,4)

NER1=NER1006 1 day split dosing
N = number of subjects normal at visit 1 with data at indicated visit
n = number of subjects normal at visit 1 and abnormal at the indicated visit

3.3.4.1.4 Persistence Analysis

In a persistence analysis, we consider only subjects who are normal at visit 1, have extreme laboratory values at visit 2, and continue to have extreme laboratory values at visit 3. A persistence analysis evaluates the presence of sustained extreme laboratory values from visit 2 to visit 3. The number of subjects *n* with laboratory values outside the normal reference range at visit 3 among subjects *N* that are outside the normal reference range at visit 2 is given in Tables 12-14.

The NER1006 arms have at most 44% of subjects whose extreme urea values persist from visit 2 to visit 3 (Tables 12-14). For sodium in MORA study, NER1006 1 day split dosing has a greater percentage of subjects who persist into visit 3 compared to NER1006 2 day split dosing (Table 13: NER1006 1 day split dosing 4/47 (9%) vs. NER1006 2 day split dosing 0/35 (0%)). These results should be interpreted with caution because the counts of subjects who have extreme values at visit 2 are low in the comparator arms.

Table 12. Study NOCT: Proportion and percentage (*n/N* (%)) of extreme laboratory values at visit 3 among subjects who are extreme at visit 2 by visit and treatment arm. Also shown is the risk differences (RD) and 95% confidence interval (CI) between treatment arms.

	Trisulfate *n/N* (%)	NER2 *n/N* (%)	RD (CI)
SODIUM	0/12 (0)	8/102 (8)	8 (2,14)
UREA	0/0 (-)	1/5 (20)	-
ALT	1/7 (14)	6/23 (26)	12 (-19,43)
CREAT	2/7 (29)	3/18 (17)	-12 (-49,25)
CL	1/4 (25)	7/53 (13)	-12 (-55,31)
K	0/10 (0)	0/6 (0)	0 (0,0)

- No estimates given because there are no subjects with extreme values at visit 2 in the Trisulfate arm
NER2=NER1006 2 day split dosing
N = number of subjects normal at visit 1, abnormal at visit 2, and data at visit 3 present
n = number of subjects normal at visit 1, abnormal at visit 2, and abnormal at visit 3

Table 13. Study MORA: Fraction and percentage (*n/N* (%)) of extreme laboratory values at visit 3 among subjects who are extreme at visit 2 by visit and treatment arm. Also shown is the risk differences (RD) and 95% confidence interval (CI) between treatment arms.

	MOVIPREP *n/N* (%)	NER1 *n/N* (%)	NER2 *n/N* (%)	NER1- MOVIPREP RD (CI)	NER2-MOVIPREP RD (CI)	NER2- NER1 RD (CI)
SODIUM	1/5 (20)	4/47 (9)	0/35 (0)	-11 (-46,24)	-20 (-55,15)	-9 (-17,-1)
UREA	4/4 (100)	3/8 (38)	4/9 (44)	-62 (-95,-29)	-56 (-89,-23)	6 (-41,53)
ALT	5/13 (38)	4/20 (20)	5/24 (21)	-18 (-49,13)	-17 (-48,14)	1 (-23,25)
CREAT	1/4 (25)	2/10 (20)	1/5 (20)	-5 (-54,44)	-5 (-60,50)	0 (-43,43)
CL	4/6 (67)	7/56 (12)	4/45 (9)	-55 (-94,-16)	-58 (-97,-19)	-3 (-15,9)
K	1/13 (8)	1/6 (17)	0/6 (0)	9 (-24,42)	-8 (-24,8)	-17 (-46,12)

NER1=NER1006 1 day split dosing, NER2=NER1006 2 day split dosing
N = number of subjects normal at visit 1, abnormal at visit 2, and data at visit 3 present
n = number of subjects normal at visit 1, abnormal at visit 2, and abnormal at visit 3

Table 14. Study DAYB: Fraction and percentage (*n/N* (%)) of extreme laboratory values at visit 3 among subjects who are extreme at visit 2 by visit and treatment arm. Also shown is the risk differences (RD) and 95% confidence interval (CI) between treatment arms.

	SP+MS *n/N* (%)	NER1 *n/N* (%)	RD (CI)
SODIUM	1/18 (6)	1/15 (7)	1 (-17,19)
UREA	3/3 (100)	2/6 (33)	-67 (-104,-30)
ALT	1/4 (25)	4/18 (22)	-3 (-50,44)
CREAT	1/6 (17)	1/3 (33)	16 (-45,77)
CL	0/0 (-)	4/24 (17)	-
K	0/2 (0)	2/7 (29)	29 (-4,62)

- No estimates given because there are no subjects with extreme values at visit 2 in the SP+MS arm
NER1=NER1006 1 day split dosing
N = number of subjects normal at visit 1, abnormal at visit 2, and data at visit 3 present
n = number of subjects normal at visit 1, abnormal at visit 2, and abnormal at visit 3

3.3.4.2 Blood Pressure

The following abbreviations are used for blood pressure parameters:

DIABPO: orthostatic diastolic blood pressure (mmHg)

SYSBPO: orthostatic systolic blood pressure (mmHg)

DIABPS: supine diastolic blood pressure (mmHg)

SYSBPS: supine systolic blood pressure (mmHg)

DIAORTHO: orthostatic change in diastolic blood pressure (mmHg); defined as supine diastolic blood pressure-standing diastolic blood pressure

SYSORTHO: orthostatic change in systolic blood pressure (mmHg); defined as supine systolic blood pressure-standing systolic blood pressure

3.3.4.2.1 Hypotension Analysis

For all 3 studies, the percentage of subjects with hypotension (SYSBPO or SYSBPS < 90 mmHg) are less than or equal to 1% (Tables 15-17), and there is no indication of a difference between treatment arms (pairwise Fisher's exact test p-values > 0.49; not shown).

Table 15. Study NOCT: Fraction and percentage (*n/N* (%)) of subjects who have systolic blood pressure < 90 mmHg at visit 1 or visit 2.

	Trisulfate *n/N* (%)	NER2 *n/N* (%)
SYSBPO Visit 1	0/265 (0)	0/261 (0)
SYSBPO Visit 2	2/265 (1)	0/261 (0)
SYSBPS Visit 1	0/265 (0)	0/262 (0)
SYSBPS Visit 2	0/265 (0)	1/262 (0)

NER2=NER1006 2 day split dosing
N = number of subjects with data at indicated visit
n = number of subjects with systolic blood pressure < 90 mmHg at indicated visit

Table 16. Study MORA. Fraction and percentage (*n/N* (%)) of subjects who have systolic blood pressure < 90 mmHg at visit 1 or visit 2.

	MOVIPREP *n/N* (%)	NER1 *n/N* (%)	NER2 *n/N* (%)
SYSBPO Visit 1	1/253 (0)	0/259 (0)	0/251 (0)
SYSBPO Visit 2	0/253 (0)	2/259 (1)	1/251 (0)
SYSBPS Visit 1	0/242 (0)	0/247 (0)	0/233 (0)
SYSBPS Visit 2	0/242 (0)	0/247 (0)	0/233 (0)

NER1=NER1006 1 day split dosing, NER2=NER1006 2 day split dosing
N = number of subjects with data at indicated visit
n = number of subjects with systolic blood pressure < 90 mmHg at indicated visit

Table 17. Study DAYB. Fraction and percentage (*n/N* (%)) of subjects who have systolic blood pressure < 90 mmHg at visit 1 or visit 2.

	SP+MS	NER1
	n/N (%)	*n/N* (%)
SYSBPO Visit 1	0/235 (0)	0/229 (0)
SYSBPO Visit 2	1/235 (0)	0/229 (0)
SYSBPS Visit 1	0/235 (0)	0/231 (0)
SYSBPS Visit 2	0/235 (0)	0/231 (0)

NER1=NER1006 1 day split dosing
N = number of subjects with data at indicated visit
n = number of subjects with systolic blood pressure < 90 mmHg at indicated visit

3.3.4.2.2 Orthostatic Change Analysis

For all 3 studies, the percentage of subjects at visit 2 with diastolic or systolic orthostatic change > 20 mmHg are less than or equal to 6% (Tables 18-20), and there is no indication of a difference between treatment arms (pairwise Fisher's exact test p-value > 0.19, not shown). For NOCT study in Figure 4, the NER1006 2 day split dosing SYSORTHO range ([21, 49] mmHg) and DIAORTHO range ([25, 33] mmHg) are greater than the Trisulfate ranges (SYSORTHO: [21, 38] mmHg; DIAORTHO: [22, 33] mmHg). For MORA study in Figure 5, the NER1006 SYSORTHO ranges (NER1006 1 day split dosing [21, 42] mmHg, NER1006 2 day split dosing [21, 35] mmHg) are greater than the MOVIPREP range ([21, 30] mmHg). For DAYB study in Figure 6, the range for SYSORTHO is greater in the NER1006 1 day split dosing SYSORTHO range ([21, 40] mmHg) is greater than the SP+MS range ([27, 30] mmHg).

Table 18. Study NOCT. Fraction and percentage (*n/N* (%)) of subjects who have orthostatic change > 20 mmHg at visit 2.

	Trisulfate	NER2
	n/N (%)	*n/N* (%)
DIAORTHO	2/265 (1)	3/261 (1)
SYSORTHO	8/265 (3)	12/261 (5)

NER2=NER1006 2 day split dosing
N = number of subjects with data
n = number of subjects with orthostatic change > 20 mmHg

Table 19. Study MORA. Fraction and percentage (*n/N* (%)) of subjects who have orthostatic change > 20 mmHg at visit 2.

	MOVIPREP	NER1	NER2
	n/N (%)	*n/N* (%)	*n/N* (%)
DIAORTHO	0/236 (0)	0/240 (0)	0/224 (0)
SYSORTHO	8/236 (3)	15/240 (6)	14/224 (6)

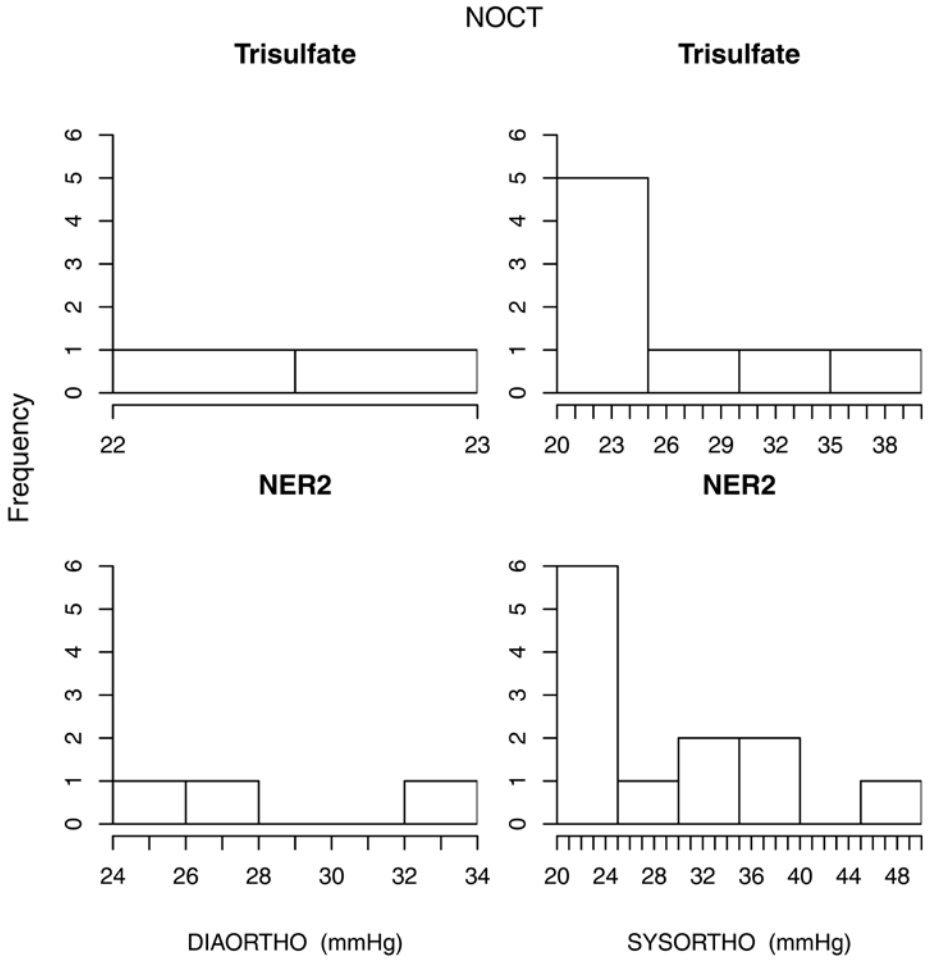
NER1=NER1006 1 day split dosing, NER2=NER1006 2 day split dosing
N = number of subjects with data
n = number of subjects with orthostatic change > 20 mmHg

Table 20. Study DAYB. Fraction and percentage (*n/N* (%)) of subjects who have orthostatic change > 20 mmHg at visit 2.

	SP+MS	NER1
	n/N (%)	*n/N* (%)
DIAORTHO	0/233 (0)	0/229 (0)
SYSORTHO	4/233 (2)	7/229 (3)

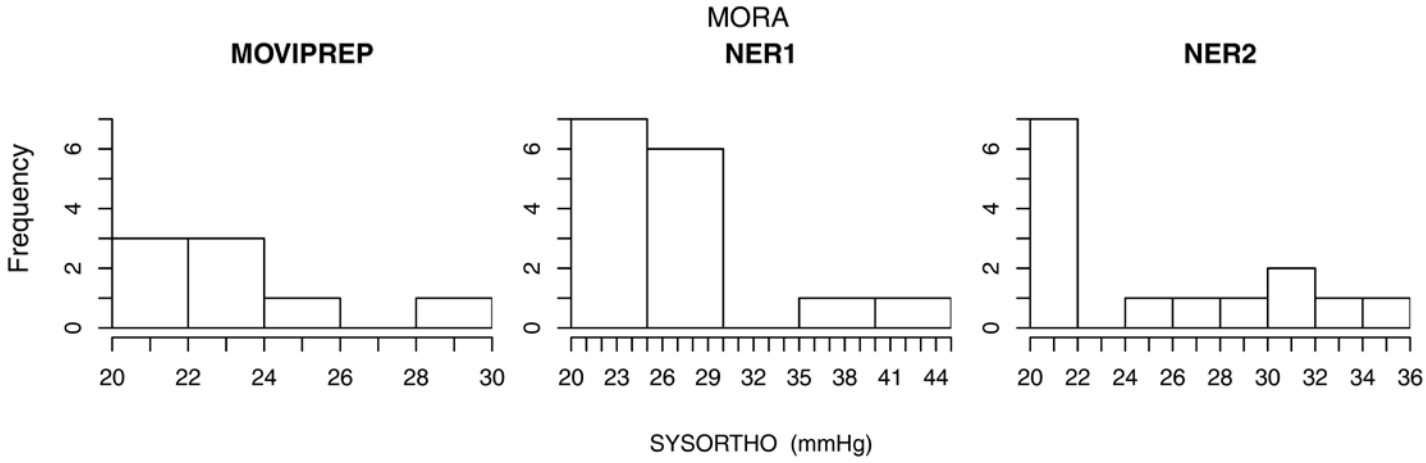
NER1=NER1006 1 day split dosing
N = number of subjects with data at visit 2
n = number of subjects with orthostatic change > 20 mmHg

Figure 4. Study NOCT: Histogram of systolic and diastolic orthostatic change > 20 mmHg by treatment arm at visit 2.



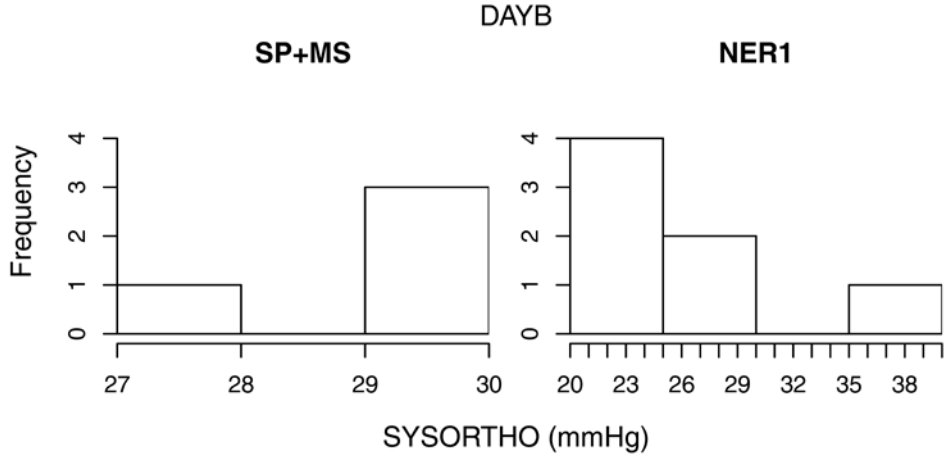
NER2=NER1006 2 day split dosing

Figure 5. Study MORA. Histogram of systolic orthostatic change > 20 mmHg by treatment arm at visit 2; no changes observed for diastolic blood pressure.



NER1=NER1006 1 day split dosing and NER2=NER1006 2 day split dosing

Figure 6. Study DAYB: Histogram of systolic orthostatic change > 20 mmHg by treatment arm at visit 2; no changes observed for diastolic blood pressure.



NER1=NER1006 1 day split dosing

3.3.4.3 Sensitivity Analysis

Laboratory and blood pressure analyses in Sections 3.3.4.1 and 3.3.4.2 used the sponsor's derived analysis variable *visitnum*, an indicator for the visit that laboratory and blood pressure parameters were measured. We repeated laboratory and blood pressure analyses using time variables, which contain date and time, to exclude any laboratory and blood pressure parameters that occurred after colonoscopy started at visit 2.

In NOCT study, the safety analysis sample sizes decreased by at most 15 for any laboratory or blood pressure parameter. In MORA and DAYB, the safety analysis sample sizes decreased by at most 4. The quantitative results changed slightly, but the qualitative conclusions for laboratory and blood pressure parameters in Sections 3.3.4.1 and 3.3.4.2 remained unchanged.

4 SUMMARY AND CONCLUSIONS

4.1 Statistical Issues

The three studies analyzed in this review are multi-center, randomized, active-controlled, phase III trials. The studies were not powered for formal hypothesis testing of the safety endpoints considered in this review. Therefore, results should not be considered confirmatory, but as supportive evidence if the same trend persists in multiple studies. We performed many comparisons without adjustment for type I error resulting in a conservative analysis of safety outcomes, i.e., the probability is higher for concluding a safety signal.

The percentage of subjects with laboratory data at visit 1 and a subsequent visit decreases with follow-up time and can be as low as 61% in DAYB study SP+MS treatment arm. Missing data may affect the reliability and generalizability of the estimates for difference in mean change and shift analyses at later visits. Additionally, low counts of laboratory values in the shift and persistence analyses may be insufficient to satisfy the normal approximation in the computation

of confidence intervals. Interpretation of differences between treatment arms in the shift and persistence analyses should be conservative.

4.2 Collective Evidence

The safety analysis population includes 527 subjects in NOCT study (265 Trisulfate, 262 NER1006 2 day split dosing), 793 subjects in MORA study (262 MOVIPREP, 269 NER1006 1 day split dosing, 262 NER1006 2 day split dosing), and 471 subjects in the DAYB study (238 SP+MS, 233 NER1006 1 day split dosing). For NOCT study and DAYB study, there are no notable imbalances in the demographic characteristics. For MORA study, subject demographic characteristics are generally balanced with the possible exception for the percentage of males (MOVIPREP 52%, NER1006 1 day split dosing 46%, NER1006 2 day split dosing 41%). Laboratory parameters are generally balanced across treatment arms in each study at baseline (visit 1).

The greatest mean absolute change typically occurs at visit 2 for many laboratory parameters. In the NER1006 arm of NOCT study, mean absolute change for sodium, urea, CREAT, CL, and K appears to decrease towards zero. In the NER1006 arms of MORA study, mean absolute change for sodium, urea, ALT, CL, and K appears to decrease towards zero.

Differences in mean absolute change between comparator and NER1006 mostly occur at visit 2. In NOCT study, NER1006 2 day split dosing has a greater mean absolute change from visit 1 to visit 2 than Trisulfate for sodium (DMC 1.85; CI (1.48, 2.22)), ALT (DMC 1.96; CI (0.31, 3.61)), and CL (DMC 2.30; CI (1.89, 2.71)). For MORA study, both NER1006 arms have greater mean changes from visit 1 to visit 2 than MOVIPREP for sodium (NER1006 1 day split dosing: DMC 1.52; CI (1.17, 1.87); NER1006 2 day split dosing: DMC 1.19; CI (0.80, 1.58)) and CL (NER1006 1 day split dosing: DMC 1.98, CI (1.61, 2.35); NER1006 2 day split dosing: DMC 1.92, CI (1.06, 2.78)). For DAYB study, NER1006 1 day split dosing has a greater mean change than SP+MS arm for ALT at visit 2 (DMC 2.15; CI (0.78, 3.52)) and visit 3 (DMC 1.76; CI (0.45, 3.07)).

For NOCT study, NER1006 2 day split dosing has greater percentages of extreme values than Trisulfate for all laboratory parameters except K. The difference is seen in either visit 2 or visit 3. For MORA study, NER1006 1 and 2 day split dosing arms have greater percentages of extreme values than MOVIPREP at visit 2 for sodium (NER1006 1 day split dosing: RD 18, CI (12, 24); NER1006 2 day split dosing: RD 13, CI (9, 17)) and CL (NER1006 1 day split dosing: RD 23, CI (17, 29); NER1006 2 day split dosing: RD 17, CI (11, 23)). NER1006 1 day split dosing has a greater percentage of extreme values than NER1006 2 day split dosing for sodium at visit 3. For DAYB study, the NER1006 arm has a greater percentage of extreme values than SP+MS at visit 2 for ALT (RD 7; CI (3, 11)) and CL (RD 11; CI (7, 15)).

The NER1006 arms have at most 44% of subjects whose extreme urea values persist from visit 2 to visit 3. For sodium in MORA study, NER1006 1 day split dosing has a greater percentage of subjects who persist into visit 3 compared to NER1006 2 day split dosing (NER1006 1 day split dosing 4/47 (9%) vs. NER1006 2 day split dosing 0/35 (0%)). These results should be interpreted with caution because the counts of subjects who have extreme values at visit 2 are low in the comparator arms.

For all 3 studies, the percentage of subjects with hypotension (orthostatic or supine systolic blood pressure < 90 mmHg) are less than or equal to 1%, and there is no indication of a difference between treatment arms. Although percentages of orthostatic change > 20 mmHg are small (≤ 6%) across all studies and there are no differences between treatment arms, NER1006 arms consistently have greater ranges of orthostatic change than the comparator. These ranges can be as wide as [21, 49] mmHg in NER1006 2 day split dosing arm of the NOCT study. High orthostatic changes are suggestive of significant intravascular volume loss and dehydration.

We repeated laboratory and blood pressure analyses using time variables, which contain date and time, to exclude any laboratory and blood pressure parameters that occurred after colonoscopy started at visit 2. In NOCT study, the safety analysis sample sizes decreased by at most 15 for any laboratory or blood pressure parameter. In MORA and DAYB, the safety analysis sample sizes decreased by at most 4. The quantitative results changed slightly, but the qualitative conclusions for laboratory and blood pressure parameters remained unchanged.

4.3 Conclusions and Recommendations

This review focuses on comparisons of laboratory and blood pressure parameters between treatments arms to detect extreme values and their persistence after colonoscopy. We have two potential safety concerns. Firstly, NER1006 arms have greater percentages of more extreme sodium (42%), ALT (10%), and CL (26%) values at visit 2 than the comparator. In contrast to the sponsor's conclusion that all extreme shift values for sodium move back towards normal at visits 3 and 4, our findings for sodium and urea may indicate otherwise, at times the percentage of extreme values increases during visits 3 and 4. Secondly, across all studies, NER1006 arms consistently have greater ranges of orthostatic change at visit 2 than the comparator that can be as wide as [21, 49] mmHg.

APPENDIX

Appendix Table 1. Study NOCT: Sample size, mean, 95% confidence interval (CI), and difference in mean change (DMC) from visit 1 between treatment arms by visit and laboratory parameters.

	Trisulfate (*N*)	Mean (CI)	NER2 (*N*)	Mean (CI)	DMC (CI)
SODIUM Visit 1	263	140.87 (140.58,141.17)	259	140.92 (140.62,141.21)	0.04 (-0.38,0.46)
SODIUM Visit 2	260	141.11 (140.78,141.44)	257	144.59 (144.26,144.92)	1.85 (1.48,2.22)
SODIUM Visit 3	253	140.92 (140.61,141.24)	253	141.27 (140.98,141.57)	0.09 (-0.16,0.34)
SODIUM Visit 4	219	140.81 (140.44,141.18)	204	141.29 (140.98,141.60)	-0.11 (-0.42,0.20)
UREA Visit 1	261	2.48 (2.40,2.56)	257	2.51 (2.41,2.60)	0.02 (-0.10,0.15)
UREA Visit 2	258	2.07 (1.99,2.15)	255	2.22 (2.14,2.30)	-0.10 (-0.18,-0.02)
UREA Visit 3	250	2.35 (2.27,2.43)	251	2.44 (2.34,2.54)	-0.01 (-0.09,0.07)
UREA Visit 4	214	2.50 (2.40,2.59)	203	2.46 (2.37,2.56)	-0.03 (-0.11,0.05)
ALT Visit 1	263	27.81 (25.87,29.75)	257	27.13 (25.23,29.03)	-0.68 (-3.40,2.04)
ALT Visit 2	259	29.75 (27.44,32.07)	255	31.02 (28.39,33.65)	1.96 (0.31,3.61)
ALT Visit 3	253	26.40 (24.47,28.32)	250	26.46 (24.43,28.5)	0.28 (-1.03,1.59)
ALT Visit 4	216	26.46 (24.27,28.66)	202	26.42 (24.17,28.67)	0.01 (-1.48,1.50)
CREAT Visit 1	262	78.31 (76.34,80.29)	258	78.41 (76.43,80.39)	0.10 (-2.71,2.90)
CREAT Visit 2	259	81.62 (79.54,83.70)	256	84.19 (81.88,86.50)	1.21 (-0.10,2.52)
CREAT Visit 3	251	79.88 (77.81,81.96)	252	80.12 (78.08,82.16)	-0.30 (-1.40,0.80)
CREAT Visit 4	215	80.73 (78.44,83.03)	203	80.01 (77.70,82.33)	-1.02 (-2.25,0.21)
CL Visit 1	263	101.49 (101.10,101.89)	259	101.83 (101.40,102.27)	0.34 (-0.23,0.91)
CL Visit 2	260	100.74 (100.31,101.17)	257	106.16 (105.75,106.57)	2.30 (1.89,2.71)
CL Visit 3	253	102.18 (101.79,102.57)	253	102.62 (102.19,103.05)	0.04 (-0.25,0.33)
CL Visit 4	216	101.74 (101.3,102.17)	203	102.32 (101.84,102.79)	0.07 (-0.24,0.38)
K Visit 1	263	4.31 (4.27,4.35)	259	4.35 (4.31,4.39)	0.04 (-0.03,0.10)
K Visit 2	257	4.38 (4.32,4.43)	255	4.44 (4.38,4.50)	-0.02 (-0.08,0.04)
K Visit 3	253	4.33 (4.27,4.39)	253	4.27 (4.24,4.31)	-0.02 (-0.06,0.02)
K Visit 4	216	4.31 (4.25,4.37)	203	4.33 (4.27,4.39)	-0.01 (-0.07,0.05)

At Visit 1, difference in laboratory means, not DMC, is calculated.
NER2=NER1006 2 day split dosing

Appendix Table 2. Study MORA: Sample size, mean, 95% confidence interval (CI), and difference in mean change (DMC) from visit 1 between treatment arms by visit and laboratory parameters.

	MOVIPREP (*N*)	Mean (CI)	NER1 (*N*)	Mean (CI)	NER2 (*N*)	Mean (CI)	NER1-MOVIPREP DMC (CI)	NER2-MOVIPREP DMC (CI)	NER2-NER1 DMC (CI)
SODIUM Visit 1	254	140.67 (140.38,140.97)	262	140.68 (140.39,140.98)	257	141.03 (140.68,141.38)	0.01 (-0.4,0.43)	0.36 (-0.10,0.82)	0.35 (-0.12,0.81)
SODIUM Visit 2	243	140.73 (140.42,141.04)	245	143.44 (143.03,143.86)	242	143.32 (142.93,143.72)	1.52 (1.17,1.87)	1.19 (0.80,1.58)	-0.33 (-0.78,0.12)
SODIUM Visit 3	248	141.07 (140.75,141.38)	251	140.85 (140.50,141.20)	251	140.98 (140.67,141.30)	0.26 (-0.03,0.55)	0.09 (-0.24,0.42)	-0.17 (-0.50,0.16)
SODIUM Visit 4	200	140.94 (140.64,141.23)	208	140.76 (140.44,141.07)	194	141.31 (140.94,141.68)	-0.04 (-0.31,0.23)	0.12 (-0.25,0.49)	0.16 (-0.21,0.53)
UREA Visit 1	256	5.37 (5.18,5.57)	263	5.60 (5.39,5.82)	255	5.55 (5.35,5.74)	0.23 (-0.07,0.52)	0.17 (-0.10,0.45)	-0.06 (-0.35,0.24)
UREA Visit 2	248	4.63 (4.43,4.82)	250	5.11 (4.89,5.32)	244	5.13 (4.94,5.33)	-0.06 (-0.22,0.10)	-0.08 (-0.24,0.08)	-0.02 (-0.20,0.16)
UREA Visit 3	249	5.42 (5.21,5.64)	253	5.64 (5.42,5.85)	249	5.52 (5.31,5.74)	0.10 (-0.06,0.26)	0.02 (-0.14,0.18)	-0.08 (-0.24,0.08)
UREA Visit 4	203	5.44 (5.23,5.66)	207	5.44 (5.23,5.66)	191	5.57 (5.35,5.78)	0.03 (-0.13,0.19)	0.01 (-0.15,0.17)	-0.02 (-0.18,0.14)
ALT Visit 1	255	25.36 (23.49,27.22)	262	25.47 (23.26,27.69)	259	24.30 (22.50,26.10)	0.12 (-2.78,3.02)	-1.06 (-3.65,1.54)	-1.17 (-4.03,1.68)
ALT Visit 2	247	27.46 (25.40,29.51)	248	28.90 (26.84,30.96)	248	28.92 (26.98,30.86)	1.05 (-0.79,2.89)	1.10 (-0.41,2.61)	0.05 (-1.73,1.83)
ALT Visit 3	249	23.97 (22.26,25.67)	252	25.17 (23.19,27.15)	254	24.71 (22.88,26.53)	1.00 (-0.80,2.80)	-0.36 (-1.93,1.21)	-1.36 (-3.22,0.50)
ALT Visit 4	203	23.78 (21.94,25.63)	208	23.96 (21.79,26.14)	195	23.41 (21.47,25.35)	-0.21 (-2.27,1.85)	-1.41 (-2.84,0.02)	-1.20 (-3.16,0.76)
CREAT Visit 1	256	78.85 (71.67,86.02)	263	74.39 (72.45,76.33)	259	73.03 (70.96,75.11)	-4.46 (-11.93,3.00)	-5.81 (-13.32,1.69)	-1.35 (-4.20,1.49)
CREAT Visit 2	248	74.92 (72.85,77.00)	250	76.56 (74.46,78.66)	249	75.18 (73.12,77.24)	-3.08 (-10.04,3.88)	-2.84 (-9.82,4.14)	0.24 (-0.94,1.42)
CREAT Visit 3	249	75.17 (73.06,77.29)	253	77.16 (71.26,83.06)	254	72.95 (70.99,74.91)	-0.58 (-9.42,8.26)	-3.54 (-10.5,3.42)	-2.96 (-8.51,2.59)
CREAT Visit 4	203	75.80 (73.56,78.03)	208	74.49 (72.39,76.59)	195	73.98 (71.73,76.24)	-4.31 (-12.72,4.10)	-4.24 (-12.67,4.19)	0.07 (-1.26,1.40)
CL Visit 1	254	101.92 (101.56,102.27)	263	101.96 (101.14,102.79)	259	101.78 (100.94,102.63)	0.05 (-0.86,0.95)	-0.13 (-1.06,0.79)	-0.18 (-1.36,1.01)
CL Visit 2	242	102.60 (102.23,102.97)	246	105.52 (105.03,106.01)	245	104.98 (104.51,105.45)	1.98 (1.61,2.35)	1.92 (1.06,2.78)	-0.06 (-0.96,0.84)
CL Visit 3	248	102.52 (101.68,103.37)	253	102.93 (102.56,103.30)	253	102.77 (102.40,103.14)	0.30 (-0.78,1.38)	-0.09 (-1.19,1.01)	-0.39 (-1.49,0.71)
CL Visit 4	202	102.52 (102.15,102.90)	208	102.60 (102.23,102.97)	192	102.81 (102.42,103.20)	0.47 (-0.49,1.43)	0.61 (-0.45,1.67)	0.14 (-1.27,1.55)
K Visit 1	254	4.36 (4.32,4.40)	262	4.37 (4.32,4.43)	257	4.39 (4.33,4.45)	0.02 (-0.05,0.09)	0.04 (-0.04,0.11)	0.02 (-0.06,0.10)
K Visit 2	241	4.25 (4.19,4.31)	244	4.38 (4.32,4.44)	240	4.29 (4.23,4.35)	0.01 (-0.05,0.07)	0.03 (-0.03,0.09)	0.02 (-0.04,0.08)
K Visit 3	248	4.36 (4.30,4.42)	251	4.40 (4.34,4.46)	251	4.36 (4.30,4.42)	0.01 (-0.05,0.07)	0.00 (-0.06,0.06)	-0.01 (-0.07,0.05)
K Visit 4	200	4.40 (4.34,4.46)	207	4.45 (4.39,4.51)	194	4.44 (4.39,4.50)	-0.02 (-0.08,0.04)	0.01 (-0.07,0.09)	0.03 (-0.05,0.11)

At Visit 1, difference in laboratory means, not DMC, is calculated.
NER1=NER1006 1 day split dosing, NER2=NER1006 2 day split dosing

Appendix Table 3. Study DAYB: Sample size, mean, 95% confidence interval (CI), and difference in mean change (DMC) from visit 1 between treatment arms by visit and laboratory parameters.

	SP+MS (*N*)	Mean (CI)	NER1 (*N*)	Mean (CI)	DMC (CI)
SODIUM Visit 1	238	140.22 (139.91,140.54)	230	140.32 (139.99,140.65)	0.10 (-0.36,0.56)
SODIUM Visit 2	229	139.32 (138.95,139.69)	226	141.32 (140.93,141.72)	0.39 (0.00,0.78)
SODIUM Visit 3	237	140.05 (139.69,140.40)	227	140.19 (139.82,140.56)	0.09 (-0.24,0.42)
SODIUM Visit 4	145	140.33 (139.88,140.78)	143	140.79 (140.34,141.24)	0.18 (-0.25,0.61)
UREA Visit 1	238	5.02 (4.84,5.19)	232	5.09 (4.92,5.27)	0.07 (-0.18,0.33)
UREA Visit 2	231	4.33 (4.15,4.51)	229	4.99 (4.82,5.17)	-0.15 (-0.29,-0.01)
UREA Visit 3	236	4.99 (4.81,5.17)	228	5.18 (4.98,5.37)	0.05 (-0.11,0.21)
UREA Visit 4	144	5.10 (4.85,5.36)	144	5.07 (4.85,5.28)	0.13 (-0.03,0.29)
ALT Visit 1	238	22.37 (20.96,23.78)	231	23.97 (21.95,25.98)	1.59 (-0.87,4.06)
ALT Visit 2	231	23.85 (22.15,25.56)	227	26.94 (24.72,29.15)	2.15 (0.78,3.52)
ALT Visit 3	237	21.46 (20.09,22.83)	227	23.20 (21.30,25.11)	1.76 (0.45,3.07)
ALT Visit 4	146	20.93 (19.31,22.56)	142	24.3 (21.87,26.73)	1.13 (-0.73,2.99)
CREAT Visit 1	238	71.50 (69.73,73.26)	232	71.78 (70.00,73.57)	0.29 (-2.22,2.80)
CREAT Visit 2	230	75.88 (74.06,77.71)	229	75.38 (73.44,77.32)	-0.86 (-1.80,0.08)
CREAT Visit 3	237	73.65 (71.79,75.51)	229	74.48 (71.24,77.71)	1.12 (-1.66,3.90)
CREAT Visit 4	146	75.25 (72.8,77.7)	143	73.94 (71.55,76.33)	-0.40(-1.58,0.78)
CL Visit 1	238	102.89 (102.56,103.23)	231	103.14 (102.75,103.53)	0.25 (-0.28,0.77)
CL Visit 2	229	100.63 (100.2,101.06)	226	104.18 (103.67,104.69)	-0.19 (-0.64,0.26)
CL Visit 3	236	103.21 (102.8,103.62)	227	103.25 (102.82,103.68)	-0.07 (-0.42,0.28)
CL Visit 4	144	102.79 (102.34,103.25)	143	102.64 (102.21,103.07)	0.21 (-0.18,0.60)
K Visit 1	238	4.30 (4.26,4.34)	230	4.28 (4.24,4.32)	-0.02 (-0.09,0.05)
K Visit 2	229	4.25 (4.21,4.29)	225	4.15 (4.09,4.21)	0.04 (0.00,0.08)
K Visit 3	236	4.40 (4.36,4.44)	227	4.30 (4.24,4.35)	0.00 (-0.04,0.04)
K Visit 4	145	4.40 (4.34,4.46)	142	4.38 (4.32,4.44)	0.02 (-0.06,0.10)

At Visit 1, difference in laboratory means, not DMC, is calculated.
NER1=NER1006 1 day split dosing

Appendix Table 4. Normal reference ranges for laboratory values by study and selected study sites.

	Reference Upper Limits for Laboratory Parameter (units)					
Site No.	**Sodium (mmol/L)**	**Potassium (mmol/L)**	**Chloride (mmol/L)**	**ALT (IU/L)**	**AST (IU/L)**	**Bilirubin (µmol/L)**
NOCT						
101	134 - 144	3.5 - 5.2	97 - 108	0 - 32/44	0 - 60	0 - 6.84
102	133 - 145	3.4 - 5.4	96 - 108	0 - 40/55	0 - 35/50	0 - 23.95
103	134 - 144	3.5 - 5.2	97 - 108	0 - 32/44	0 - 40	0 - 20.52
104	133 - 145	3.4 - 5.1	97 - 107	5 - 40	5 - 40	1.71 - 20.52
105	136 - 146	3.5 - 5.3	98 - 110	2 - 40/60	2 - 35/50	3.42 - 20.52
106	134 - 144	3.5 - 5.2	97 - 108	0 - 32/44	0 - 40	0 - 20.52
107	134 - 144	3.5 - 5.2	97 - 108	0 - 32	0 - 40	0 - 6.84
108	135 - 143	3.5 - 5.3	98 - 110	6/9 - 29/46	10 - 35	0 - 20.52
109	134 - 144	3.5 - 5.2	97 - 108	0 - 32/44	0 - 40	0 - 20.52
110	136 - 145	3.5 - 5.1	97 - 107	10 - 56	5 - 41	1.71 - 17.1
111	134 - 144	3.5 - 5.2	97 - 108	0 - 32/44	0 - 40	0 - 6.84
112	134 - 144	3.5 - 5.2	97 - 108	0 - 32/44	0 - 40	0 - 20.52
MORA						
201	136 - 145	3.5 - 5.1	98 - 107	12 - 78	9 - 37	3.42 - 17.1
202	135 - 145	3.45 - 4.45	98 - 107	0 - 31/41	0 - 31/37	0 - 20.18
203	136 - 145	3.5 - 5.1	98 - 107	0 - 33/41	0 - 32/40	0 - 18.81
204	135 - 144	3.6 - 4.8	98 - 106	7 - 31	0 - 31/37	0 - 7.7
302	136 - 145	3.5 - 4.5	98 - 107	7 - 40	7 - 40	0 - 20
303	136 - 145	3.4 - 4.5	97 - 108	0 - 36/51	0 - 36/51	0 - 21

402	133 - 146	3.6 - 5.5	98 - 109	0 - 35/50	0 - 35/50	0 - 4.96
403	136 - 145	3.5 - 5.1	98 - 107	0 - 34.9	0 - 34.9/49.9	1.71 - 20.52
404	135 - 145	3.3 - 4.5	95 - 105	0 - 33/43.8	0 - 30.6/34.2	0 - 3
501	135 - 145	3.5 - 5.0	98 - 108	7 - 45	7 - 45	5.13 - 20.52
502	136 - 146	3.5 - 5.2	98 - 107	1 - 31/40	1 - 31/40	3.42 - 20.52
503	135 - 148	3.6 - 5.2	96 - 108	0 - 31/45	0 - 29/36	3.42 - 20.52
504	135 - 148	3.5 - 5.2	98 - 108	10 - 50	10 - 40	0 - 5.13
505	135 - 145	3.5 - 5.3	98 - 110	0 - 31/41	0 - 32/38	0 - 5.13
601	136 - 145	3.5 - 5.1	98 - 107	5 - 50	5 - 50	3.42 - 20.52
602	135 - 145	3.5 - 5.3	97 - 107	5 - 31/41	5 - 31/37	5.13 - 20.52
603	136 - 146	3.5 - 5.5	98 - 106	10 - 31/41	0 - 32/40	3.42 - 17.1
604	135 - 148	3.5 - 5.1	90 - 110	0 - 32/42	0 - 32/38	0 - 17.1
605	136 - 145	3.5 - 5.1	98 - 107	0 - 31/41	0 - 32/38	0 - 20.52
606	136 - 145	3.5 - 5.1	98 - 107	0 - 33/41	0 - 32/40	0 - 20.52
701	135 - 145	3.5 - 5.5	98 - 110	5 - 40	4 - 50	3.42 - 20.52
702	135 - 147	3.5 - 5.1	98 - 107	5 - 33	5 - 32	3.25 - 17.1
703	136 - 145	3.5 - 5.1	98 - 107	10 - 33/41	10 - 32/40	0 - 20.52
704	135 - 145	3.4 - 5.5	10 - 80	5 - 30/40	5 - 40	1.71 - 5.13
705	135 - 146	3.5 - 5.1	98 - 111	7 - 31/41	10 - 38	3.42 - 20.52
801	135 - 145	3.5 - 5.0	100 - 107	10 - 42	10 - 42	2/5 - 17/25
802	133 - 146	3.5 - 5.3	95 - 108	0 - 45	14/17 - 36/59	0 - 21
804	133 - 146	3.5 - 5.3	95 - 108	7 - 40	N/A	0 - 20

808	135 - 145	3.6 - 5.0	95 - 107	10 - 50	10 - 45	3 - 21
DAYB						
450	136 - 145	3.4 - 4.4	98 - 107	0 - 34.9/49.9	0 - 34.9/49.9	2 - 21
451	132 - 146	3.4 - 4.5	98 - 107	10 - 30.9/40.9	10 - 34.9/49.9	0 - 4.96
452	136 - 145	3.8 - 5.3	98 - 106	10 - 35/50	10 - 35/50	0 - 18.64
550	135 - 145	3.5 - 5.1	98 - 110	5/10 - 35/40	5/10 - 30/45	1.71 - 8.55
552	136 - 146	3.5 - 5.1	101 - 109	0 - 35/50	0 - 35/50	0 - 3.42
553	135 - 148	3.5 - 5.0	96 - 108	6 - 41/59	5 - 33/35	0.17 - 4.28
650	136 - 145	3.5 - 5.1	96 - 111	0 - 33/41	0 - 32/40	0 - 18.81
651	135 - 145	3.5 - 5.5	96 - 111	0 - 33/41	0 - 32/38	0 - 18.81
652	136 - 145	3.5 - 5.1	98 - 107	0 - 33/41	0 - 31/37	0 - 18.81
653	136 - 146	3.5 - 5.1	90 - 110	0 - 35/45	0 - 31/35	3.42 - 20.52
752	136 - 146	3.5 - 5.1	98 - 107	0 - 34.9	0 - 34.9/39.9	3.42 - 17.1
753	135 - 145	3.5 - 5.0	95 - 105	5 - 41	4 - 38	0 - 4.28
754	N/A	N/A	N/A	N/A	N/A	N/A
850	133 - 146	3.5 - 5.3	95 - 108	10 - 36/41	10 - 31/37	0 - 21
852	136 - 145	3.4 - 4.5	98 - 107	5 - 40	5 - 40	0 - 2.99
950	135 - 145	3.5 - 4.7	97 - 107	0 - 34/44	0 - 29/34	0 - 5
951	135 - 145	3.5 - 5.0	96 - 107	0 - 31/41	0 - 31/37	0 - 17
952	135 - 145	3.2 - 4.5	96 - 107	0 - 34	0 - 31	0 - 5
953	135 - 147	3.5 - 5.0	96 - 109	0 - 40	0 - 31	0 - 17

Source: Norgine, B.V.'s response, dated August 15, 2017, to FDA information request

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/s/

THANH V TRAN
03/02/2018

CLARA KIM
03/05/2018

MARK S LEVENSON
03/05/2018