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APPLICATION NUMBER:

209381Orig1s000

CLINICAL REVIEW(S)

UNIFIED CLINICAL REVIEW
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III

Application Type	NDA
Application Number(s)	209381
Priority or Standard	Standard
Submit Date(s)	April 13, 2017
Received Date(s)	April 13, 2017
PDUFA Goal Date	May 13, 2018 (accounting for 3-month extension due to major amendment)
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Review Completion Date	April 26, 2018
Established Name	Polyethylene glycol 3350, sodium ascorbate, sodium sulfate, ascorbic acid, sodium chloride, and potassium chloride for oral solution
Proposed Trade Name	PLENVU™
Therapeutic Class	Osmotic laxative
Applicant	Norgine BV
Formulation(s)	Powder for oral solution
Dosing Regimen	2-Day split dose and 1-Day split dose regimen
Indication(s)	Cleansing of the colon in preparation for colonoscopy
Intended Population(s)	Adults 18 years and older

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OND=Office of New Drugs

Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	10
1.1	Recommendation on Regulatory Action	10
1.2	Risk Benefit Summary and Assessment.....	10
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies.....	15
1.4	Recommendations for Postmarket Requirements and Commitments	15
2	INTRODUCTION AND REGULATORY BACKGROUND	15
2.1	Product Information.....	16
2.2	Tables of Currently Available Treatments for Proposed Indications	17
2.3	Availability of Proposed Active Ingredient in the United States	19
2.4	Important Safety Issues with consideration to Related Drugs.....	19
2.5	Summary of Presubmission Regulatory Activity Related to the Submission	20
2.6	Other Relevant Background Information: Combination Rule.....	24
3	ETHICS AND GOOD CLINICAL PRACTICES	26
3.1	Submission Quality and Integrity	26
3.2	Compliance with Good Clinical Practices.....	26
3.3	Financial Disclosures.....	28
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	28
4.1	Chemistry Manufacturing and Controls	28
4.2	Clinical Microbiology.....	28
4.3	Preclinical Pharmacology/Toxicology	28
4.4	Clinical Pharmacology	30
4.4.1	Mechanism of Action	30
4.4.2	Pharmacodynamics.....	30
4.4.3	Pharmacokinetics.....	30
5	SOURCES OF CLINICAL DATA.....	32
5.1	Tables of Studies/Clinical Trials	32
5.2	Review Strategy.....	33
5.3	Discussion of Individual Studies/Clinical Trials	33
5.3.1	Study NOCT (NER1006-01/2014) - 2-Day split dosing	33
5.3.2	Study MORA (NER1006-02/2014) 2- and 1-Day (morning only) - split dosing.....	51
5.3.3	Post Hoc Analysis Based on Video Recordings in Studies NOCT (ADV) and MORA (ADV2).....	56
5.3.4	Study DAYB (NER1006-03/2014) 1-Day (Day Before-only) Split Dosing.....	56
6	REVIEW OF EFFICACY	58
6.1	Indication	58
6.1.1	Methods	58
6.1.2	Demographics.....	58

6.1.2.1	Study NOCT	58
6.1.2.2	Study MORA	59
6.1.3	Subject Disposition.....	60
6.1.3.1	Study NOCT	60
6.1.3.2	Study MORA	63
6.1.4	Analysis of Primary Efficacy Endpoint(s)	68
6.1.4.1	Primary Efficacy: Cleansing Success Rate (Responder Rate) in Overall Colon (mFAS)	69
6.1.4.2	Supportive Analyses (Per Protocol).....	78
6.1.5	Analysis of Secondary Endpoints(s)	81
6.1.5.1	Adenoma Detection Rate in Overall and Ascending Colon	81
6.1.5.2	Polyp Detection Rate in Overall and Ascending Colon.....	83
6.1.6	Other Endpoints (Supportive Secondary Endpoints)	84
6.1.6.1	Bowel Cleansing Success Rates Using the Boston Bowel Preparation Scale (BBPS)	84
6.1.6.2	Compliance (Assessed Using Patient Diary)	85
6.1.6.34	Tolerance and acceptability:	86
6.1.6.3	Post Hoc Efficacy Analysis During Advancement Phase Based on the Prerecorded Videos Taken During the Colonoscopy.....	86
6.1.7	Subpopulations.....	95
6.1.8	Analysis of Clinical Information Relevant to Dosing Recommendations	96
6.1.9	Discussion of Persistence of Efficacy and/or Tolerance Effects.....	97
7	REVIEW OF SAFETY.....	97
7.1	Methods	101
7.1.1	Studies/Clinical Trials Used to Evaluate Safety.....	101
7.1.2	Categorization of Adverse Events.....	101
7.1.3	Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence	102
7.2	Adequacy of Safety Assessments	102
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations	102
7.2.2	Explorations for Dose Response	103
7.2.3	Special Animal and/or In Vitro Testing	103
7.2.4	Routine Clinical Testing.....	103
7.2.5	Metabolic, Clearance, and Interaction Workup.....	103
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class	103
7.3	Major Safety Results	104
7.3.1	Deaths.....	104
7.3.2	Nonfatal Serious Adverse Events.....	104
7.3.3	Dropouts and/or Discontinuations.....	107
7.3.4	Significant Adverse Events	109
7.3.5	Submission Specific Primary Safety Concerns	111
7.4	Supportive Safety Results.....	111
7.4.1	Common Adverse Events.....	111
7.4.1.1	Trial NOCT	111

7.4.1.2 Trial MORA.....	112
7.4.2 Laboratory Findings	114
7.4.3 Vital Signs	133
7.4.4 Electrocardiograms (ECGs)	134
7.4.5 Special Safety Studies/Clinical Trials	135
7.4.6 Immunogenicity.....	135
7.5 Other Safety Explorations	135
7.5.1 Dose Dependency for Adverse Events	135
7.5.2 Time Dependency for Adverse Events.....	136
7.5.3 Drug-Demographic Interactions.....	136
7.5.4 Drug-Disease Interactions	136
7.5.4.1 Safety in Patients with Renal Impairment	137
7.5.5 Drug-Drug Interactions	140
7.6 Additional Safety Evaluations.....	140
7.6.1 Human Carcinogenicity.....	140
7.6.2 Human Reproduction and Pregnancy Data	140
7.6.3 Pediatrics and Assessment of Effects on Growth.....	140
7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	141
7.7 Additional Submissions / Safety Issues.....	141
8 POSTMARKET EXPERIENCE	142
9 OTHER INFORMATION	142
9.1 Labeling Recommendations	142
9.2 Advisory Committee Meeting	143
10 APPENDICES	144
Appendix-A: Studies supporting the combination rule	144
Appendix-B: BOCLIR questionnaire	158
Appendix-C: Patient diary	163
Appendix-D: Subject listing for Select Adverse Events of Interest (related to dehydration) across all 3 Studies	166

Table of Tables

Table 1: Composition of NER1006 formulations	17
Table 2: Summary of FDA-approved bowel preparation products in order of approval.....	18
Table 3: Results of inspected sites, per Office of Scientific Investigation	27
Table 4: Plasma Pharmacokinetic Data Following Two-Day Split-Dosing Regimen of PEG 3350, Sodium Ascorbate, Sodium Sulfate, Ascorbic Acid, Sodium Chloride and Potassium Chloride in Healthy Subjects (N=21)	31
Table 5: Studies supportive of efficacy and safety.	32
Table 6: Study NOCT - Schedule of assessments	42
Table 7: Study NOCT - HCS-score descriptors.....	45
Table 8: Study NOCT - Final HCS grading.....	45
Table 9: Study NOCT-Different scales to support efficacy of products approved for bowel prep	47
Table 10: Study NOCT- BBPS-score descriptors.....	48
Table 11: Study MORA - Study visits.....	53
Table 12: Study NOCT-Baseline Demographic Characteristics (Full Analysis Set)	59
Table 13: Study MORA - Baseline Demographic Characteristics (Full Analysis Set)	60
Table 14: Study NOCT-Patient Disposition (Full analysis set).....	61
Table 15: Study NOCT-Major Protocol Deviations (FAS)	63
Table 16: Study MORA-Patient Disposition (Full analysis set).....	64
Table 17: Study MORA-Major protocol deviations (FAS)	66
Table 18: Study MORA-Non-compliance with inclusion/exclusion criteria	67
Table 19: Study NOCT-Primary efficacy analysis (mFAS population).....	69
Table 20: Study MORA-Primary efficacy analysis (mFAS population).....	70
Table 21: Study NOCT - Comparison of number of patients (%) in each grade of cleansing between the treatment groups	71
Table 22: Study MORA - Comparison of number of patients (%) in each grade of cleansing between the treatment groups	72
Table 23: Study NOCT-Number of patients with score of 2 in each colon segment among patients in Grade B.....	73
Table 24: Study MORA - Number of patients with scores of 2 in each colon segment among patients in Grade B.....	73
Table 25: Study NOCT - Assessment of efficacy rates for colonoscopist and first reader	74
Table 26: Study MORA - Assessment of efficacy rates for colonoscopist and first reader	74
Table 27: Study NOCT-Assessment of efficacy rates for colonoscopist, first and second reader (among patients with second reader)	75
Table 28: Study MORA - Assessment of efficacy rates for colonoscopist, first and second reader (among patients with second reader)	75
Table 29: Study NOCT- Efficacy comparison based on time elapsed between completion of bowel preparation and start of colonoscopy	76
Table 30: Study MORA - Efficacy comparison based on time elapsed between completion of bowel preparation and start of colonoscopy	76
Table 31: Cecal Intubation Time - NOCT	77
Table 32: Cecal Intubation Time (MORA).....	78
Table 33: Study NOCT - Primary efficacy analysis (per-protocol set)	79

Table 34: Study MORA - Primary efficacy analysis (per-protocol set)	79
Table 35: Study NOCT - Cleansing rates in ascending colon (mFAS)	80
Table 36: Study MORA - Cleansing rates in ascending colon (mFAS)	81
Table 37: Study NOCT - Adenoma detection rate in overall and ascending colon (mFAS).....	82
Table 38: Study MORA - Adenoma detection rate in overall and ascending colon (mFAS)	82
Table 39: Study NOCT - Polyp detection rate in overall and ascending colon (mFAS).....	83
Table 40: Study MORA-Polyp detection rate in overall and ascending colon (mFAS).....	83
Table 41: Study NOCT-Overall and segmental efficacy based on Boston Bowel Preparation Scale (mFAS).....	84
Table 42: Study MORA-Overall and segmental efficacy based on Boston Bowel Preparation Scale (mFAS).....	85
Table 43: Study NOCT-Bowel Preparation Compliance According to Patient Diary	86
Table 44: Study MORA-Bowel Preparation Compliance According to Patient Diary	86
Table 45: Study NOCT-Patient disposition	87
Table 46: Study MORA-Patient disposition	87
Table 47: Study NOCT (ADV)-Cleansing success rate in overall colon on advancement (Revised mFAS).....	88
Table 48: Study MORA (ADV2)-Cleansing success rate in overall colon on advancement (Revised mFAS).....	89
Table 49: Study NOCT (ADV)-Cleansing success rate in overall colon based on worst score results (mFAS).....	90
Table 50: Study MORA (ADV2)-Cleansing success rate in overall colon on advancement based on worst score results (mFAS).....	90
Table 51: Study NOCT (ADV)-Cleansing success rate in overall colon on advancement using BBPS (mFAS).....	91
Table 52: Study MORA (ADV2)-Cleansing success rate in overall colon on advancement using BBPS (mFAS).....	91
Table 53: Study NOCT (ADV)-Washing Events (Revised mFAS)	92
Table 54: Study MORA (ADV2)-Washing Events (Revised mFAS)	93
Table 55: Overall HCS by age groups (mFAS)	95
Table 56: Overall HCS by age groups (mFAS)	95
Table 57: Efficacy analysis by Gender, NOCT	96
Table 58: Efficacy analysis by Gender, MORA	96
Table 59: Efficacy comparison between 2-Day split-dose and 1-Day morning split dose regimens of NER1006	97
Table 60: Treatment-emergent adverse events observed in at least 1% of patients in clinical trials NOCT, MORA and DAYB.....	99
Table 61: Summary of TEAEs in clinical trials NOCT, MORA, and DAYB.....	104
Table 62: Trial NOCT- "Severe" AEs	109
Table 63: Trial DAYB- "Severe" AEs.....	110
Table 64: NOCT; Treatment-Emergent Adverse Events occurring in ≥ 1 % of patients by Preferred Term (safety set 2)	111
Table 65: MORA-Treatment-emergent adverse events occurring in ≥ 1 % of patients by preferred term (Safety set 2)	112

Table 66: DAYB-Treatment-emergent adverse events occurring in ≥ 1 % of patients by preferred term (Safety set 2).....	113
Table 67: Incidence of shifts in laboratory measures from normal at baseline (Visit 1) to abnormal at post-baseline visits (Clinical trials NOCT and MORA) (DB7 Analysis).....	116
Table 68: Shift analysis of selected laboratory parameters (seen in greater frequency on NER1006 than comparator at Visit 2) (Applicant's analysis)	117
Table 69: Hyper- and hyponatremia incidence at Visit 2 by CTCAE criteria (NOCT and MORA)	120
Table 70: Hyper- and hypokalemia incidence at visit 2 by CTCAE criteria (NOCT and MORA)	121
Table 71: Changes in Renal Function Parameters by CTCAE grade (Visit 3).....	123
Table 72: Persistence analysis - Clinical Trials NOCT and MORA	124
Table 73: Narratives of select patients with persistent extreme laboratory values.....	125
Table 74: Incidence of Shifts in Liver Enzyme and Bilirubin Levels from Normal at Baseline to High (>ULN) at Post-Baseline Visits – NOCT, MORA and DAYB Trials	129
Table 75: DB7 analysis of shift from a normal baseline in ALT at post-baseline visits	130
Table 76: Patients meeting liver parameter outlier criteria of interest at any post-baseline visit	131
Table 77: Liver-related laboratory values in Patient (b) (6) in MORA.....	132
Table 78: Proportion and percentage (n/N (%)) of patients who have systolic blood pressure < 90 mmHg at visit 1 (baseline) or visit 2 (post-dose).....	133
Table 79: Proportion and percentage (n/N (%)) of patients who have orthostatic changes (systolic or diastolic) of > 20 mmHg.....	134
Table 80: Incidence of ECG outliers by treatment and regimen in trials NOCT and MORA....	135
Table 81: Proportions and percentages of TEAEs by demographic subgroups.....	136
Table 82: Proportions and percentages of TEAEs by disease subgroups	137
Table 83: Proportion of Patients with Change in Renal Function Parameters (Creatinine, and/or Creatinine Clearance) by Baseline Renal Function	138
Table 84: Proportion of Patients in whom Changes in Renal Function Parameters (Creatinine, and/or Creatinine Clearance) at Visit 3 also Persisted at Visit 4, by Baseline Renal Function..	139

Table of Figures

Figure 1: Study NOCT - Study Schedule (Protocol version 3.0)	34
Figure 2: Study NOCT - Study Schedule (Protocol versions 5.0, 6.0, 7.0).....	34
Figure 3: Study MORA - Study Schedule (Version 3.0)	52
Figure 4: Study MORA - Study Schedule (Version 4.0, 5.0, and 6.0)	52
Figure 5: Study NOCT-Patient Disposition (all enrolled patients).....	62
Figure 6: Study MORA-Patient disposition (all enrolled patients)	65
Figure 7: Study NOCT (ADV) - cumulative distribution function of the number of washing events	92
Figure 8: Study NOCT (ADV)-cumulative distribution function of the total washing time.....	93
Figure 9: Study MORA (ADV2)-cumulative distribution function of the number of washing events	94
Figure 10: Study MORA (ADV2)-cumulative distribution function of the total washing time...	94

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The clinical review team recommends approval of NDA 209381, proposing Plenvu for the indication of “cleansing of the colon in preparation for colonoscopy in adults.”

1.2 Risk Benefit Summary and Assessment

Plenvu (NER1006) is a low-volume bowel preparation indicated for cleansing of the colon prior to colonoscopy in adults. It is a fixed combination product containing previously approved osmotic laxatives and electrolytes, and is qualitatively similar in its composition to the approved product, Moviprep, though the specific quantities and doses of the individual components differ. Plenvu contains polyethylene glycol (PEG) 3350, sodium ascorbate, sodium sulfate (b) (4) ascorbic acid, sodium chloride, and potassium chloride, with different active ingredient combination across the two doses (PEG3350, sodium sulfate, electrolytes in Dose 1; PEG3350, ascorbate, electrolytes in Dose 2). Each dose is administered as a 500 mL oral solution, followed by 500 mL of mandatory clear fluids. Thus, the total dose and additional fluid volume for Plenvu is 2L.

The clinical program included trials NOCT, MORA and DAYB, which were randomized, parallel group, non-inferiority studies of the efficacy, safety, and tolerability of Plenvu in patients undergoing colonoscopy, against an active comparator. Plenvu was compared with the commercially available bowel preparations of Moviprep® (PEG plus electrolyte solution) (in MORA), a Trisulfate-based preparation (Suprep®; in NOCT) and a sodium picosulfate + magnesium salt-based bowel preparation (SP+MS; Citrafleet®; which is not approved in the U.S., in DAYB). While NOCT evaluated only the 2-day split dosing regimen of Plenvu (NER-2), MORA evaluated both 1-day AM dosing (NER-1), and the 2-day split dosing regimens. The studies were open-label, but the evaluators were blinded to the treatment. For the purposes of this NDA review, NOCT and MORA were considered the key trials, as trial DAYB did not include a US-approved active comparator.

The efficacy of Plenvu, as compared with 2 US-approved active comparators in trials NOCT and MORA, was demonstrated. The primary endpoint in both trials was the proportion of patients with overall bowel cleansing success. Overall bowel cleansing success corresponded to grades A or B on the Harefield Cleansing Scale (HCS). Evaluation of cleansing success was conducted on withdrawal of the colonoscope. In study NOCT, the 2-day, split dose regimen was demonstrated to be non-inferior to the comparator (trisulfate solution), with a success rate of 85% in each group. In study MORA, 2 different regimens of Plenvu were tested, a 2-day, split dose regimen, and a 1-day (day of procedure) morning-only dose regimen, against a 2-day, split dose regimen of PEG+ electrolyte solution. Both dosing regimens of Plenvu were demonstrated to be non-inferior to the comparator, with response rates of 92% for the Plenvu 2-day split dose regimen, 89% for the Plenvu 1-day morning-only regimen, and 88% for the comparator. While the review team notes confounding factors were present, including evaluation of efficacy on withdrawal of scope rather than insertion, poor documentation of the total volume of extra fluid ingested, and

differences in dietary instructions pre-dosing, in general the data support that Plenvu is efficacious in the studied populations. Further, *post hoc* analyses to support this indication were consistent with the efficacy demonstrated on the primary endpoint, including evaluation of the cecal intubation rates, time to complete procedure, *post hoc* analysis of efficacy graded on insertion (rather than withdrawal of scope), and adenoma detection rate.

Clinical trials for Plenvu were sufficient to assess the safety of the proposed drug product, relative to approved bowel preparations, and the demonstrated safety profile supports approval. The overall percentage of patients with treatment-emergent adverse events (TEAE)s was numerically higher in patients treated with Plenvu relative to the approved drugs in these trials: 27.3% vs. 18.1% (NER-2 vs. Suprep; Trial NOCT), and 18.5%, 17.7% vs. 11.5% (NER-1, NER-2 vs. Moviprep; Trial MORA). Common TEAEs included nausea, vomiting, signs and symptoms of dehydration, and electrolyte abnormalities. Hypernatremia was the most commonly observed electrolyte abnormality and is likely caused by inadequate water intake and/or excessive water loss. Electrolyte changes generally trended towards normal over time and while a few individuals demonstrated persistence of these changes, the proportion was small and it was not possible to draw definitive conclusions regarding the relative safety of Plenvu as compared to the active comparators. Transient elevations in liver enzymes were noted in few individuals, and reversed with time. No patient met all three criteria for Hy's law. No new cardiovascular safety signals were identified. The overall picture of signs/symptoms and laboratory findings do not suggest occurrence of new-onset renal injury. There were no deaths in the clinical trials of Plenvu, and the overall incidences of serious adverse events (SAE)s, severe TEAEs and treatment/trial discontinuations were small, and comparable across investigational product and approved treatment arms. Overall, the safety review for Plenvu did not raise any specific safety concerns outside of what is known for this drug class.

In summary, Plenvu was demonstrated to be efficacious in cleansing of the colon prior to colonoscopy. The risks identified are generally consistent with risks associated with other bowel preparation products, including but not limited to dehydration and electrolyte abnormalities. The risks appear to be moderate and manageable, and the benefits of having an additional (low volume) option for colonoscopy preparation appear to outweigh the identified risks, supporting approval.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Analysis of Condition</u>	Colonoscopy is the current standard of care for visualizing the colonic mucosa. It is used for screening/diagnostic purposes, including for screening and diagnosis of colon cancer, and for therapeutic or surgical interventions related to the colonic mucosa. To ensure adequate visualization, a successful bowel cleaning must occur, so that the colon is free of any fecal residue. An inadequate level of bowel cleansing results in a delay in the diagnosis of potentially significant pathology including colorectal cancer, and will result in further costs and patient burden if the procedure has to be repeated.	The use of a safe, convenient and effective bowel cleansing preparation is an essential step ahead of colonoscopy to prepare the colon.
<u>Current Treatment Options</u>	Bowel cleansing preparations approved by the U.S. FDA include four major classes: PEG-electrolyte solutions, oral sulfate solutions, sodium picosulfate, and sodium phosphate. These orally administered, multi-ingredient, large volume preparations are administered as one-day or two-day split dose regimens. The osmotic and/or stimulant laxative effects of the active ingredients in these preparations results in a copious, watery diarrhea, thus clearing out the colon for effective visualization. Bowel preps are followed by ingestion of additional clear fluids to ensure adequate hydration.	An efficient bowel-cleansing agent should be easy to use, of low volume, and not cause significant dehydration or electrolyte abnormalities, especially in patients with co-existing diseases, and/or on medications that predispose to fluid/electrolyte abnormalities. Inadequate dose intake due to product limitations will result in an incomplete bowel preparation. Bowel preparations that offer additional convenience to the patient via a reduced dosing volume, flexibility in dosing time, enhanced palatability, etc., and offer an improved safety profile, without compromising efficacy, are desirable.
<u>Benefit</u>	Two controlled clinical trials were used to demonstrate the efficacy of Plenvu in bowel cleansing. In both trials, efficacy was assessed based on the proportion of patients achieving a score of “A” or “B” on the Harefield Cleansing Scale. This defined “overall cleansing success” which was assessed by a blinded evaluator, on withdrawal of the colonoscope. In trial NOCT, Plenvu was demonstrated to be non-inferior to the comparator (Trisulfate solution), with a comparable proportion of patients achieving overall cleansing success in each treatment arm (85% in each group).	Plenvu was demonstrated to be efficacious (non-inferior to approved products) in cleansing of the colon prior to colonoscopy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	In trial MORA, 2 dosing regimens of Plenvu were evaluated (2-day, split dose, and same day, morning-only administration) against a comparator (PEG+ electrolyte solution). Both dosing arms were demonstrated to be non-inferior to the comparator (response rates were 92%, 89%, 88%) for the Plenvu split dose, vs. Plenvu morning-only, vs. comparator. Additional supportive efficacy measures, such assessment of efficacy on insertion of scope, and adenoma detection rate, all generally supported the efficacy of Plenvu as demonstrated by the primary efficacy endpoint.	
Risk	In clinical trials, the percentage of subjects with TEAEs was numerically higher with Plenvu relative to the approved drugs: 27.3% vs. 18.1% (NER-2 vs. SUPREP; Trial NOCT), and 18.5%, 17.7% vs. 11.5% (NER-1, NER-2 vs. Moviprep; Trial MORA). Common TEAEs included nausea, vomiting, signs and symptoms of dehydration, electrolyte abnormalities (especially hypernatremia) and headache. However, the incidence of serious AEs, or TEAEs leading to trial or treatment discontinuation was small and comparable across treatments. The 1-day AM regimen had a somewhat higher incidence of abdominal pain, vomiting, signs and symptoms of dehydration than the 2-day split regimen. There were no deaths in the trials. The overall incidence of clinically significant electrolyte abnormalities with Plenvu was low, and generally peaked during Visit 2 (post-dose and pre-colonoscopy). Hypernatremia was the most commonly observed electrolyte abnormality and is likely caused by inadequate water intake and/or excessive water loss. The majority of electrolyte changes noted reversed over time and did not require medical intervention. Changes in liver enzymes, in particular, ALT, occurred at a greater frequency with Plenvu, but were mild, and transient in nature and likely due to dehydration that occurred more frequently with Plenvu. No patients met all three criteria for Hy's law. No new cardiovascular safety signals were identified. The overall picture of signs/symptoms and laboratory findings do not suggest occurrence of new onset renal injury.	Clinical trials for Plenvu were acceptable to assess general safety of the proposed drug product, relative to approved bowel preparations. The higher incidence of nausea, vomiting, and signs and symptoms of dehydration could be related (but cannot be conclusively attributed) to the low dosing volume of Plenvu, but did not translate to higher trial discontinuation rates. Overall, the safety review for Plenvu did not raise any specific safety concerns outside of what is known for this drug class.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	The safety profile of Plenvu appears similar to approved bowel cleansing products. Therefore, the proposed wording in the prescribing information is expected to be adequate for risk management, including recommendations to consume additional fluids <i>ad libitum</i> (to avoid dehydration), as well as consideration for laboratory testing in patients who are predisposed to dehydration and electrolyte abnormalities (due to their concomitant disease or medication status). The Agency is aware of the theoretical risk that systemically-absorbed PEG (a major component of Plenvu) could be metabolized <i>in vivo</i> into “toxic metabolites” such as ethylene glycol, diethylene glycol, glycolic acid, glyoxylic acid, and others. While this risk is considered theoretical, it remains an uncertainty that should be addressed.	The proposed Prescribing Information will be adequate to communicate and manage the major risks with Plenvu. Further assessment of the absorption of PEG3350 associated with the marketed formulation, and assessment for the presence of any downstream metabolites will be addressed in a post-marketing requirement.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

Pediatric assessment as required under the Pediatric Research Equity Act (PREA) will be conducted, as described in the agreed initial pediatric study plan (iPSP). These studies will address dose-finding, safety, efficacy and tolerability of Plenvu in pediatric patients from age 1 to <17 years of age.

In addition, a FDAAA-required safety PMR will be issued for a phase 1 pharmacokinetic (PK) study to adequately characterize the PK of PEG 3350 and its metabolites, ethylene glycol (EG), diethylene glycol (DEG), glycolic acid (GA), diglycolic acid (DGA), oxalic acid (OA) and hydroxyethoxyacetic Acid (HEAA) in healthy subjects using a method with an adequate bioanalytical sensitivity for all analytes.

2 Introduction and Regulatory Background

The subject of this NDA is Plenvu (referred to as NER1006 during development, and below throughout this document), a low-volume split-dosing formulation of bowel preparation containing osmotically-active ingredients for colon cleansing before colonoscopy. Colonoscopy may be performed for a variety of indications, in order to diagnose or treat various conditions of the large intestine. In adults, the most common indication for colonoscopy is screening, surveillance, or diagnosis of colorectal cancer. The active ingredients in Plenvu have been used in different quantities in previously approved bowel preparations.

Colorectal screening by colonoscopy is established as a standard of care for early detection of colorectal cancer in subjects 50 years and older. The U. S. Multi-Society Task Force on Colorectal Cancer defines an adequate colonoscopy examination as one that allows confidence that lesions other than small (≤ 5 mm) polyps are generally not obscured by the residual colonic contents.^{1,2} Effective bowel cleansing is, therefore, a prerequisite for achieving a high quality colonoscopy procedure to achieve recommended targets of adenoma detection rate (ADR) of approximately 25% and a cecal intubation rate (CIR) of 90%-95%.³ Inadequate bowel preparation for colonoscopy can result in missed lesions, cancelled procedures, increased procedural time, increased costs, and a potential increase in adverse event rates. Lower ADRs are

1 Wexner SD, Beck DE *et al.* American society of colon and rectal Surgeons; American society of gastrointestinal endoscopy; Society of American gastrointestinal and endoscopic surgeons. A consensus document on bowel preparation before colonoscopy. *Gastrointest Endosc* 2006; 63: 894-909.

2 Mamula P, Adler DG *et al.* Colonoscopy preparation. *Gastrointest Endosc* 2009; 69: 1201-1209.

3 Quality Indicators for GI Endoscopic Procedures: American Society for Gastrointestinal Endoscopy (ASGE) communication, published in *Gastrointestinal Endoscopy*, Vol 81, No1, 2015.

associated with higher rates of interval cancers.⁴ In addition, studies have shown that 28% to 42% patients with inadequate (Fair) bowel preparation had adenomas that were detected on repeat examination within 3 years, including up to 27% with advanced adenomas.^{5,6,7} The practice guidelines recommend a minimum unadjusted CIR of 90-95% for complete examination of cecum because the medial wall of the cecum between the appendicular orifice and ileocecal (IC) wall cannot be visualized from a distance.

Split-dosing of the bowel preparations (defined as giving a portion, usually half, of the bowel preparation the evening prior to the procedure day, and the remaining portion early on the day of the procedure) has emerged as an important factor in bowel cleansing efficacy and compliance;⁸ the American College of Gastroenterology guidelines for colorectal cancer (CRC) screening recommend that the bowel preparations be administered via split-dosing.

2.1 Product Information

The two doses of NER1006 will be administered orally as a split-dosing regimen. Both doses are reconstituted with water. The Applicant proposes to administer NER1006 as a 2-day split dosing regimen or a one-day (day of colonoscopy) split-dosing regimen. In the 2-day split-dosing regimen, the first dose will be given in the evening a day prior to the procedure and the second dose in the morning on the day of the procedure. In the same-day split-dosing regimen, both doses will be given on the day of procedure.

- Dose 1: Provided as one (b) (4), contains PEG 3350, sodium sulfate, sodium chloride, potassium chloride, sucralose, citric acid and mango flavor, to be reconstituted with 16 fl. oz. (500 mL) of water.
- Dose 2: Provided as two pouches. Pouch A contains PEG 3350, sodium chloride, potassium chloride, aspartame and fruit punch. Pouch B contains sodium ascorbate and ascorbic acid. Both pouches are to be combined and reconstituted with 16 fl. oz. (500 mL) of water.
- Details of the active ingredients and other constituents are shown in Table 1.

4 Corly DA, Jensen CD, et al. Adenoma detection rate and risk of colorectal cancer and death. N Eng J Med 2014; 370: 1298-1306.

5 Meenes SB, Kim HM et al. The impact of fair colonoscopy preparation on colonoscopy use and adenoma miss rates in patients undergoing outpatient colonoscopy. Gastrointest Endosc 2013; 78: 510-516.

6 Lebwohl B, Kastrinos F et al. The impact of suboptimal bowel preparation on adenoma miss rates and the factors associated with early repeat colonoscopy. Gastrointest Endosc 2011; 73: 1207-1214.

7 Choksi RV, Hovis CE et al. Prevalence of missed adenoma in patients with inadequate bowel preparation on screening colonoscopy. Gastrointest Endosc 2102; 75: 1197-1203.

8 Cohen LB. Split dosing of bowel preparation for colonoscopy: an analysis of its efficacy, safety, and tolerability. Gastrointest Endos 2010; 72:406-12

Table 1: Composition of NER1006 formulations

Ingredient (g)	NER1006 (Dose 1) (in 500 mL or 16 fl. oz.) (g)	NER1006 (Dose 2) (in 500 mL or 16 fl. oz.) (g)	
		(b) (4) A	(b) (4) B
PEG 3350	100.00	40.00	
Sodium sulfate	9.00	--	
Sodium Chloride	2.0	3.2	
Potassium chloride	1.0	1.2	
Ascorbic acid	--		7.54
Sodium Ascorbate	--		48.11
Others	Sucralose: (b) (4) Mango flavor (b) (4) Citric acid (b) (4)	Aspartame (b) (4) Fruit punch flavor (b) (4)	

Source: Summarized from the Applicant's NDA 209381 submission, Module 2.3 P Table 2.3.P.1

Reviewer comments:

The active ingredients used in NER1006 (PEG, sulfates and ascorbates) have been used alone or in combination in previously approved bowel preparations. The active ingredients in NER1006 are same as in MOVIPREP bowel preparation (used as a comparator in one of the clinical studies conducted by the Applicant) but with different concentrations. The differences between NER1006 and MOVIPREP include the proportion of different ingredients. For example, PEG 3350 was reduced from 200 gm to 140 gm, sodium sulfate was reduced from 15 gm to 9 gm, and the dose of ascorbate (ascorbic acid and sodium ascorbate) was increased from 21.2 gm to 55.65 gm. It is noted that MOVIPREP was developed by the same Applicant. The unique feature of this submission is that it is intended to be low volume. The volume in which the active ingredients are reconstituted, as well as the recommended volume of "additional fluid" to be ingested after the dose, is less than that recommended with other approved bowel preparation products, such as MOVIPREP.

2.2 Tables of Currently Available Treatments for Proposed Indications

The products that have been approved are summarized in Table 2 below.

Table 2: Summary of FDA-approved bowel preparation products in order of approval

Product (s) Name NDA / ANDA #	Formulation	Year of Approval	Dosing / Administration
Colyte 18-983	Powder for oral solution (in 1 gallon) Sodium Sulfate, 21.50 g (anhydrous) Sodium Chloride, 5.53 g Sodium Bicarbonate, 6.36 g Potassium Chloride, 2.82 g PEG-3350, 227.10 g	1984	Ingestion of 1 gallon of oral solution
GoLYTELY 19-011	Powder for oral solution (in 1 gallon) Sodium Sulfate, 21.5g Sodium Chloride, 5.53 g Sodium Bicarbonate, 6.36 g Potassium Chloride, 2.82 g PEG-3350, 227.1 g	1984	Ingestion of 1 gallon of solution prior to colonoscopy
NuLYTELY and TriLYTE: Generic 19-797 and 76-491	Powder for oral solution (in 4 L): Sodium Chloride, 11.2 g Sodium Bicarbonate, 5.72 g Potassium Chloride, 1.48 g PEG-3350, 420 g	1991 2004	Ingestion of 4 liter of solution on the day prior to colonoscopy
HalfLyte and Bisacodyl tablets bowel prep kit 21-551	One 5 mg Bisacodyl delayed release tablet. HalfLyte powder for 2 L solution: PEG-3350, 210 g Sodium Chloride, 5.6 g Sodium Bicarbonate, 2.86 g Potassium Chloride, 0.74 g	2004* 2007 2010	Ingestion of one 5 mg tab bisacodyl tablet; following by 2 L HalfLyte solution in water on the day prior to colonoscopy
OSMOPREP 21-892	Per tablet 1.5 g total of Sodium Phosphate as -monobasic monohydrate 1.102 g -dibasic anhydrous, 0.398 g	2006	Ingestion of 32 tablets with 2 quarts of clear liquids as split dose (20 tablets on the evening before, and 12 tablets on the day of colonoscopy)
MOVIPREP 21-881 (split dose used as the comparator in MORA study)	Each Pouch A contains: Sodium Sulfate, 7.5 g Sodium Chloride, 2.69 g Potassium Chloride, 1.015 g PEG-3350, 100g Each Pouch B contains: Sodium Ascorbate, 5.9 g Ascorbic Acid, 4.7 g	2006	Ingestion of a 2 liter Solution, containing contents of one pouch A and one pouch B, either as split dose (2-day) or evening only (1-day) regimen. Additional fluids may be needed
SUPREP 22-372	Per total 12 oz. dose Sodium Sulfate, 35.02 g Potassium Sulfate 6.26 g (2.8g or 72 mEq K) Magnesium Sulfate 3.2 g (2.66 mMoles) Sodium Benzoate, (b) (4)	2010	Ingestion of 2- 6 oz. bottles as split dose regimen

Table 2: Summary of FDA-approved bowel preparation products in order of approval

Product (s) Name NDA / ANDA #	Formulation	Year of Approval	Dosing / Administration
PREPOPIK 202535	Powder for reconstitution in 5 oz. liquid; each of the two packets contains: Sodium Picosulfate, 10 mg Magnesium Oxide, 3.5 g Citric acid, 12.0 g	2012	Ingestion of two 5-oz solution (each 5 oz. solution contains one packet), either as split dose or full dose regimen. Additional clear liquids are needed after each dose
SUCLEAR 203595	One 6-oz oral solution contains Sodium sulfate, 17.5 g Potassium sulfate, 3.13 g Magnesium sulfate, 1.6 g + 2-L jug with Powder for oral solution: PEG 3350, 210g Sodium Chloride, 5.6 g Sodium Bicarbonate 2.86 g Potassium Chloride 0.74 g	2013	Two doses administered as a split dose (preferred) or day-before regimens: 1 st dose: 6 oz. fluid reconstituted to 16 oz. with water; 2nd dose: Dissolve powder in the jug in 2L water. follow up with additional water;
COLPREP 204553	Kit includes two 200 ml bottles with 22.7 g powder for oral solution, containing: sodium sulfate 17.5 g, potassium sulfate 3.13 g, and magnesium sulfate 1.6 g	2016	Ingestion of two 200 ml solution diluted to 16 oz., in a 2-day split regimen; additional fluids after each dose are required
CLENPIQ 209589	Ready-to-drink 160 mL oral solution contains: Sodium picosulfate, 10 mg Magnesium oxide, 3.5 g Anhydrous citric acid, 12 g	2017	Two doses administered as split-dose (preferred) or day-before regimens; follow up with 40 oz. of clear liquids after 1 st dose; and 24 oz. after 2 nd dose

source: reviewer's table, compiled from Dr. Donna Griebel's Division Director Summary Review for SUPREP dated August 2010 and Dr. Lee's clinical review dated December 2012, with additional information (recent approvals).

*The initial approved dose of bisacodyl in the HalfLyte and Bisacodyl Tablets Bowel Prep Kit was 20 mg. Subsequently, the reduced dose of 10 mg was approved in 2007 due to concern of ischemic colitis. The currently approved dose is 5 mg (approved in 2010)

2.3 Availability of Proposed Active Ingredient in the United States

Currently, NER1006 is not approved or marketed in the United States or any other country. As stated above in Section 2.2, the active ingredients of the NER1006 (PEG, sodium sulfate, sodium Ascorbate, and ascorbic acid) have been used in several approved bowel preparations (Refer to Table 2 above).

2.4 Important Safety Issues with consideration to Related Drugs

Known safety issues with osmotic laxative bowel preparations, described in the labeling of related approved products, include risk of electrolyte abnormalities, renal impairment, seizures,

cardiac arrhythmias, colonic mucosal aphthous ulcerations and rare cases of serious ischemic colitis.

2.5 Summary of Presubmission Regulatory Activity Related to the Submission

NER1006 was developed under IND 120089, submitted on December 18, 2013. During the development, the Applicant had the following three meetings with the Division that are summarized below:

- End of phase 2 (EOP2) meeting on April 16, 2014
- Pre-NDA meeting on February 2, 2016
- Type C meeting on February 3, 2016

EOP 2 Meeting:

o Endpoint(s), Co-primary endpoint model and dosing:

- The Division did not agree to the proposed two “alternative primary endpoints” using both an overall success rate and mean change in the Harefield Cleansing Scale (HCS) for ascending colon. The Division recommended that the Applicant redefine the primary endpoint to be a clinical response based on a pre-specified definition of successful bowel cleansing (e.g., proportion of subjects with “excellent” bowel cleansing).
- The Division did not agree to the proposed statistical design and testing strategy. The Division recommended that both co-primary endpoints, by definition, should demonstrate a statistically significant treatment benefit in order to declare the trial successful. The Applicant’s proposed gate-keeping scheme using the Hochberg method at each step for multiplicity adjustment was inadequate.
- The Applicant clarified that they wanted to design the study such that success could be declared when the ascending colon meets pre-specified criteria, but the overall assessment (results on the overall colon endpoint) does not show non-inferiority. The Agency stated that this scenario would be highly unlikely to support an approval, since it is clinically important to visualize the mucosa along the entire colon during colonoscopy.
- The Division recommended that the proposed non-inferiority (NI) margin should not be larger than the differences in effect sizes observed in recent trials to avoid “biocreep.” The Applicant was referred to the draft FDA guidance entitled “Guidance for Industry: Non-Inferiority Clinical Trials” and requested to provide detailed justification for the proposed NI margin using historical data on the primary efficacy endpoint(s).
- The Division expressed concern about the proposed morning-only dosing of the product. The Applicant was referred to the American College of Gastroenterology guidelines for cancer screening, which recommend that bowel preparations be given in split doses to achieve adequate visualization, which is critical for early detection of lesions.

- The Division recommended achieving the target of “excellent” score on the proposed HCS scale and expressed concern regarding definitions of various sub-scores that are not well-defined and not sufficiently used by the colonoscopist to be reproducible. The Applicant stated that they will have central and local readings.
 - The Division raised concern regarding assessment of the efficacy of cleansing while withdrawing the colonoscope for the current submission. The underlying reason for the concern was that while advancing the colonoscope, cleaning with water and suctioning of the fecal residue is done routinely. This will result in bias towards NI.
 - The Division asked if the phase 2 studies established the time interval necessary for the patients to complete the cleansing and leave their homes to travel to colonoscopy. This will be important information for planning phase 3 studies, labeling, and assessing whether the time interval is in fact more representative of “day before dosing.”
- **Use of non-approved comparator [sodium picosulfate + magnesium citrate salt (SP+MS) based product]:** The Division did not agree with use of this comparator and stated that if it were used in one of the three phase 3 studies (DAYB), the study could not be used to establish NI, as the product was not approved in the United States. In order for a study using this comparator to support approval, superiority must be established.
 - **Changes from (b) (4) to one pouch dosing:** The Division agreed with the Applicant’s proposal to change from (b) (4) to one pouch for the first dose formulation in the phase 3 program. The Division stated that this is acceptable as long as patients are adequately educated regarding preparation and self-administration.
 - **Additional Label Indication:** The Division did not agree with the Applicant’s proposal that these phase 3 studies would support (b) (4).
(b) (4)
The Division recommended that for these labeling claims the Applicant needs to conduct efficacy and safety studies for the proposed indications.
 - **Evaluation in specific subgroups of patients:** The Division asked the Applicant to provide justification and rationale for proposed exclusion of patients with moderate renal and cardiac impairment. However, the Division agreed that no special studies for hepatic impairment nor a thorough QT study are required.

Utility of patient-reported outcome (PRO) instrument, BOCLIR, (b) (4)
(b) (4): The Division stated that the PRO instrument, BOCLIR, (b) (4)
intended by the Applicant (b) (4)
the BOCLIR is not considered fit for purpose based on
current Agency standards.

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- o **Addressing the Combination Rule:** As the current formulation has two or more active ingredients, the Combination Rule needs to be addressed under CFR 300.50. The Division recommended that the Applicant submit evidence (e.g., pharmacodynamic (PD) or clinical efficacy data, or both) to demonstrate that individual components each make a contribution to adequate bowel preparation. In reference to data from the OUT and OPT studies (where different dosing regimens containing different amounts of active components were studied), the Agency also requested the Applicant to provide a brief summary of the effect of each variation (effect of ascorbate dose, effect of liquid intake, etc) on PD or clinical endpoints, presented by the total osmolality of each dose and the total dose.
 - o **Additional Comments:**
 - As osmotic preparations are known to cause fluid shifts, dehydration, and electrolyte derangements, the Division recommended clinical monitoring and follow-up of labs up to Day 7 post-colonoscopy.
 - The systemic exposure to the active components of proposed product, including PEG-3350, sulfate and ascorbate, should be characterized.

Pre-NDA meeting:

- o The Applicant proposed cleansing success rate using the HCS, based on success corresponding to Grades A and B. The proposed definition based on HCS was considered similar to the definition of successful bowel cleanse used for the approval of MOVIPREP; however, the criterion to define success rates for the approval of SUPREP, a comparator used by the Applicant in one study, was different. The Applicant agreed to provide an explanation to support whether any differences between the scale (e.g., scoring method) used in the phase 3 trials and the scale(s) used to support approval of the comparator products would be likely to impact the results of the trials. The Division recommended that the Applicant should justify the use of HCS to establish NI.
- o The Division stated that in addition to the overall cleansing success, defined as Grades A and B on the HCS, the proportion of subjects who achieved Grade A (empty and clean or clear liquid) with complete visualization of the mucosa for NER1006 vs. the comparator product would be reviewed.
- o The Division reiterated the concern, previously communicated to the Applicant in an Advice letter dated September 15, 2014, that any bowel cleansing that occurred during advancement of scope would result in a bias towards NI; thereby assessment of bowel cleansing after irrigation with the scope is not acceptable to support a successful bowel cleansing endpoint. After the studies were completed, the Applicant conducted *post hoc* analyses obtained from the endoscopy videos to support that washing with the endoscope during insertion would not impact the interpretability of the NI analyses.
- o The Division stated that the proposed endpoint for the cleansing of ascending colon (b) (4) [REDACTED]. It is important to visualize the mucosa along the entire colon

during colonoscopy, as communicated previously in the EOP2 meeting minutes, dated May 6, 2014. In addition, the Division noted that the comparators do not have a specific indication for cleansing the ascending colon; therefore, demonstrating non-inferiority to a product not approved for that specific indication would not be sufficient (b) (4). The Division could consider the endpoint further only if superiority was demonstrated over the comparator.

- o The Division raised concern regarding proposed completion of the preparation 1 hour before the colonoscopy for both the NER1006 and the comparator (MOVIPREP) arms in one study (Study MORA), because the current labeling for the comparator (MOVIPREP) recommends that the preparation and fluid intake be completed at least 2 hours before the colonoscopy. The proposed completion of the preparation 1 hour before colonoscopy instead of 2 hours may bias the trial results towards NI. The Division recommended administration of the comparator should be consistent with the approved labeling for demonstrating NI.
- o The Division stated that the efficacy and safety results of a single trial (Study MORA), for the 1-Day morning split dose, would need to be both clinically meaningful and statistically persuasive to support approval of this regimen.
- o The Division stated that the type of meal and the time interval between the last meal and initiation of the bowel preparation were different in NER1006 and MOVIPREP arms. The potential impact of these differences on the efficacy outcome will be considered during the NDA review.
- o The Applicant stated that the colonoscopists were provided with the user manual that explained how “visualization of the mucosa” should be performed and recorded to achieve standardization across the study sites.
- o The Division did not agree to the Applicant’s proposed plan to pool efficacy data from the different phase 3 studies.
- o The proposed strategy for the assessment and supportive statistical analysis of the Boston Bowel Preparation Scale (BBPS) was acceptable for exploratory purposes.
- o The Division recommended that the results of the laboratory analyses to assess electrolytes and renal function at 48-72 hours after the colonoscopy, 1 week post-colonoscopy follow-up, and any abnormal laboratory values that were followed until resolution should be included in the NDA.
- o The Division stated that data provided in the integrated summary of safety (ISS) and integrated summary of efficacy (ISE) will not be relied upon to support product labeling and these analyses will be considered exploratory.

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- The Division reiterated that the Fixed Combination (FC) Rule should be addressed as discussed at the EOP2 meeting. The Applicant was requested to submit proposed evidence supporting that each component of the NER1006 makes a contribution to adequate bowel preparation. The Applicant was also requested to address how variation in diet, amount of liquid intake, and dosing regimen contribute to the bowel preparation and provide a short summary of the effects of each variation. In addition, the effect of different dosing regimens on PD or clinical endpoint(s) should also be presented by total osmolarity of each dose and the total dose. The data to support the FC rule can be submitted in Module 2 of the NDA. The Applicant proposed to address the FC rule by providing pharmaceutical development and clinical data.
 - It was unclear to the Division whether the Applicant had measured metabolites of PEG 3350, including, but not limited to, ethylene glycol (EG) and diethylene glycol (DEG). The Division recommended that the additional metabolites of PEG 3350, including, but not limited to, DEG and EG, in previously collected specimens of plasma and urine should be measured. In addition, the systemic exposure to the potentially toxic metabolites of the EG and DEG (glycolic acid, glyoxylic acid, glycoaldehyde, oxalic acid, 2-hydroxyethoxyacetic acid (HEAA), and diglycolic acid) should be reported. The Division suggested that a subset of toxic metabolites may be studied and a justification provided. The Applicant stated that the biologic samples from the clinical trials are no longer available for additional analyses. In the post-meeting discussion, the Division determined that it is acceptable to conduct the PK evaluation of PEG 3350-related metabolites in humans in a post-marketing trial.
 - **Type C meeting:** Issues related to chemistry manufacturing and controls were discussed. Overall, the Applicant's proposals were appropriate. However, the Division expressed potential concerns about chemical instability as well as the acceptance criterion of the drug product.

Following this meeting, the Applicant submitted an initial NDA in September, 2016. However, the statistical review team identified a number of problematic issues concerning the dataset, which were communicated to the Applicant during the filing review. The Applicant subsequently decided to withdraw the application in November, 2016, in order to address these concerns prior to a resubmission of the NDA.

2.6 Other Relevant Background Information: Combination Rule

NER1006 is a combination product consisting of two drugs in Dose 1 and three drugs in Dose 2; therefore, the Fixed-Combination Drug Rule (21 CFR 300.50)⁹ is applicable.

⁹Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug. <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=300.50>

The Applicant has submitted the studies conducted during the MOVIPREP development program, and the NER1006 program, and supportive literature to support the contribution of each of the components of Dose 1 and Dose 2. The active ingredients in NER1006 are same as in MOVIPREP bowel preparation (which was previously owned by the Applicant) but are in different concentrations. Furthermore, the active ingredients (PEG 3350, sulfates and ascorbates) of NER1006 have been used alone or in combination in previously approved bowel preparations.

The basic principle of the studies is that there is no osmotic barrier between the colonic lumen and extracellular space; it is known that fecal water attains the osmolality of 350 mOsm/L. The introduction of a hyperosmotic load stimulates equalization of this osmolality via osmosis. The osmolality of a drug is based on volume of deionized water added to the powder formulation to reach an osmolality close to 350 mOsm/L, i.e., the osmolality of fecal water (V350). Thus, the V350 represents the volume to which the osmotic component would expand in the human bowel, and thus the volume of stool that would be triggered. Furthermore, studies have shown that stool output is proportional to the osmolality of the administered osmotic product and approximately 3 L of fecal effluent output is required for optimal colon cleansing.

The Applicant performed a series of *in vitro* osmolality studies for the evening and morning formulations, alone and in combination. The different amounts of active ingredients in the morning and evening formulations of NER1006 were evaluated; e.g., sodium sulfate (3, 6, and 9 g), PEG 3350 (20, 40, and 100 g) and ascorbate (30 and 50 g). Osmolality was calculated using a calibrated osmometer where deionized water was added in 50 mL increments until an osmolality of approximately 350 mOsm/L was reached. The candidate formulations associated with the larger V350 value (predicted stool output) were formulated with electrolytes/sweetener/flavor and tested in phase 1 (Study OUT) and phase 2 (Study OPT) clinical studies. The stool output and cleansing success rate of several formulations of NER1006 and MOVIPREP, with varying quantities of active ingredients, were finally evaluated. The data showed that cleansing success (HCS grade A+B) was achieved where median stool output was $\geq$ 3 L. At the request of the Division, the Applicant measured the contribution of osmolality of each active ingredient of the NER1006 formulation used in phase 3 trials. The studies support that each ingredient of NER1006 contributes to the overall osmolality of the product used in phase 3 trials.

For details of the *in vitro* and clinical studies to support the Fixed-Combination Drug Rule see Appendix-A.

Reviewer's comment:

The studies show that each of the osmotically-active components, i.e., the 140 g PEG, 9 g sodium sulfate and 56 g ascorbate, contributes to the efficacy of NER1006; changing/lowering the concentrations of any of the osmotically-acting components in NER1006 would reduce its effectiveness proportionately. This reviewer concludes that the Combination Rule has been addressed.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was acceptable for review. It was complete and appropriately organized. Required electronic information was readily available.

3.2 Compliance with Good Clinical Practices

The Applicant states that the studies were conducted in accordance with the U.S. Code of Federal Regulations (CFR) governing the protection of human subjects (21 CFR 50), IRBs (21 CFR 56), and the obligations of the clinical investigators (21 CFR 312). Both studies were conducted in accordance with U.S. Title 21 CFR on Good Clinical Practices (GCPs), which is consistent with the ethical principles set forth in the Declaration of Helsinki, the International Conference on Harmonization, and the Food and Drug Administration.

An Office of Scientific Investigation (OSI) audit was requested for the sites listed in Table 3 due to high enrollment of study patients.

Table 3: Results of inspected sites, per Office of Scientific Investigation

Name and type of inspected entity/Address	Protocol # /Site #/ # of Subjects	Inspection Dates	Classification
CI: Marco Antonio Álvarez González, M.D. Hospital del Mar Passeig Maritim 25-29 Barcelona, Spain	NER1006-02/2014 (MORA) Site 705 113 Subjects	September 12 to 15, 2017	NAI
CI: Maria Wisniewska-Jarosinska, M.D., Ph.D. Ul. Pilota Stanislaw Wigury 19 Lodz, Lodzkie, 90-302, Poland	NER1006-02/2014 (MORA) Site 605 98 Subjects	September 18 to 20, 2017	VAI
CI: Peter Uebel, M.D. Praxis für Innere Medizin und Gastroenterologie und Allgemeinmedizin Ludwigshafen Hospital Leininger Str. 51-53, Ludwigshafen am Rhein, 45136 Germany	NER1006-02/2014 (MORA) Site 402 102 Subjects	October 23 to 27, 2017	*NAI
CI: Michael P. DeMicco, M.D. Anaheim Clinical Trials, Suite 303 1211 West La Palma Avenue Anaheim, CA 92801	NER1006-01/2014 (NOCT) Site 102 142 subjects	October 12 to 17, 2017	NAI
CI: Joseph B. Henderson, M.D. Cumberland Research Associates 2109 Valleygate Drive, Ste. 102 Fayetteville, NC 208304	NER1006-01/2014 (NOCT) Site 109 96 subjects	November 7 to 15, 2017	*NAI
CI: Kenneth Lee Kelln, M.D. Advanced Research Institute 5896 South Ridgeline Drive, Ste. C South Ogden, UT 84405	NER1006-01/2014 (NOCT) Site 110 125 subjects	October 25 to November 2, 2017	NAI
CRO: (b) (4)	NER1006-01/2014 (NOCT) NER1006-02/2014 (MORA)	October 15 to 24, 2017	*NAI

Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data may be unreliable.

*Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

source: Clinical Inspection Summary report by Dr. Susan Leibenhaut, MD (OSI), dated 12/4/2017

In summary, 5/6 inspected sites received a compliance classification of “no action indicated” (NAI). The 6th site was noted to have inadequacies in records due to flooding at the site causing

destruction of some portions of records. Despite these discrepancies, the report from the OSI investigator concluded that results from this study site may be used in support of the indication.

Refer to the clinical inspection summary report by Dr. Susan Leibenhaut, dated 12/04/2017.

3.3 Financial Disclosures

The Applicant certified that, in compliance with 21 CFR 54, no financial disclosures were applicable to any of the studies conducted in support of this application.

The Applicant submitted Form FDA 3454 and certified that the clinical investigators did not participate in any financial arrangement with the Applicant of the covered studies whereby the value of compensation to the Investigator for conducting the study would affect the outcome of the study [as defined in 21 CFR 54.2(a)]; had no proprietary interest in this product or significant equity interest in the Applicant of the covered study [as defined in 21 CFR 54.2(b)]; and was not the recipient of significant payments of other sorts [as defined in 21 CFR 54.2(f)].

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The application technical lead for the Office of Pharmaceutical Quality (OPQ), Dr. Hitesh Shroff, notes in his review that the ‘applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.’ The application is recommended for approval from a drug substance perspective. Please refer to review by Dr. Erica Englund and Dr. Donna Christner in this regard. The overall control strategy for the drug product is deemed adequate based on raw material controls, drug product specification including appearance, assay, impurities, water content, content uniformity, and microbial limits. A 24-month expiry period when stored between 20 to 25°C in the proposed container system is granted, and the reconstituted solution is recommended for use within 6 hours. Please refer to Drug Product review by Dr. Sarah Ibrahim and Dr. Moo Jhong Rhee in this regard. In addition, the Office of Process and Facilities (OPF) has made a final overall ‘adequate’ recommendation for the drug substances and drug product manufacturing and testing facilities involved in this application. Please refer to the facilities review by Dr. Xiaohui (Sherry) Shen and Dr. B.J. Ryan in this regard. All manufacturing procedures and operations are performed in accordance with current Good Manufacturing Practices and the drug product manufacturing process was deemed acceptable. Please refer to Process review by Dr. Kejun Cheng and Dr. N. Chidambaram in this regard.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

No non-clinical approvability issues were identified. No new nonclinical studies were submitted in support of this 505(b)(2) NDA. The Applicant submitted the nonclinical safety information

initially generated during the Moviprep oral suspension (NDA 21881) development program (full study reports were provided to this NDA submission), as well as on published literature for the safety of the individual ingredients and flavor enhancers of Plenvu.

NER1006 contains a lower dose of PEG 3350 and sodium sulfate, and higher dose of sodium ascorbate, compared to Moviprep. The nonclinical safety of Moviprep was established under NDA 21881 and was summarized in the nonclinical review for Plenvu. The safety of the ascorbate/ascorbic acid levels in Plenvu is supported by toxicology information from published literature:

- In a 13-week repeat-dose toxicity studies with ascorbic acid, the NOAELs were reported to be 16,900 and 21,500 mg/kg/day for male and female mice, respectively, and 8,100 and 9,100 mg/kg/day for male and female rats, respectively. The NOAELs in rats and mice provide adequate safety margins for the proposed doses.
- Ascorbic acid was negative in mutagenicity studies, and had no carcinogenic potential at doses up to 7,200 mg/kg/day in mice (NTP 1983¹⁰) and up to 2,000 mg/kg/day in rats.¹¹

Novel excipients: The two flavoring agents used in the proposed drug product have not been previously used in FDA-approved products [Fruit punch flavor # (b) (4); Mango flavor # (b) (4)]. Based on a safety assessment of individual ingredients (b) (4) of the two flavoring agents using toxicology information available in the published literature, the non-clinical reviewers conclude that there are no safety concerns regarding their use in PLENVU at the proposed levels.

(b) (4) During the review cycle the Agency identified that the anticipated total exposure of (b) (4) from the excipients and flavors was reported to be higher than the ICH Q3D permitted daily exposure limits. The Applicant adequately addressed this concern in a response to information request, received 11/13/17. In this, the Applicant notes that the potential maximal daily (b) (4) exposure presented was based on available data from excipient suppliers. To mitigate the potential concern, the Applicant tested all exhibit batches of PLENVU and the results demonstrated that actual levels of (b) (4) were (b) (4) for all tested samples. These results suggest that the actual maximal exposure to (b) (4) from the dose of PLENVU was well below the maximal daily limit.

Overall, there were no safety concerns from a nonclinical perspective regarding the qualitative and quantitative composition of PLENVU, including high dose ascorbic acid/sodium ascorbate as well as novel flavoring agents. The levels of impurities and degradants were deemed to be within acceptable ranges.

¹⁰ Carcinogenesis bioassay of L-ascorbic acid (vitamin C) (Cas no. 50-81-7) in F344/n rats and B6C3F1 mice (feed study). National Toxicology Program technical report series no. 247, 1983.

¹¹ Scientific Opinion on the re-evaluation of ascorbic acid (E 300), sodium ascorbate (E301) and calcium ascorbate (E 302) as food additives. EFSA Panel on Food additives and Nutrient Sources added to Food (ANS). EFSA Journal 2015; 13 (%):4087.

Please refer to the nonclinical review in DARRTs dated 11/29/2017 by Drs. Dinesh Gautam and Sushanta Chakder for details.

4.4 Clinical Pharmacology

The Clinical Pharmacology reviewers found NDA 209381 to be acceptable. No bridging study was conducted as the phase 3 formulation was the same as the to-be-marketed formulation. The NDA submission did not include *in vitro* drug-drug interaction or metabolism studies. Per the Clinical Pharmacology reviewer, as PLENVU is proposed for a single use in colon cleansing before colonoscopy, the lack of *in vitro* or *in vivo* drug-drug interaction studies is acceptable. The reviewers find the proposed dose/dosing regimens to be acceptable. Additionally, the Applicant's proposals to administer other oral medications at least 1 hour before Plenvu, and to avoid use of stimulant laxatives (e.g., bisacodyl, sodium picosulfate) were found acceptable. Regarding dosing in the renal impairment population, reviewers note that they "do not believe the phase 3 study contains adequate number of patient with moderate renal impairment (only approximately 5%) to make any conclusion about the relative safety in this population."

A post-marketing requirement to assess PK of PEG and potential PEG metabolites will be recommended (see Section 1.4 above).

Please refer to the finalized Clinical Pharmacology review in DARRTs by Drs. Dilara Jappari and Insook Kim for additional details.

4.4.1 Mechanism of Action

The primary mode of action is osmotic action of the components of PLENVU (PEG 3350 plus sodium sulfate components in Dose 1, and sodium ascorbate/ascorbic acid plus PEG 3350 components in Dose 2), which induce the laxative effect. The physiological consequence is increased water retention in the lumen of the colon, resulting in loose stools.

4.4.2 Pharmacodynamics

The osmotic effect of the unabsorbed PEG, ascorbate, and sulfate ions, when ingested, produces a copious watery diarrhea.

4.4.3 Pharmacokinetics

The pharmacokinetic parameters for PEG 3350, ascorbate and sulfate are shown in Table 4.

Table 4: Plasma Pharmacokinetic Data Following Two-Day Split-Dosing Regimen of PEG 3350, Sodium Ascorbate, Sodium Sulfate, Ascorbic Acid, Sodium Chloride and Potassium Chloride in Healthy Subjects (N=21)

PK Parameter	PEG 3350 Mean (SD)	Ascorbate¹ Mean (SD)	Sulfate¹ Mean (SD)
C _{max} [µg/mL]	2.7 (1.17)	70.8 (22.37)	17.6 (4.80)
t _{max} [h]	3.0 (0.61)	16.8 (0.75)	8.1 (5.51)
AUC(0-t _{last}) [(µg/mL)*h]	17.3 (7.19)	433.1 (157.29)	206.2 (74.32)
V _d [L]	48,481 (29,811)	1,026 (675)	231 (205)
t _{1/2} [h]	4.1 (2.34)	7.2 (6.16)	10.5 (15.19)

¹ Baseline-corrected

SD = standard deviation; C_{max} = maximum concentration; t_{max} = time to maximum concentration from start of dosing; AUC(0-t_{last}) = area under the curve from t₀ to t_{last}; V_d = volume of distribution; t_{1/2} = half-life.

Source: Compilation of PK information from Tables 11.4.1.11, 11.4.1.15, and 15.2.3.48 from Applicant's CSR for Phase I study NER1006-01/2011 (OUT).

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The studies supporting the efficacy and safety are summarized in Table 5.

Table 5: Studies supportive of efficacy and safety.

Trial Identity	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Sites and Countries
<i>Controlled Studies to Support Efficacy and Safety</i>							
NER1006-01/2014 (NOCT)	Phase 3, MC, R, SB, AC (SUPREP - approved in the US), PG	2-Day Split Dosing regimen	Grade A and B cleansing rate as per HCS scale	2 days FU 7 days	621	Patients undergoing a screening, surveillance, or diagnostic colonoscopy	12 sites in the United States
NER1006-02/2014 (MORA)	Phase 3, MC, R, SB, AC (MOVIPREP - approved in the US), PG	2-Day Split Dosing regimen and 1-Day Morning Split-Dosing Regimens	Grade A and B cleansing rate as per HCS scale	1 or 2 days FU 7 days	849	Patients undergoing a screening, surveillance, or diagnostic colonoscopy	29 study sites across European Union (7 countries: Belgium, France, Germany, Italy, Poland, Spain, and United Kingdom)
<i>Study to Support Safety</i>							
NER1006-03/2014- (DAYB)	Phase 3, MC, R, SB, AC (CITRAFLEET ¹ - not approved in the US), PG	1-day, day before-only, split dosing	Grade A and B cleansing rate as per HCS scale	1 Day	515	Patients undergoing a screening, surveillance, or diagnostic colonoscopy	19 study sites across European Union (7 countries: Germany, Italy, Netherlands, Poland, Spain, and United Kingdom)

¹ Sodium Picosulfate and Magnesium Salt (SP+MS) Solution

MC, multi-center; R, randomized; SB, single blind (investigator); AC, active control; PG, parallel group; HCS, Harefield Cleansing Scale; FU, follow-up
source: reviewer's table compiled from information submitted in clinical study reports

5.2 Review Strategy

The Applicant submitted three phase 3 trials, NER1006-01/2014 (NOCT), NER1006-02/2014 (MORA) and NER1006-3/2014 (DAYB) to support the indication of colon cleansing in preparation for colonoscopy in adults. All the trials were multicenter, randomized, parallel group and used active comparators. The comparators used in two trials, NOCT and MORA, are approved in the US; whereas in one trial, DAYB, the comparator used is not approved in the US (Table 5). Therefore, Trials NOCT and MORA were considered adequate to assess the efficacy and safety of NER1006. Data from the third phase 3 trial (DAYB) were considered supportive data for safety evaluation, but were not considered appropriate to support the efficacy claim.

Because the trials utilized different administration regimens and different active comparators, both safety and efficacy data are evaluated by individual trial, rather than in a pooled fashion.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Study NOCT (NER1006-01/2014) - 2-Day split dosing

Title

A multicenter randomized parallel group phase III study comparing the bowel cleansing efficacy, safety and tolerability of NER1006 (a low volume bowel cleansing solution) versus a Trisulfate bowel cleansing solution using a 2-day split-dosing regimen in adults.

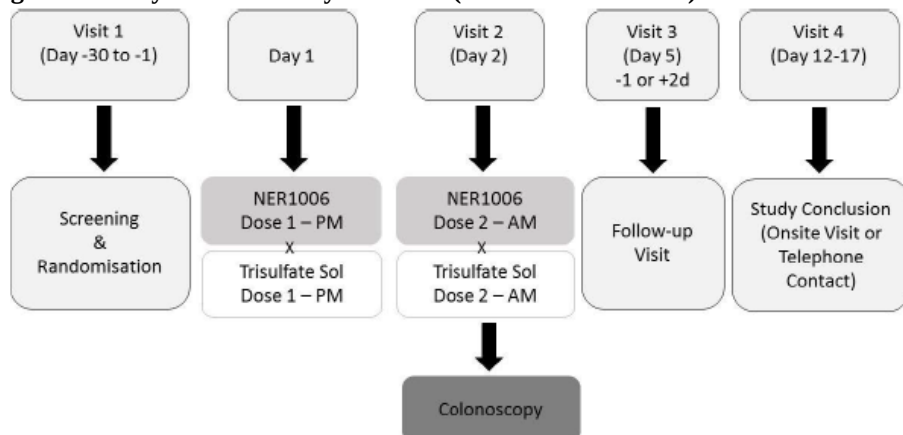
Study Objectives

To evaluate the efficacy and safety of 2-day split-dosing regimen of NER1006 for bowel preparation in patients undergoing screening, surveillance or diagnostic colonoscopy.

Study Design

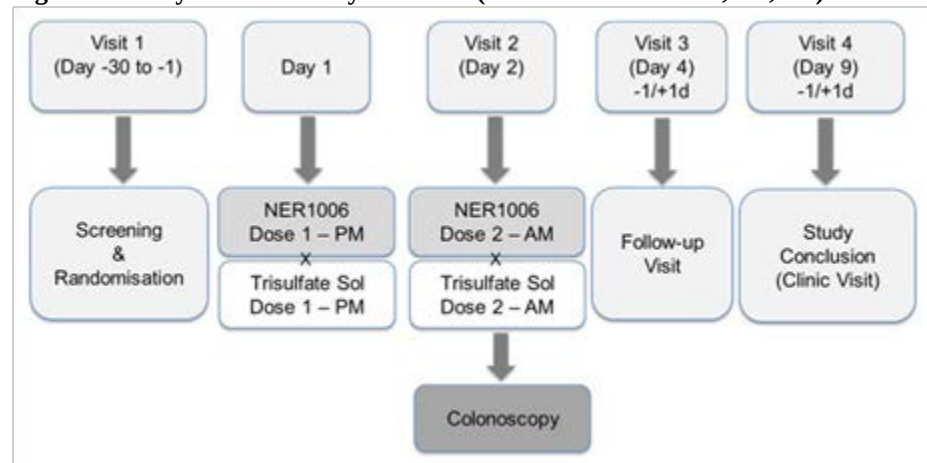
This was a randomized, single blind, multicenter, active comparator, and parallel group trial conducted in the United States at 12 sites in subjects aged 18 to 85 years. The study duration for each patient was maximum 40- 47 days (including the screening period). The trial was conducted over a period of 9 months, initiated on September 29, 2014 and completed on June 22, 2014. The study schedule is shown in Figure 1 and Figure 2. Follow-up of laboratory parameters 3 and 7 days post-colonoscopy were performed.

Figure 1: Study NOCT - Study Schedule (Protocol version 3.0)



Abbreviations: AM, morning; d, day; h, hour; PM, evening; sol, solution
source: Adapted from the Applicant's CSR (NOCT) Figure 9-1

Figure 2: Study NOCT - Study Schedule (Protocol versions 5.0, 6.0, 7.0)



source: Adapted from the Applicant's CSR (NOCT) Figure 9-2

Reviewer comments:

The study design is appropriate. The follow-up of laboratory parameters 7 days post-colonoscopy is important to assess the lab changes that are likely to occur after the administration of bowel preparations and to determine whether they have returned to baseline.

Choice of control group:

The active comparator used is Trisulfate solution (SUPREP).

Protocol amendments;

The original protocol (15 JUL 2014) was amended three times during the course of the study. The key changes in each amendment are summarized below.

Amendment-1: Version 2.0, dated 25 NOV 2014, leading to Protocol Version 5.0, dated 25 NOV 2014

- Replaced all references to “e-PRO” and “e-diary” with “PRO” and “diary” respectively. Instructions provided to use paper patient diary and PRO. Responses from patient diary and PRO were reviewed for completeness and transcribed to the electronic database capture system by the site staff.
- Clarification provided that the “assessment of tolerability using PRO” referred to the use of the BOCLIR questionnaire.
- Visit 3 and Visit 4 timeframes were modified to earlier timeframes for the purposes of monitoring patients for any potential kidney injury. Visit 3 was rescheduled on Day 4 (previously Day 5) and Visit 4 on Day 9 (previously Days 12 to 17) with a window of -1/+1 Day. This includes making Visit 4 as clinic visit.
- Study sites were allowed to schedule the intake of the investigational medicinal product ± 2 hours before or after the suggested approximate time in the protocol.
- Clarification regarding documenting the site colonoscopist’s experience and personal adenoma detection rate (ADR) (based on colonoscopies performed per month in the last 12 months) via a questionnaire.
- Clarification regarding scoring: Intraprocedural cleaning to be conducted prior to the assessment and the scoring of segmental cleansing to be done during the withdrawal phase of the colonoscopy.
- Added clarifications to exclusion criterion “known hypersensitivity to PEGs, ascorbic acid and sulfates or any other component of the study drug or comparator” because it did not include sulfa drug allergy/intolerance as these are different compounds.

Amendment-2: Version 1.0, dated 17 MAR 2015, leading to Protocol Version 6.0, dated 17 MAR 2015.

- Increased the number of patients to be randomized from 540 to 620 to account for a 20% drop-out rate (in the previous version of the protocol it was 10%).
- Added clarification in the assessment of orthostatic blood pressure; included supine followed by standing blood pressure measurements.
- Added clarification in the definition, recording and follow-up of adverse events (AEs); include events occurring from the time of informed consent until 14 days after the last dose.
- Added clarification that all serious AEs (SAEs) to be followed up until the outcome was resolved or stabilized at a level acceptable to the investigator or up to 3 months after the last dose.
- Patients with missing colonoscopy data were excluded from the per protocol set.

- Patients with low compliance rate (consumption of <75% of at least one of the doses, regardless of the amount of mandatory additional fluids consumed) were excluded from the per protocol analysis set.
- Patients with major protocol deviations related to the eligibility criteria were excluded as decided prior to database lock.
- Revised the assessment of superiority for the alternative primary endpoint. The following closed test procedures were followed:
 1. If both alternative primary endpoints demonstrate NI:
 - If both alternative primary endpoints show advantage of NER1006 compared to Trisulfate with a 1-sided p value <0.025, NER1006 will be declared superior for both alternative primary endpoints.
 - If one of the alternative primary endpoint has a 1-sided p value ≥ 0.025 , then the other primary endpoint must achieve a 1-sided p value of <0.0125 to be declared superior.

Amendment-3: Version 1.0, dated 25 June 2015, leading to Protocol Version 7.0, dated 25 June 2015.

- Amended to include three distinct population analyses on the data; namely, the full analysis set (FAS), the modified full analysis set (mFAS), and the per protocol (PP) set.
 - FAS: All randomized patients in the study
 - mFAS: All randomized patients, excluding subjects who were randomized but subsequently failed to meet entry criteria AND in whom it was confirmed that the patient did not ingest any study drug
 - PP set: All patients of the FAS who met all the following criteria:
 - Fulfilled entry criteria
 - Study drug compliance rate of at least 75% of each dose of bowel preparation according to their patient diary (regardless of the amount of additional fluids taken)
 - Post-baseline data for at least one of the two alternative primary endpoints is available
 - No major protocol deviations
- Changed the analysis population for the primary evaluation of efficacy to the modified FAS (mFAS). FAS and PP set will be used as supportive in nature.

Reviewer comment:

The changes made in the protocol do not appear to affect the efficacy and safety of the trials.

- **Study Population**

- **Key Inclusion criteria**

- Male and non-pregnant female outpatients and inpatients aged ≥ 18 to ≤ 85 years undergoing a screening, surveillance, or diagnostic colonoscopy.

- **Key exclusion criteria:**

1. Patients with past history within the last 12 months or current episode of severe constipation (requiring repeated use of laxatives/enema or physical intervention before resolution), known or suspected ileus, gastrointestinal obstruction, gastric retention, bowel perforation, toxic colitis, or megacolon.
2. Ongoing severe acute inflammatory bowel disease.
3. Impaired consciousness that might predispose them to pulmonary aspiration.
4. History of significant gastrointestinal surgeries, including colonic resection, sub-total colectomy, abdomino-perineal resection, de-functioning colostomy, Hartmann's procedure and de-functioning ileostomy or other similar surgeries involving structure and function of the small or large bowel.
5. Active intestinal bleeding episodes or with a clinically significant low hemoglobin level (<9 g/dL for women and <11 g/dL for men) at screening.
6. Regular use of laxatives or colon motility-altering drugs (i.e., more than 2-3 times per week) in the last 28 days prior to screening and/or laxative use within 72 hours prior to administration of the preparation.
7. Patients with known glucose-6-phosphate dehydrogenase deficiency.
8. Known phenylketonuria.
9. Known hypersensitivity to PEGs, ascorbic acid and sulfates (not including sulfa-based products) or any other component of the study drug or comparator.
10. Past history within the last 12 months or evidence of any ongoing clinically relevant electrocardiogram (ECG) abnormalities (e.g., arrhythmias).
11. History of uncontrolled hypertension with systolic blood pressure >170 mmHg and diastolic blood pressure >100 mmHg.
12. Cardiac insufficiency (New York Heart Association grades III or IV).
13. Moderate to severe renal insufficiency (i.e., with glomerular filtration rate [GFR], <60 mL/min/1.73 m²).
14. Serum albumin <3.4 g/dL.
15. Known liver disease of grades B and C according to the Child Pugh classification.
16. Dehydration at screening as evaluated by the investigator from physical examination and laboratory investigations.
17. Clinically significant electrolyte abnormalities, whether pre-existing or noted at screening, such as hypernatremia, hyponatremia, hyperphosphatemia, hypermagnesemia, hypokalemia, hypocalcemia, dehydration, or those secondary to the use of diuretics or angiotensin-converting enzyme inhibitors.

18. Patients with any other clinically significant hematological parameters including coagulation profile at screening.
19. Clinically relevant findings on physical examination based on the investigator's judgment.
20. Concurrent participation in an investigational drug or device study or participation within 3 months of study entry
21. Patients who were pregnant or lactating, or intending to become pregnant.
22. History of drug or alcohol abuse within the 12 months prior to dosing.
23. Undergoing colonoscopy for foreign body removal and/or decompression.
24. Inability to follow study procedures, e.g. cognitively impaired, debilitated, or fragile patients as per investigator judgement.
25. Patients ordered to live in an institution on court or authority order.

Reviewer comment:

The inclusion and exclusion criteria are appropriate.

• **Study treatment:**

Patients were dispensed NER1006 or Trisulfate solution and were provided instructions on dosing and dietary restrictions.

NER1006

Two doses (powder for oral solution) of NER1006 were provided to the patient.

- Dose 1 (evening dose): This was in one sachet that contained PEG 3350, sodium sulfate, electrolytes and mango flavor, and was reconstituted with 16 fl. oz. (500 mL) of water.
- Dose 2 (morning dose): This was in two sachets that contained PEG 3350, sodium ascorbate, ascorbic acid, electrolytes and fruit punch flavor, and was reconstituted with 16 fl. oz. (500 mL) of water.

For more details of the composition of the two formulations for Dose 1 and Dose 2 please see Table 1.

Dosing Instructions:

The dosing commenced in the evening of the day before colonoscopy.

Day before colonoscopy (Dose 1):

Dose 1 was taken at approximately 6 PM on the evening prior to the colonoscopy examination. The patients were instructed to drink at the rate of approximately 8 oz. every 15 minutes until the reconstituted solution was finished. Over the next 30 minutes, patients were instructed to drink the mandatory clear fluids (16 fl. oz.) at the rate of approximately 8 fl. oz. every 15 minutes. Additional water/clear fluids could be drunk *ad libitum*.

Day of colonoscopy (Dose 2):

Dose 2 was instructed to be started at 6 AM (10-12 hours after the Dose 1). The patients were instructed to mix the two sachets of Dose 2 powder for solution with water (16 fl. oz.). The patients were asked to drink the reconstituted solution and mandatory clear fluids as for Dose 1. All fluid intakes were to be completed at least 2 hours prior to colonoscopy.

A window of +/- 2 hours start time for both study drug administrations was acceptable. All other activities had to be aligned according to the study drug start time to ensure that the colonoscopy was performed at least 2 hours after the last fluid intake.

Dietary Restrictions:

Day prior to colonoscopy: Patients were allowed to take light breakfast and light lunch on the day prior to the procedure. Intake of the reconstituted solution was started at least 3 hours after the lunch. Patients were allowed clear fluids after lunch prior to administration of solution and continue to take clear fluids until 2 hours prior to the colonoscopy. No dinner was permitted.

Day of colonoscopy: Breakfast was not permitted on the day of colonoscopy. Patients were allowed to take clear fluids or water up to 2 hours prior to colonoscopy.

Trisulfate solution (Active comparator) administration

A 2-day split-dosing regimen of Trisulfate solution was administered as a split-dose preparation, consistent with the US prescribing information, as follows:

Day before colonoscopy (Dose 1):

- Beginning at approximately 6 PM on the evening prior to the colonoscopy examination, patients were instructed to dilute the 6 fl. oz. of Trisulfate solution (Dose 1) in a mixing cup with water and fill up to 16 fl. oz. mark and drink all the contents. They were also instructed to drink two additional cups (16 oz. each) of water over the next hour.

Day of colonoscopy (Dose 2):

- At approximately 6 AM (10-12 hours after Dose 1), patients were instructed to dilute the 6 fl. oz. of Trisulfate solution (Dose 2) in a mixing cup with water and fill up to 16 fl. oz. and drink all the contents. They were also instructed to drink two additional cups (16 oz. each) of water over the next hour. Intake of the complete preparation and mandatory additional water had to be complete at least 2 hours prior to colonoscopy.

Dietary Restrictions:**Day prior to colonoscopy:**

Only light breakfast or clear liquids were permitted.

Day of colonoscopy:

Only clear liquids were permitted until after colonoscopy.

Reviewer comments:

- *Patients in the NER1006 arm were instructed to take additional water/clear fluids ad libitum in addition to the study protocol. However, patients in the Trisulfate solution group were not instructed to take additional water/clear fluids ad libitum. In the labeling for Trisulfate solution, patients are allowed to take clear fluids on the day prior to and on the day of colonoscopy until after the colonoscopy. This difference could bias the results of the non-inferiority trial in favor of NER1006. Additional information regarding the total volume of fluid ingested by patients in both arms was requested from the Applicant (FDA information request from 8/11/17); however, the Applicant notes that they did not collect information from patients regarding the total volume of fluid ingested (outside of the required clear liquids per administration instructions), so it is not possible to ascertain whether or not these differences in instructions in regard to the need to drink additional fluids after ingestion of each dose affected the efficacy outcomes.*

Lack of instructions for taking additional clear liquids in the comparator arm could lead to patients not taking adequate fluids during the bowel preparation. Decreased fluid intake may affect efficacy due to inadequate fluids available for colon washout. In addition, decreased fluid intake could cause dehydration and associated electrolyte abnormalities, which are major safety concerns in these bowel preparations.

- *Dietary Restriction: Patients were allowed to take light breakfast and lunch on the day prior to the colonoscopy in NER1006 group and only light breakfast in the comparator group. Intake of an additional meal (lunch) may add to the colonic load that needs to be cleared by the bowel preparation and may cause incomplete evacuation of the colonic contents in NER1006 group compared with Trisulfate solution group. It may be ideal to compare the efficacy of two products when taken with the same dietary restrictions to isolate the effect of the study drug. However, the Applicant reports that this approach was chosen to compare the effect of the whole regimen (drug + dietary restrictions + fluid requirements) from one approved regimen to a new proposed regimen. This approach is reasonable. Further, the limitations here would serve only to bias in favor of the comparator, given that additional food intake may result in additional fecal residue to clean. Thus, this difference in diet does not negatively impact the rigor of the non-inferiority comparison.*

Assignment to the treatment:

Patients were randomly assigned in a 1:1 ratio to receive either NER1006 or Trisulfate solution. An interactive web response system (IWRS) was used for the randomization. (b) (4)

generated the randomization schedule for the IWRS, which linked sequential patient randomization numbers to treatment codes. The randomization was not stratified.

The randomization numbers were blocked, and within each block the same number of patients was allocated to each treatment group. The block size was not revealed to the site staff.

Blinding:

The site colonoscopist and central readers were blinded to the study drug assignment. Central readers were also blinded to the previous assessment of the colon cleansing in the study. Patients and other site staff were instructed not to inform the blinded colonoscopist of the study drug assignments.

Procedures and schedule:**Study procedures:**

There were 4 in-person visits:

Screening/Baseline (Visit 1: Day 30 to -1): Eligibility criteria and medical history were reviewed and laboratory and physical examination were performed. Eligible patients were randomly assigned to NER1006 or Trisulfate product in a 1:1 ratio.

Day before colonoscopy (Day 1): Patients were instructed to self-administer the assigned bowel preparations (Dose 1) on the day prior to the colonoscopy and to complete the study diary.

Day of colonoscopy (Visit 2: Day 2): Patients self-administered Dose 2 on the day of colonoscopy in the early morning at home. Physical examination, EKG, PRO compliance and labs were performed before the colonoscopy.

Follow up visit 1 (Visit 3: Day 4 $\pm$ 1 day): Patients returned 2 days after the colonoscopy on Day 4, for the follow-up visit; physical examination and labs were performed and any AEs documented.

Follow up visit 2 (Visit 4: Day 9 $\pm$ 1 day): Patients returned 7 days after the colonoscopy on Day 9, for the follow up visit; the labs were performed and any AEs documented. For details of the scheduled assessment and procedures see Table 6.

Table 6: Study NOCT - Schedule of assessments

Assessments	Visit 1 – Screening/ Randomization	Day Before Colonoscopy	Visit 2 – Day of Colonoscopy	Visit 3 – Follow-Up	Visit 4 – Follow-Up ^a
Protocol Version 3.0	Day –30 to –1	Day 1	Day 2	Day 4 (–1/+2 days)	Day 12-17
Protocol Version 5.0, 6.0, or 7.0	Day –30 to –1	Day 1	Day 2	Day 4 (–1/+1 day)	Day 9 (–1/+1 day)
Informed consent and HIPAA authorization	X				
Inclusion and exclusion criteria review	X				
Demographic data	X				
Medical history (and concomitant diseases)	X				
Physical examination	X		X ^b	X	
Body weight, orthostatic blood pressure, pulse rate, body temperature	X		X ^b		
Height	X				
12-lead ECG	X		X ^b		
Hematology/clinical chemistry laboratory tests	X		X ^c	X	X ^d
Coagulation profile	X				
Urinalysis	X		X		
Pregnancy test (where applicable)	X		X		
Concomitant medication review	X		X	X	X
Eligibility check ^e	X				
Randomization	X				
Supply of IP, dosing instructions, and measuring/mixing container to eligible patients	X				
PRO compliance/acceptability/tol- erability assessment/completion (BOCLIR)			X		
Recording and review of adverse events ^f	X		X	X	X
Administration of IP by patients		X ^g	X ^g		
Patient completion of study		X	X		

Table 6 (continued): Study NOCT - Schedule of assessments:

Assessments	Visit 1 – Screening/ Randomization	Day Before Colonoscopy	Visit 2 – Day of Colonoscopy	Visit 3 – Follow-Up	Visit 4 – Follow-Up ^a
Protocol Version 3.0	Day –30 to –1	Day 1	Day 2	Day 4 (–1/+2 days)	Day 12-17
Protocol Version 5.0, 6.0, or 7.0	Day –30 to –1	Day 1	Day 2	Day 4 (–1/+1 day)	Day 9 (–1/+1 day)
diary					
Ingestion of mandatory/recommended additional clear fluids		X	X		
Eligibility check prior to colonoscopy			X ^h		
Colonoscopy procedure and clinical assessments ⁱ			X		
Histology specimens			X		
Harefield Cleansing Scale ^j			X		
Boston Bowel Preparation Scale ^k			X		
Return of unused IP/Drug accountability			X		

Abbreviations: BOCLIR, Bowel Cleansing Impact Review; ECG, electrocardiogram; HIPAA, Health Insurance Portability and Accountability Act; IP, investigational product; PRO, patient-reported outcomes

^a Under Protocol Version 3.0, in the event that any patients had abnormal clinical chemistry or hematology parameters, or new/unresolved adverse events at Visit 3 that required clinic follow-up, these patients were asked to attend the clinic for Visit 4. All other patients required a telephone contact for safety follow-up and study conclusion at Visit 4. Under Protocol Versions 5.0, 6.0, or 7.0, all patients were required to attend a follow-up clinic visit at Visit 4.

^b Body weight, ECG, orthostatic blood pressure, pulse rate, and body temperature were to be collected on the day of colonoscopy; to be performed 1 to 2 hours (±30 minutes) before the procedure. A physical examination was required before colonoscopy. Body weight, arterial blood pressure and pulse rate readings were to be obtained 1 to 2 hours (±30 minutes) after the end of the colonoscopy. A physical examination was also required after colonoscopy.

^c Laboratory evaluations on the day of colonoscopy were to be conducted between 1 to 2 hours (±30 minutes) before the colonoscopy procedure.

^d Under Protocol Version 3.0, blood sample collection only for out of range clinical chemistry and hematology laboratory results from Visit 3. Under Protocol Version 5.0, 6.0, or 7.0, blood sample collection for clinical chemistry and hematology analyses were done at Visit 4.

^e Patients were advised not to take the allocated IP until they had received confirmation from the investigator.

^f In the event that adverse events were not able to be closed out at the follow-up visit (Visit 4) due to non-resolution at that time, they were to be followed up until 28 days after last patient last visit.

^g IP: Patients self-administered the evening and morning doses starting at the scheduled times (as applicable per regimen) in the evening of the day before colonoscopy and morning of the day of colonoscopy.

^h Eligibility check prior to colonoscopy on the day of procedure was to confirm the patient's informed consent and continued eligibility status as determined from screening and Visit 2 assessments.

ⁱ Performed by site colonoscopist.

^j Performed by site colonoscopist and first central reader (and, if required, a second central reader).

^k Performed by the first and if applicable, second central reader.

Source: Appendix 16.1.1 of the Applicant's CSR

Prior and concomitant therapy

With the exception of laxatives, there was no restriction on prior and/or concomitant medications. Medications prescribed for treatment-emergent AEs, occasional use of aspirin, or acetaminophen were also permitted.

Use of laxative/enema/colon motility-altering drugs was not permitted within 28 days of screening, or within 72 hours prior to administration of preparation. All concomitant medications

used within 28 days before the date of screening until the end of the study, as well as sedatives and/or anesthesia and intravenous fluids used during colonoscopy, were recorded.

Treatment compliance

The study drug was dispensed under the supervision of the investigator, a qualified member of the investigational staff, or by a pharmacist. Patients were instructed at screening on how to reconstitute and administer the study drug. The start and end times of study drug and additional water intake, volume of study drug, and additional (mandatory) clear fluids consumed were recorded in a patient diary.

Criteria for discontinuing patients from the study were as follows:

- Patient no longer wished to participate or comply with the requirements of the study protocol
- The physician felt in the best interest of the patient to withdraw for safety
- Deviation from the dosing regimen plan specified in the protocol (e.g., incorrect administration of the doses or failure to comply with study visits)

Study Endpoints

Primary Efficacy endpoints:

The Applicant had proposed two “alternative primary efficacy endpoints”:

- Cleansing success rate in overall colon using the HCS scale
- Cleansing rate in ascending colon using the segmental cleansing score system of the HCS

The first primary endpoint was overall bowel cleansing (success or failure) of the colon preparation. The efficacy variable was assessed as a binary outcome of overall success or failure. Successful treatment was defined as bowel cleansing grades of either Grade A or Grade B on the HCS, assessed by the blinded colonoscopist(s) during colonoscopy. Grades C and D were considered failure.

The second primary endpoint was limited to the cleansing rate of the ascending colon. Success was defined as bowel cleansing grades of “Excellent plus Good” using segmental cleansing scoring of HCS. The ordinal score of 4 corresponded to “Excellent” and a score of 3 corresponded to “Good” cleansing.

Reviewer comments:

The preparation needs to cleanse the entire colon (all 5 segments in the HCS) to accomplish full colonoscopy, reaching the ileo-cecal (IC) valve. Assessment of the ascending colon (one of five segments) should be considered only as a part of the whole colon and cannot be accepted as a separate criterion for efficacy. These concerns were previously communicated to the Applicant (refer to regulatory history above). The approach of assessing only the ascending colon is limited by the following: 1) results are redundant with the primary endpoint (refer to statistical review); 2) the multiplicity control procedures were not appropriate to support the manner in which this endpoint was assessed (refer to statistical review); and 3) from a clinical perspective,

the entire colon needs to be visualized; it is unclear what the utility of achieving good cleansing on the right colon (separate from the whole colon) would be to clinicians.

Assessment of efficacy based on primary endpoint:

The overall quality of bowel cleansing was assessed by the site colonoscopist according to the HCS during the colonoscopy.

The video recording of the study site colonoscopy procedure was assessed by the blinded central colonoscopist. If there was agreement between the site and central colonoscopists, evaluation by the central colonoscopist was considered final. If there was disagreement between the site and central colonoscopist, the video recording was evaluated by the second central colonoscopist and his/her evaluation was considered final.

The central reader(s) evaluated the video recordings of colonoscopy independently. The quality of scoring by the site colonoscopist and central readers was reviewed monthly in a blinded fashion. Rates of grade agreement/disagreement and success/failure disagreement frequency between central readers and site colonoscopist by site were reviewed.

HCS: The quality of colon cleansing was based on a score of 0-4 for the five segments of the colon: ascending colon and cecum, transverse colon, descending colon, sigmoid colon, and rectum. The score with description of the assessment is shown in Table 7.

Table 7: Study NOCT - HCS-score descriptors

Segment score	Description
0	Irremovable, heavy, hard stool
1	Semisolid, only partially removable stools
2	Brown liquid/removable semi-solid stools
3	Clear liquid (Good*)
4	Empty and clean (Excellent*)

source: reviewer's table, compiled from the Applicant's clinical study report section 9.5.1.1.1

Note: Scores of 2, 3, and 4 corresponded to success scores.

*For the purpose of this study, a score of 3 was defined as "Good" and a score of 4 was defined as "Excellent."

Based on the scoring for the five segments, a Grading of A, B, C, or D was assigned automatically. The grading criteria are shown in Table 8.

Table 8: Study NOCT - Final HCS grading

Grade	Description
A	All 5 segments scored 3 or 4
B	1 or more segments scored 2, remaining scored 3 or 4
C	1 or more segment scored 1
D	1 or more segment scored 0

source: reviewer's table, compiled from the Applicant's clinical study report section 9.5.1.1.1

Reviewer comments:

- *The HCS was developed in the early 1990s in order to support the research program for the new PEG-based bowel preparations; however, the HCS has not been used as an*

efficacy tool in clinical trials to support approval of bowel preparation. The original version included the assessment scheme for five colon segments; the assessment was scored using 3-level grading (A: excellent, B: good, and C: failed). Subsequently, it was observed that 3-grade output gave insufficient information regarding cleansing quality; therefore, the scale was expanded to the current 4-grade tool. A validation study¹² was performed using the Aronchick Scale as the criterion-standard comparator; a modified version of the Aronchick Scale has previously been used for approval of bowel preparations. The comparison between the HCS with the Aronchick Scale was based on expert assessment of video recordings of colonoscopies carried out as part of a clinical trial evaluating 2 different bowel preparation formulations. The HCS is applied while withdrawing the colonoscope and additional cleansing is done by washing and suctioning while inserting the colonoscope. In another study (Parmer et al.¹³), an assessment of the HCS was done for validity and reliability. For this, three experts and investigators rated 323 colonoscopy videos comparing the HCS with the Aronchick Scale for construct validity and correlations between the experts' ratings were good; however, there was only moderate agreement between investigators and experts. The inter-observer variability yielded slight to fair agreement. Reliability was observed to be fair.

- The scale used for measuring efficacy of bowel preparation while withdrawing may not be appropriate for the clinical trials, as significant cleansing may be achieved by washing and suctioning during insertion. While scores obtained in this way reflect the ultimate ability to complete a successful colonoscopy or not (which arguably is the most clinically important outcome), a more direct evaluation specifically of the action of the drug itself (rather than action of drug plus endoscopist's effort in washing/suctioning) would be obtained by assigning scores on insertion of the scope, prior to any washing.

In the current submission, the efficacy assessment was performed while withdrawing the colonoscope. These concerns were discussed with the Applicant at several meetings. To address these concerns, the Applicant conducted a post hoc assessment based on the video recordings of the original colonoscopy procedures to evaluate the efficacy during insertion.

- Different assessment scales have been used for assessing the cleansing of colon for evaluating the efficacy of approved bowel preparation products. Some of them are summarized in Table 9. In addition, some of these assessments were done while inserting the colonoscope and some while inserting and upon withdrawal.
- Overall, the HCS appears fit for purpose of efficacy assessment for a bowel cleansing agent, despite the limitations noted. The reviewer notes that a score of "B," which would have been considered a success, could have included multiple segments with only

¹² Marc Halphen et al. Validation of the Harefield cleansing Scale: a tool for the evaluation of bowel cleansing quality in both research and clinical practice. *Gastrointest Endosc* 2013; 78; 121-31.

¹³ Parmar et al. Validated scales for colon cleansing: A systematic review. *Am J Gastroenterol* 2016 Feb;111(2):197-204.

mediocre cleaning (i.e., multiple segments scored 2, which includes removable semi-solid stools, could be permitted to attain a “B”). If the majority of patients with “A or B” in fact have “B” and many segments scored 2, that is a relatively low bar of effectiveness. This was assessed further by the reviewer, see Section 6.1.4 exploratory analyses below.

Table 9: Study NOCT-Different scales to support efficacy of products approved for bowel prep

Product approved	Scale used
Visicol	A scale similar to Aronchick Scale
Half-Lytely	Colonic cleansing based on 4 point scale
Osmo prep	
Suprep	
Suclear	
Moviprep	Overall Gut cleansing scale based on 5-point verbal rating. It is similar to that used in this Application.
Prepopik	Aronchick Scale

source: reviewer’s table

- *Several other tools are available for research and clinical practice, including the Aronchick Scale, Ottawa Bowel Preparation Quality Scale (OBPQS), Boston Bowel Preparation Scale (BBPS), and Chicago Bowel Preparation Scale (CBPS). The Aronchick scale evaluates bowel preparation before any attempt at washing or suctioning. The BBPS, CBPS and HCS scoring is done after washing and suctioning during withdrawal.*
- *It is unclear at this time if a central vs. local reading is a more accurate way to assess efficacy in clinical trials for bowel preparations. The reviewer thinks that the efficacy assessment during primary examination at the start of procedure may be more informative and appropriate, as the colonoscopist has complete information about the baseline preparation and also how much washing and suctioning was required to achieve the optimal cleansing. However, there is less inter-observer variability with the use of a small group of central readers, as opposed to many local site colonoscopists. The approach taken for this program (looking first for agreement between site and central read, using second central read if discrepancy occurs) attempts to address these issues.*
- *There are published studies suggesting validation of the Aronchick scale,¹⁴⁻¹⁵ Ottawa Bowel Preparation scale (OBPS),¹⁶ and HCS.¹⁷ However, there are several limitations to*

¹⁴ Aronchick CA et al. Validation of an instrument to assess colon cleansing (abstract). Am J Gastroenterol 1999; 94: 2667

¹⁵ Aronchick et al. A novel tableted purgative for colonoscopic preparation: efficacy and safety comparisons with Colyte and Fleet Phospho-soda. Gastrointest Endosc 2000; 52: 346-52

¹⁶ Alaa Rostom et al. Validation of a new scale for the assessment of bowel preparation quality. Gastrointest Endosc 2004; 59: 482-6.

¹⁷ Marc Halphen et al. Validation of the Harefield cleansing Scale: a tool for the evaluation of bowel cleansing quality in both research and clinical practice. Gastrointest Endosc 2013; 78; 121-31.

these analyses. A recent systemic review by Parmar et al¹⁸ assessed validity and reliability of existing scales. The authors concluded that most of the published scales have limitations and there is no head-to-head comparison between any scales to demonstrate superiority of one over the other. None of the scales included validation with a direct and impactful clinical outcome such as missed lesions in follow up, or quality indicators such as polyp or adenoma detection, or insertion and withdrawal times. Between-scale comparison of the repeat colonoscopy time interval, ease, and pertinent of use for auditing is needed.

Secondary efficacy endpoints:

- Adenoma detection rate (ADR) in the ascending colon: proportion of patients with at least one adenoma in the ascending colon.
- ADR: proportion of patients with at least one adenoma in the overall colon.
- Polyp detection rate (PDR) in the ascending colon: proportion of patients with at least one polyp in the ascending colon.
- PDR: proportion of patients with at least one polyp in the overall colon.

Supportive secondary endpoints

- “Excellent plus Good” cleansing rate for the other four colon segments.
- Bowel cleansing success rate using the BBPS.
- Tolerability using the PRO, Bowel Cleansing Impact Review (BOCLIR).
- Compliance and acceptability as assessed using a PRO.

Boston Bowel Preparation Scale (BBPS)

Video recordings of each colonoscopy performed were viewed independently by a central reader(s) to assess the quality of bowel cleansing (Table 10). The quality of cleansing was scored as 0-3 for each of the three segments: right colon (cecum and ascending colon), transverse colon including hepatic and splenic flexure, and left colon (descending colon, sigmoid colon, and rectum). The maximum score of 9 was for a clean colon without any residue staining. Overall success was considered with a total score of ≥ 6 and a score of at least 2 in each segment.

Table 10: Study NOCT- BBPS-score descriptors

Segment Score	Description
0	Unprepared colon segment with mucosa not seen due to solid stool that could not be cleared
1	Portion of mucosa of the colon segment seen, but other areas of the colon segment not well seen due to staining, residual stool and/or opaque liquid
2	Minor amount of residual staining, small fragments of stool and/or opaque liquid, but mucosa of colon segment seen well
3	Entire mucosa of colon segment seen well with no residual staining, small fragments of stool or opaque liquid

source: reviewer’s table, compiled from the Applicant’s clinical study report section 9.5.1.1.2.

¹⁸ Parmar R, et al. Validated Scales for Colon Cleansing: A Systematic Review. American Journal of Gastroenterology. 2016; 111; 197-204.

Reviewer comments:

The secondary and supportive endpoints are appropriate. However, the proposed multiple testing procedure for assessment of key secondary endpoints was not considered appropriate by the statistical reviewer; please refer to detailed discussion in the statistical review by Shala Farr, PhD, dated 3/7/2018 for additional discussion.

The BBPS use is considered supportive.

Adenoma detection rate (ADR) and polyp detection rate (PDR)

The overall and segmental adenoma and polyp counts and ADR/PDR were determined by the site colonoscopist and confirmed on histology.

Tolerability

Tolerability of the bowel preparation was assessed using the BOCLIR questionnaire (a PRO scale to assess the impact of bowel cleansing preparation from patients' perspectives). The questionnaire comprised three scales: satisfaction (score 0-32), symptoms (score 0-42), and activities (score 0-36) with a total score of 0-110. Patients who reported a worse experience in terms of these factors scored higher on the BOCLIR scale (for details of the BOCLIR scale see Appendix-B).

Compliance and acceptability

Compliance and acceptability was assessed using the patient diary (for details see Appendix-C). The assessment included whether a patient had taken both doses of bowel preparation (regardless of how much of the mandatory additional fluids was taken) as instructed. A patient was deemed compliant if he/she took at least 75% of each dose.

Reviewer comments:

BOCLIR PRO is considered exploratory, (b) (4)
Specific concerns regarding the validity of this instrument were communicated to the Applicant early in development.

This is the first bowel preparation application to assess ADR as a key secondary endpoint. This endpoint is clinically important, as the goal of a high quality bowel prep (in the population undergoing screening colonoscopy) is to ensure clear visibility, which should result in an improved ADR. The ADR is an important measure of quality in screening colonoscopy that is documented in the literature to be associated with better outcomes in regard to interval cancer detection and cancer related deaths. See discussion in Introduction.

Statistical analysis:

Please refer to Dr. Farr's Statistical review dated March 7, 2018 for detailed evaluation of the Applicant's statistical analysis.

Briefly, the Applicant proposed to evaluate NI of NER1006 to Trisulfate solution using a NI margin of 10% (for overall bowel cleansing, a difference in success rates of no greater than 10%

in favor of Trisulfate solution and for ascending colon, a difference in “Excellent plus Good” cleansing rates of no greater than 10% in favor of Trisulfate solution). The Applicant proposed that if either endpoint is met, the study will be deemed a success. If the lower 1-sided 97.5% confidence limits for both alternative primary endpoints excluded a 10% or greater difference in favor of trisulfate solution, then non-inferiority would be concluded for both endpoints.

For the primary endpoints, the number and percentage of patients with successful cleansing were summarized for the full analysis set (FAS), modified FAS (mFAS), and per protocol (PP) sets. The corresponding 1-sided confidence interval (CI) for the difference between bowel preparations cleansing rates was determined via PROC FREQ in SAS (using exact Clopper-Pearson CI), and p-values generated using Fischer’s exact.

The Applicant proposed that key secondary endpoints would be analyzed in a hierarchical manner starting with first secondary endpoint (i.e., ADR in the ascending colon) if either of the primary endpoints showed NI. If non-inferiority was not met for either alternative primary endpoint, then the four key secondary endpoints would be summarized descriptively.

However, there were concerns with this approach (refer to statistical review).

The Applicant calculated a sample size of 620 patients assuming overall cleansing rates of 90% for both NER1006 and Trisulfate solution, NI margin of 10%, and dropout rate of 20%.

Analysis Set: The Applicant has defined the following analysis sets that were used in the efficacy analysis:

Full Analysis Set (FAS): All randomized patients.

Modified Full Analysis Set (mFAS): All randomized patients, excluding those who subsequently failed to meet entry criteria AND the patient did not receive any study drug (confirmed from their patient diary). Patients in this set were used as the primary population for all efficacy analyses. The Applicant states that this is in accordance with the ICH E9 guidance.

Reviewer comments:

It is stated on page 28 of the ICH E9 guidance¹⁹ that “there are a limited number of circumstances that might lead to excluding randomized subjects from the full analysis set including the failure to satisfy major entry criteria (eligibility violations), the failure to take at least one dose of trial medication. Such exclusions should always be justified. Subjects who fail to satisfy an entry criterion may be excluded from the analysis without the possibility of introducing bias only under the following circumstances:

a. The entry criterion was measured prior to randomization;

¹⁹ Guidance for Industry: E9 statistical Principles for Clinical Trials. Available at : <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073137.pdf>

- b. *The detection of the relevant eligibility violations can be made completely objectively;*
- c. *All subjects receive equal scrutiny for eligibility violations.*
- d. *All detected violations of the particular entry criterion are excluded.*

In some situations, it may be reasonable to eliminate from the set of all randomized subjects any subject who took no trial medication. The intention-to-treat principle would be preserved despite the exclusion of these patients provided, for example, that the decision of whether or not to begin treatment could not be influenced by knowledge of the assigned treatment.”

The analysis based on mFAS seems appropriate.

Per protocol (PP) Set

The PP set is a subset of patients in FAS who met all of the following criteria:

- Entry criteria fulfilled.
- Compliance rate of at least 75% of each dose of study drug as per patient diary.
- At least one of the complete primary endpoint data available.
- No major protocol deviations.

Pre-specified methods of handling missing data: Per the Applicant, missing data was imputed as failure.

5.3.2 Study MORA (NER1006-02/2014) 2- and 1-Day (morning only) - split dosing

Title

A multicenter, randomized, parallel group phase 3 study comparing the bowel cleansing efficacy, safety and tolerability of 2 dosing regimens of NER1006 (a low volume bowel cleansing solution) versus MOVIPREP® in adults.

Study Objectives

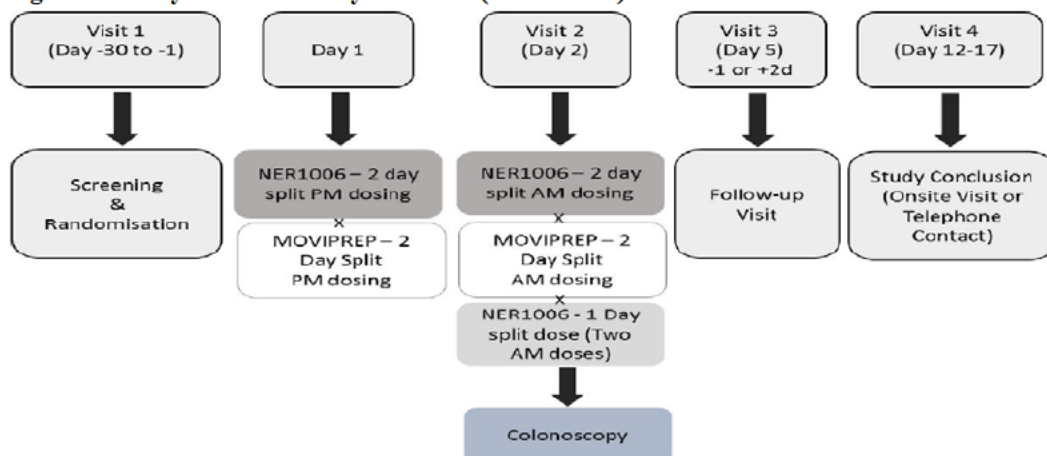
To evaluate the overall bowel (colon) cleansing rate, and the “Excellent and Good” cleansing rate in the ascending colon of a 2-day split-dosing regimen and 1-Day morning split-dosing regimen with NER1006 compared to a 2-Day split-dosing regimen with MOVIPREP, graded according to the HCS in patients undergoing screening, surveillance, or diagnostic colonoscopy.

Study Design

This was a randomized, single-blind, multicenter, active comparator, and parallel group trial conducted at 29 sites across the European Union in subjects aged 18 to 85 years. Patients were randomly assigned in a 1:1:1 ratio to receive 2-Day Split-Dosing NER1006 or 2-Day Split-Dosing MOVIPREP or 1-Day Morning Split-Dosing NER1006. The study duration for each patient was maximum of 47 days (including the screening period) for patients enrolled under Version 3.0 of the protocol and maximum of 40 days for patients enrolled under Versions 4, 5, and 6.

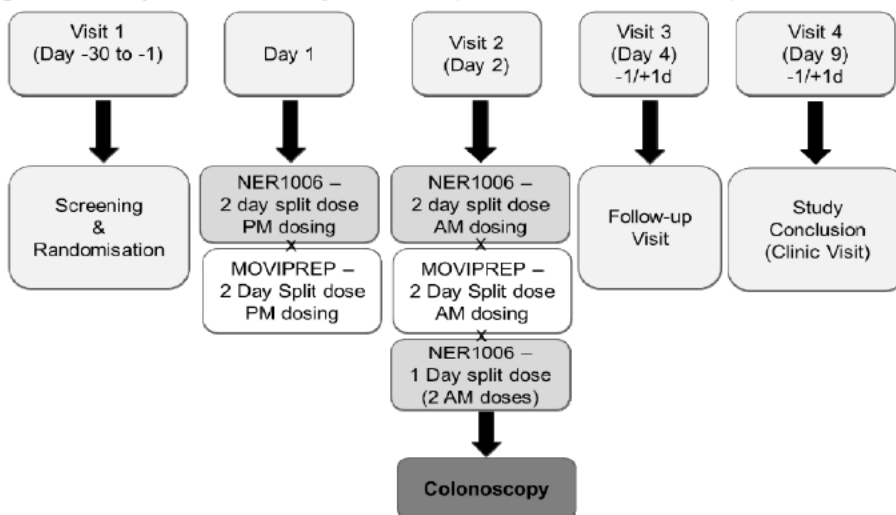
The study schedule for protocol Version 3.0 and Versions 4, 5, and 6 are shown in (Figure 3 and Figure 4).

Figure 3: Study MORA - Study Schedule (Version 3.0)



Source: Adapted from the Applicant's CSR (MORA) Figure 9-1

Figure 4: Study MORA - Study Schedule (Version 4.0, 5.0, and 6.0)



Abbreviations: AM, morning; d, day; PM, evening

Source: Adapted from the Applicant's CSR (MORA) Figure 9-2

The study included the following visits for patients enrolled under protocol Version 4.0, 5.0, or 6.0 (Table 11).

Table 11: Study MORA - Study visits

Visit 1 (Day -30 to Day -1)	Screening and randomization
Day 1	Self-administration of first dose of bowel preparation (NER1006 2-Day and MOVIPREP)
Visit 2 (Day 2)	Self-administration of first dose of bowel preparation, and day of colonoscopy (NER1006 1-Day) Self-administration of second dose of bowel preparation, and day of colonoscopy (NER1006 1-Day, NER1006 2-Day, and MOVIPREP)
Visit 3 (Day 4 ± 1 day)	Follow-up visit 1-3 days (inclusive) after the colonoscopy
Visit 4 (Day 9 ± 1 day)	Follow-up visit (clinic visit) (6-8 days [inclusive] after the colonoscopy)

source: reviewer's table, adapted from CSR (MORA) synopsis

For patients in the NER1006 and MOVIPREP 2-Day split-dosing treatment groups, the colonoscopy 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. For patients in the NER1006 1-Day morning split-dosing group, the colonoscopy was advised in the early afternoon.

Reviewer comments:

The study design is appropriate.

Efficacy endpoints:

The primary, secondary and supportive endpoints were same as for the NOCT study.

Protocol amendments:

The original protocol, dated 16 JUL 2014, was amended three times during the course of the study. The key changes in each amendment are summarized below.

Amendment 1, Version 1.0, dated 11 DEC 2014, leading to Protocol Version 4.0, dated 11 DEC 2014

The changes made were same as for the NOCT study.

Amendment 2, Version 1.0, dated 30 March 2014, leading to Protocol Version 5.0, dated 30 March, 2014.

Same as NOCT study except for the following changes:

- Increased the number of patients to be randomized from 810 to 850 to account for a 15% drop out as opposed to 10% stated in the previous version of the protocol.
- Increased the number of study sites from 30 to 40 and included United States as study location.
- Updated CRO Medical Monitor address and responsibilities.
- Added the requirement for a physical examination to be performed before and after colonoscopy.

Amendment 3, Version 1.0, dated 25 June 2014, leading to Protocol Version 6.0, dated 25 June, 2014.

Same as for the NOCT study.

Study Population

The inclusion/exclusion criteria were similar to the NOCT study except that in this study patients with only severe renal insufficiency (GFR <30 mL/min/1.73 m²) were excluded compared to NOCT study where patients with moderate to severe renal insufficiency were excluded (GFR <60 mL/min/1.73m²).

Study treatment

Patients self-administered the study drug in accordance with the treatment regimen allocated at randomization (NER1006 2-Day split-dosing regimen or NER1006 1-Day morning split-dosing regimen or MOVIPREP 2-Day split-dosing regimen). In addition, patients were instructed to take a mandatory volume of clear fluid after each dose of the study drug. Patients were provided instructions on dosing and dietary restrictions.

NER1006

- *Two-Day split dosing regimen:* NER1006 was administered as in NOCT study. Also, the dietary restrictions were the same.
- *One-Day morning split dosing regimen:* The first dose was instructed to be taken at approximately 5 AM on the day of colonoscopy followed by the second dose at 7 AM. The reconstituted volumes of the two doses and mandatory volume of water recommended were similar to the 2-Day split dosing regimen.

Dietary Restrictions for 1-Day morning split dosing regimen:

- o *Day prior to colonoscopy:* patients were allowed a light breakfast followed by a light lunch, and clear soup and/or plain yogurt for dinner, to be finished by 8 PM.
- o *Day (Morning) of colonoscopy:* Breakfast was not permitted. Patients were allowed to take clear fluids or water *ad libitum* after the dinner until 2 hours prior to colonoscopy.

MOVIPREP (Active comparator)

A 2-day split-dosing regimen: The administration of first dose commenced in the evening of the day before colonoscopy.

Day before colonoscopy (Dose 1):

- The patients were instructed to take the first dose (approximately 32 fl. oz./1 Liter) of MOVIPREP at 6 PM on the evening prior to the colonoscopy examination, at the rate of 250 mL every 15 minutes (over 1 hour), followed by 500 mL of mandatory clear fluids. Additional fluids could be taken *ad libitum*.

Day of colonoscopy (Dose 2):

- The second dose (approximately 32 fl. oz./1Liter) of MOVIPREP and mandatory clear fluids were instructed to be taken at 6 AM on the day of colonoscopy. Additional fluids could be taken *ad libitum*. However, all fluids had to be stopped at least 1 hour before the colonoscopic procedure.

Dietary Restrictions:

- *Day prior to colonoscopy:* Patients were allowed to take normal breakfast, light lunch, and clear soup and/or plain yogurt for dinner to be finished by 5 PM, an hour before starting Dose 1.
- *Day of colonoscopy:* Patients were allowed to take clear fluids or water *ad libitum* from the start of first dose until 1 hour prior to colonoscopy.

Reviewer comments:

Patients in the comparator group were allowed normal breakfast and light lunch compared to light breakfast and light lunch in the NER groups prior to the day of colonoscopy. This may result in better efficacy in the NER groups due to more restrictive diet compared to comparator. As described above, although differences in diet make it harder to isolate the effect of the drug from that of dietary changes, the difference between the dietary restrictions among the 2 arms seems fairly minor, and as long as the diet used in the trials is the same as that which will be described in the product label / instructions for use, then the comparison of the whole regimen (drug, volume of fluid, and dietary restrictions taken together) to an approved comparator and its labeled regimen appears reasonable.

Blinding: Same as for the NOCT study.

Procedures and schedule: Schedule of study procedures and assessments were same as for the NOCT study.

Prior and concomitant therapy: Use of permitted and prohibited medications, prior and or concomitant was same as for the NOCT study.

Treatment compliance: Same as for the NOCT study.

Efficacy assessment: Same as for the NOCT study.

Assessment of tolerability, compliance, and acceptability

Assessment of tolerability by BOCLIR was done only for UK patients since it was validated in English. Compliance and acceptability were same as for the NOCT study.

Statistical analysis:

Please refer to Dr. Shahla Farr's Statistical review dated March 7, 2018 for detailed evaluation of the Applicant's statistical analysis.

The Applicant proposed to evaluate the NI of NER1006 compared to Moviprep using a NI margin of 10% (i.e., for overall bowel cleansing, a difference in success rates of no greater than 10% in favor of Moviprep and for ascending colon, a difference in "Excellent plus Good" cleansing rates of no greater than 10% in favor of Moviprep). If the lower 1-sided 97.5%

confidence limits for both alternative primary endpoints excluded a 10% of greater difference in favor of Moviprep, then non-inferiority would be concluded for both endpoints. To evaluate the comparison of two NER1006 regimens, a hierarchical testing approach was used, whereby NER1006 2-Day regimen was assessed against Moviprep first and, if successful, then NER1006 1-Day was evaluated against Moviprep. A closed testing procedure was used to allow the formal statistical assessment of superiority if NI was met for at least one of the “alternative primary endpoints” for the NER1006 2-Day regimen or NER1006 1-Day regimen. The Applicant proposed that if either endpoint (i.e., cleansing success rate in overall colon and cleansing success rate in ascending colon) is met, the study will be considered a success for that regimen. If one or both of the alternative primary endpoints was met (showed NI), key secondary endpoints would be evaluated hierarchically in the order pre-specified.

Analysis Sets

FAS, mFAS, per protocol, and safety set were defined as in the NOCT study.

Pre-specified methods of handling missing data:

Same as NOCT study (missing data will be imputed as failure).

5.3.3 Post Hoc Analysis Based on Video Recordings in Studies NOCT (ADV) and MORA (ADV2)

The Applicant proposed *post hoc* analysis based on prerecorded videos performed during colonoscopy. Each video was reviewed by one of the central assessors. The primary endpoints were the same as summarized above. One of the supportive secondary endpoints based on BBPS was the same as summarized above. Other supportive secondary endpoints include the following:

1. “Worst score” analyses of alternative primary endpoints: Worst score analysis for each of the alternative primary endpoints was conducted where the worst result during either the advancement or the withdrawal phase was taken, using mFAS only.
2. Total washing events and total washing time during advancement phase. A washing event was defined when a clear stream of water was seen arising from the colonoscope and events were timed to calculate the total washing time.

The analysis was based on mFAS as well as revised mFAS which included all patients in mFAS with the exclusion of patients where no video was available during the advancement phase. Analyses using the revised mFAS were considered supportive to the mFAS analysis for the two alternative primary efficacy endpoints. The secondary endpoints were analyzed using the mFAS, except washing, where revised mFAS was used.

5.3.4 Study DAYB (NER1006-03/2014) 1-Day (Day Before-only) Split Dosing

Study DAYB was a randomized active comparator study. However, the active comparator (SP + MS) used is not approved in the United States. Therefore, the efficacy data from this study was

not considered relevant to support an efficacy analysis. A limited high-level review of the safety data from DAYB was conducted by the clinical reviewer. The clinical study protocol of the study is summarized.

Title

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 SP+MG solution using a day before-only split-dosing regimen in adults.

Study Objectives

To evaluate the overall bowel (colon) cleansing rate, and the “Excellent and Good” cleansing rate in the ascending colon of a 1-day, day before-only, split dosing with NER1006 compared to a 1-Day, day before-only, split-dosing regimen with SP+MG, graded according to the HCS in patients undergoing screening, surveillance, or diagnostic colonoscopy.

Study Design

The study design was same as NOCT and MORA studies. Patients were randomly assigned in a 1:1 ratio to receive either NER1006 or SP+ MS. The study duration and protocol amendments were same as for the MORA study.

Study treatment

Patients self-administered the drug (NER1006 or SP+MG) in accordance with the treatment regimen allocated at randomization. In addition, patients were instructed to take a mandatory volume of clear fluid after each dose of the study drug. Patients were provided instructions on dosing and dietary restrictions.

NER1006

- *1-Day before, split dosing regimen:* The first dose was instructed to be taken at approximately 6 PM on the day before colonoscopy day followed by the second dose 1-2 hours after the first dose. Both doses of NER1006 were same in composition as for the NOCT and MORA studies; also, instructions for taking drug and mandatory water/fluids volumes after each dose were the same. Additional fluids could be taken *ad libitum* until 2 hours before colonoscopy.

SP+MG (Active comparator)

One-Day before, split dosing regimen: The administration of the first dose commenced in the morning of the day before colonoscopy.

Day before colonoscopy (Dose 1):

- The patients were instructed to take the reconstituted first dose (approximately 150 mL) in the morning of the day before colonoscopy at 8 AM. Additional fluids could be taken *ad libitum*. The second dose (150 mL) was taken 6-8 hours after the first dose, between approximately 2 and 4 PM. Patients were advised to drink approximately 250 mL of clear fluids every hour while the washout effect persisted.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The proposed indication is “for cleansing of the colon in preparation for colonoscopy in adults.”

6.1.1 Methods

The data from two phase 3 trials, NER1006-01/2014 (NOCT) and NER1006-02/2014 (MORA), were used for the efficacy review. Both studies were multicenter, single-blind (only the colonoscopist was blinded), parallel group and used active approved comparators. The primary objectives were to evaluate efficacy and safety of the two NER1006 regimens compared to Trisulfate and PEG + electrolyte solution (MOVIPREP) as comparators. The primary efficacy analysis was performed during the withdrawal phase of the colonoscopy. Study NOCT evaluated the 2-Day split dosing regimen and MORA evaluated 2-Day as well as 1-Day split dosing regimens. *Post hoc* efficacy analysis during the insertion phase of the colonoscopy was also performed based on the video recordings of these two studies. See Section 5.3 for discussion of individual studies for details of the study design and conduct.

6.1.2 Demographics

The study population consisted of adult patients who were planned to undergo a screening, surveillance, or diagnostic colonoscopy. The baseline demographic parameters were similar between treatment groups in both Studies NOCT and MORA and are summarized by study, below.

6.1.2.1 Study NOCT

Table 12 summarizes the demographic characteristics of the 621 adults enrolled in the NOCT study. The majority of the patients enrolled were white (81-83%). The racial distribution among the treatment groups was similar. Patients' age distribution (18-86 years), mean age (57 years) and median age (58 years) were similar in the two treatment groups. There were similar numbers of elderly patients (≥ 65 years), ~20% in the two treatment groups. In the comparator group, the proportion of male patients was slightly higher compared to female patients, whereas in the NER1006 group the proportion of male and female subjects was similar.

Table 12: Study NOCT-Baseline Demographic Characteristics (Full Analysis Set)

Category	Treatment Group	
	Trisulfate (N=311)	Ner1006 (n=310)
Age (years)		
• Mean (SD)	57.3 (10.56)	57.7 (10.36)
• Median	58	58
• Minimum, Maximum	18, 81	22, 86
Age Groups (years), n (%)		
• ≤65	248 (79.7)	249 (80.3)
• >65	63 (20.3)	61 (19.7)
Gender		
• Male	169 (54.3)	158 (51)
• Female	142 (45.7)	152 (49)
Race, n, (%)		
• White or Caucasian	252 (81)	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
• Others	3 (1)	0
Body weight (Kg)		
• Mean (SD)	86.51 (19.17)	85.91 (18.02)
• Median	85.90	84.65
• Minimum, Maximum	42.9, 143.8	46.6, 154.2

source: reviewer's table, adapted from the Applicant's Clinical Study Report on Protocol NER1006-01-2014 (NOCT), Table 11.3.

Overall baseline demographic and clinical characteristics were similar in the two treatment groups in Study NOCT.

6.1.2.2 Study MORA

Table 13 summarizes the demographic characteristics of 849 adults enrolled in the MORA study. The majority of the patients enrolled were white (97-99%). Patients' age distribution (18-84 years), mean age (54 years) and median age (57 years) were similar in the three treatment groups.

There were numerically higher proportions of patients with age >65 years in NER1006 2-Day split and 1-Day morning split dosing groups (23-26%) compared to MOVIPREP group (17%). Similarly, there was a numerically higher proportion of female patients in the two NER1006 treatment groups (54-58%) compared to the MOVIPREP group (49%). Other demographic characteristics were comparable in the three treatment groups.

Table 13: Study MORA - Baseline Demographic Characteristics (Full Analysis Set)

Category	NER1006 2-Day split dosing (N=283)	NER1006 1-Day morning split dosing (N=283)	MOVIPREP 2-Day split dosing (N=283)
Age (years)			
• Mean (SD)	56.3 (12)	55 (13)	54 (13)
• Median	57.0	57	56
• Minimum, Maximum	18, 81	20, 79	22, 84
Age Groups (years), n (%)			
• ≤65	209 (74)	219 (77)	235 (83)
• >65	74 (26)	64 (23)	48 (17)
Gender			
• Male	120 (42)	131 (46)	144 (51)
• Female	163 (58)	152 (54)	139 (49)
Race, n, (%)			
• White or Caucasian	275 (97)	279 (99)	280 (99)
• Black	6 (2)	3 (1)	1 (0.4)
• Asian	0	0	2 (0.7)
• American Indian or Alaska native	0	0	0
• Native Hawaiian or Other Pacific Islander	0	0	0
• Others	2 (0.7)	1 (0.4)	0
Body weight (Kg)			
• Mean (SD)	77 (16)	77 (16)	76 (15)
• Median	75	76	74
• Minimum, Maximum	43, 144	42, 151	44, 138

source: reviewer's table, compiled from the Applicant's Clinical study report (MORA) Table 11.3

6.1.3 Subject Disposition

6.1.3.1 Study NOCT

A total of 621 patients were randomized (full analysis set) at 12 sites in the United States (NER1006= 310; Trisulfate=311). Overall 255/310 (82.3%) patients in NER1006 and 261/311 (84%) patients in Trisulfate group completed the study. The proportion of patients that discontinued study were comparable in the two treatment groups (NER1006=55/310 (17.7%) and Trisulfate=50/311 (16.1%)). The most common reasons for the discontinuation were “other” reasons (33/55 in NER1006 and 28/50 in Trisulfate group) and withdrawal of the patient (15/55 in NER1006 and 17/50 in Trisulfate group); these were comparable in the two treatment groups. The other reasons primarily included failure of inclusion/exclusion criteria (NER 13/33 and Trisulfate 16/28) and GFR< 60 mL/min (NER1006= 16/33, Trisulfate= 12/28) (Table 14 and Figure 5).

Only 1 patient each in the NER1006 and Trisulfate solution treatment groups discontinued the study due to an AE. Two patients in the NER1006 treatment group and one patient in the Trisulfate solution treatment group discontinued the study due to non-compliance (based on investigator's assessment at the end of study).

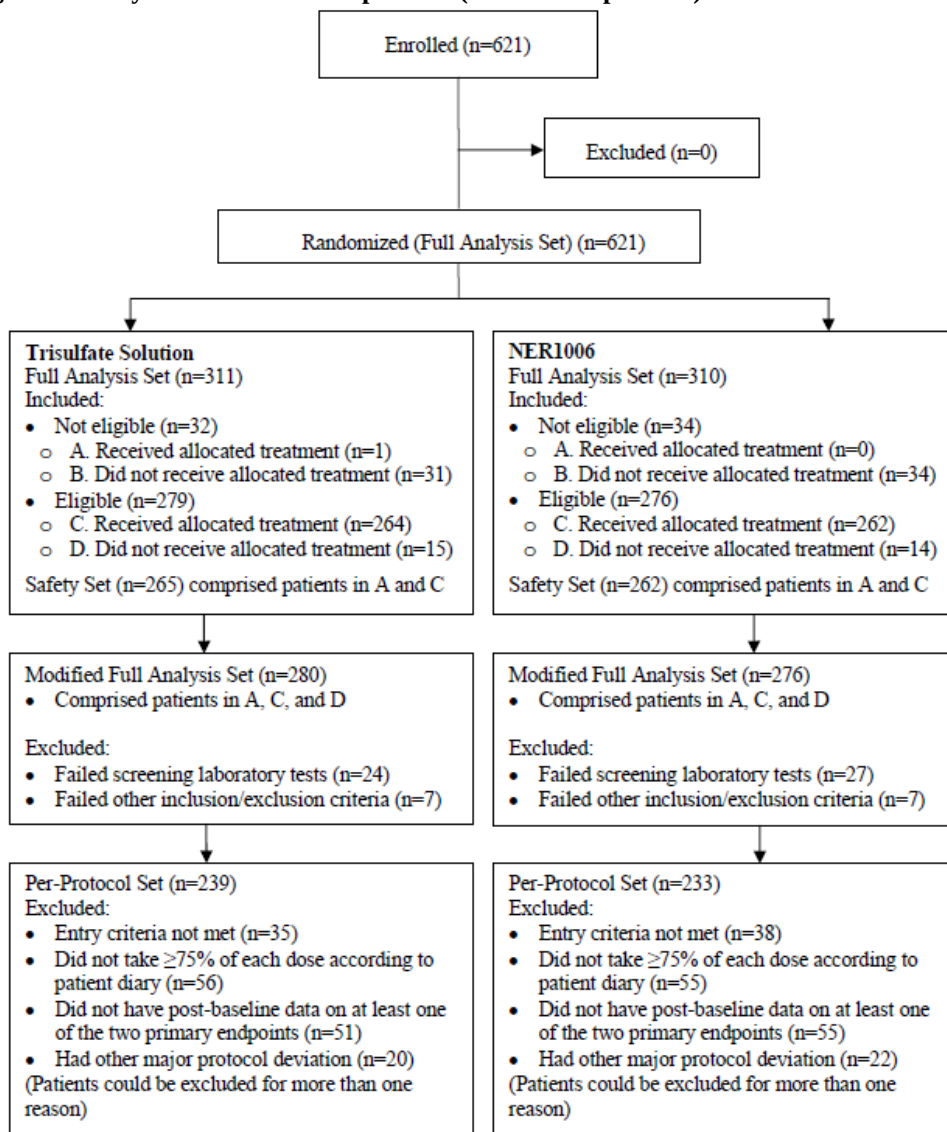
Table 14: Study NOCT-Patient Disposition (Full analysis set)

	NER1006 (N=310) N%	Trisulfate solution (N=311) N%
Total number of patients		
• Randomized	310 (100)	311 (100)
• Completed study	255 (82)	261 (84)
• Discontinued study	55 (18)	50 (16)
Primary reasons for discontinuation from study		
• Other	33 (10.6)	28 (9)
• Withdrawal of the patient	15 (4.8)	17 (5.5)
• Lost to follow up	4 (1.3)	2 (0.6)
• AE	1 (0.3)	1 (0.3)
• Non-compliant	2 (0.6)	1 (0.3)
• Lack of efficacy	0	1 (0.3)

source: reviewer's table, adapted from Applicant's clinical study report for NOCT, Table 10-1

Patients who withdrew had not received any treatment.

Figure 5: Study NOCT-Patient Disposition (all enrolled patients)



source: Applicant's clinical study report for NOCT, Figure 10.1

The primary efficacy is based on the mFAS population.

Protocol violations

Major protocol deviations that occurred during the conduct of the NOCT study are summarized in Table 15. There were 24 and 22 protocol violations in NER1006 and Trisulfate treatment groups, respectively. The most frequently reported major protocol deviations were due to study procedures/assessments [NER1006=9 (2.9%), Trisulfate= 8 (2.6%)] and study treatment compliance [NER1006= 7 (2.3%), Trisulfate= 8 (2.6%)]. Patients could have more than one major protocol deviation and appeared under multiple deviations. The proportion of patients with protocol deviations was comparable in the two treatment groups.

Table 15: Study NOCT-Major Protocol Deviations (FAS)

Deviations	NER1006 (N=310) n (%)	Trisulfate solution (N=311) n (%)
Study procedures/assessments	9 (3)	8 (2.6)
Study treatment compliance	7 (2.3)	8 (2.6)
Exclusion criteria	6 (2)	3 (1)
Inclusion criteria	1 (0.3)	0
Informed consent	0	1 (0.3)
Other protocol deviation	0	1 (0.3)
Study treatment Admin/Dispense	1 (0.3)	1 (0.3)

source: Adapted from the Applicant's Clinical Study Report (NOCT) Table 10.2.

Inclusion/Exclusion criteria:

In the NER1006 group, 3 patients (b) (6) took excluded medication at the time of screening (exclusion criterion 4); 1 patient (b) (6) had documented hypokalemia and was taking concomitant medication (exclusion criterion 16); 2 patients (b) (6) were randomized in the interactive (IWRS) prior to confirmation of laboratory results eligibility, 1 patient (b) (6) was 86 years old (more than 85 years as per inclusion criterion 2).

Note: In addition, there were 2 patients (b) (6) with GFR<60 mL/min that were not captured as protocol deviations. These were not excluded from the study and were part of the per protocol set.

- In the Trisulfate group, 1 patient (b) (6) had GFR<60 mL/min, 1 patient (b) (6) had history of hypokalemia and took concurrent medication (exclusion criterion 16), and 1 patient (b) (6) had history of gastric surgery (exclusion criterion 3).

Note: In addition, 1 patient (b) (6) was reported under the category of "other protocol deviation" and was not captured for inclusion/exclusion criteria for having GFR<60 mL/min and 1 patient (b) (6) was misreported for having low GFR of 50 mL/min under exclusion criteria, the actual screening GFR was higher (87 mL/min).

Reviewer comment:

The number of patients with major protocol deviations that may have biased the efficacy assessment were low and comparable across treatment arms, thus were unlikely to have had a major impact on the efficacy assessment. Only three of these patients had taken prohibited concomitant medication that could alter efficacy assessment. Other violations, such as those related to age or laboratory abnormalities outside the normal range, would be unlikely to affect efficacy outcomes significantly.

6.1.3.2 Study MORA

This was a three-arm study. A total of 849 patients were randomly assigned to receive 2 dosing regimens of NER1006 (2-Day split dosing and 1-Day morning split dosing) and 2-Day split dosing regimen with MOVIPREP. The patient disposition for the three treatment groups in

MORA trial are summarized in Table 16 and Figure 6. Overall 260/283 (92%) patients in NER1006 2-Day split dosing group, 262/283 (92.6%) in NER 1-Day morning split dosing, and 259 (91.5%) in the MOVIPREP groups completed the study.

The proportions of patients who discontinued the study, due to withdrawal and other reasons, were comparable in the three treatment groups (NER1006 2-Day split dosing=23/283 (8%), NER1006 1-Day morning split dosing= 21/283 (7.4%), and MOVIPREP 2-Day split dosing= 24/283 (8.5%)). The most common reason for discontinuation was withdrawal of the patient. The proportion of patients who withdrew was similar in the three treatment groups (12/23 in NER1006 2-Day split dosing, 11/21 in NER1006 1-Day split dosing, and 10/24 in MOVIPREP group).

Discontinuations due to “other” reasons were screening failure, and meeting exclusion criteria including laboratory abnormalities. The proportions of patients were comparable in each treatment group (9/23 NER1006 2-Day split dosing, 8/21 in NER1006 1-Day split dosing, and 10/24 in MOVIPREP group).

Three patients (1%) 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 were considered non-complaint based on the investigator’s assessment at the end of the study. Two patients (1 each) in the 2 NER1006 treatment groups were lost to follow-up and 1 patient was discontinued due to an AE in the MOVIPREP group.

Table 16: Study MORA-Patient Disposition (Full analysis set)

	NER1006 2-Day Split-Dosing (N=283) n (%)	NER1006 1-Day morning Split-Dosing (N=283) n (%)	MOVIPREP (N=283) n (%)
Total number of patients			
• Randomized	283	283	283
• Completed study	260 (92)	262 (92.6)	259 (91.5)
• Discontinued study	23 (8)	21 (7.4)	24 (8.5)
Primary reasons for discontinuation from study			
• Others	9 (3.2)	8 (2.8)	10 (3.5)
• Withdrawal of the patient	12 (4.2)	11 (4)	10 (3.5)
• Lost to follow up	1	1	0
• AE	0	1	1
• Non-compliant	1		3

source: Adapted from the Applicant’s clinical study protocol (MORA) Table 10-1

Reviewer Comments:

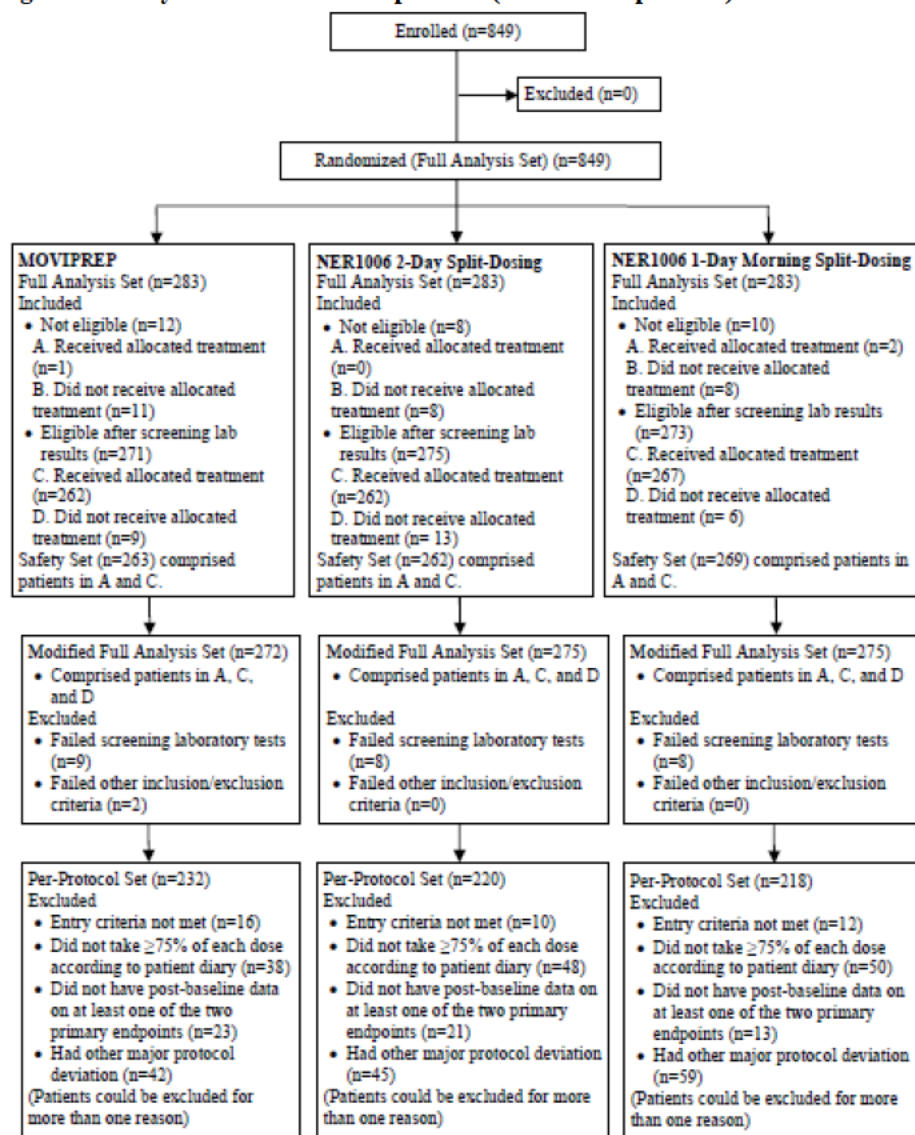
- In the 2-Day NER split-dosing regimen group, 2 patients (NER100602- (b) (6) and NER100602- (b) (6)) noted to have withdrawn were shown to have received the investigational drug.
- In the 1-Day NER split-dosing regimen group, seven patients (NER100602- (b) (6), NER100602- (b) (6), NER100602- (b) (6), NER100602- (b) (6), NER100602- (b) (6), NER100602- (b) (6), NER100602- (b) (6)).

and NER100602-(b) (6) noted to have withdrawn were shown to have received the investigational drug.

- In the MOVIPREP group, three patients (NER100602-(b) (6), NER100602-(b) (6), NER100602-(b) (6)) noted to have withdrawn were shown to have received the investigational drug.

Per analysis plan and disposition figure below, patients who received study drug (even if in withdrawal group) would have been included in the mFAS population used for primary efficacy assessment.

Figure 6: Study MORA-Patient disposition (all enrolled patients)



Note: Patients (b) (6) from the MOVIPREP treatment group were included in the safety set but did not have their colonoscopies performed. Patient (b) (6) vomited the study drug and for Patient (b) (6) there was no trained unblinded colonoscopist available to carry out the colonoscopy on the planned day; therefore, their colonoscopies could not be performed.

source: Applicant's clinical study report for NOCT, Figure 10-.1

Protocol deviation

Major protocol deviations that occurred during the conduct of the study, for the FAS, are summarized in Table 17.

There were 45 and 60 protocol violations in NER1006, 2-Day split dosing and 1-Day morning split dosing regimens, respectively, and 46 in the Moviprep 2-Day split dosing regimen. The most frequently reported major protocol deviation category was non-compliance with study treatment. The proportions of noncompliant patients in the NER1006 1-Day morning split dosing (14%) and 2-Day split dosing (8.5%) regimen were higher compared to Moviprep (6.4%).

Other reason for protocol deviation included exclusion criteria. The proportion of patients with deviations in the exclusion criteria was comparable in the three treatment groups (6-7%).

Table 17: Study MORA-Major protocol deviations (FAS)

	NER1006		MOVIPREP 2-Day split dosing (N=283) n (%)
	2-Day split dosing (N=283) n (%)	1-Day morning split dosing (N=283) n (%)	
Exclusion criteria	18 (6.4)	17 (6.0)	20 (7)
Inclusion criteria	0	0	1 (0.4)
Study treatment compliance	24 (8.5)	39 (14)	18 (6.4)
Missing endpoint assessments	1 (0.4)	1 (0.4)	6 (2)
Study treatment Admin/Dispense	0	1 (0.4)	0
Study procedures/assessments	1 (0.4)	1 (0.4)	1 (0.4)
Visiting schedule	1 (0.4)	1 (0.4)	0

Source: Adapted from the Applicant's Clinical Study Report (MORA) Table 10.2.

Study treatment compliance

Inclusion/exclusion criteria: Major protocol deviations related to noncompliance with the inclusion and exclusion criteria are summarized in Table 18 below **Error! Reference source not found.** Some patients had more than one protocol deviation.

Table 18: Study MORA-Non-compliance with inclusion/exclusion criteria

Inclusion/exclusion criteria	NER1006, 2-Day split dosing (N=18)	NER1006, 1-Day morning split dosing (N=17)	MOVIPREP 2-Day split dosing (N=21)
Withdrawal of the ICF	(b) (6)	(b) (6)	(b) (6)
Episode of severe constipation (requiring repeated use of laxatives/enema or physical intervention in the past 12 months (EC 1)			
Previous GI surgeries			
Regular use of laxatives or colon motility-altering drugs (i.e. more than 2-3 times per week) in the last 28 days prior to the screening visit (EC 4)			
Active intestinal bleeding episodes or significant low hemoglobin level (<9 g/dL for women and <11 g/dL for men) at screening (EC 5)			
History within the last 12 months or evidence of any on-going clinically relevant ECG abnormalities (e.g. arrhythmias) (EC 9)			
H/O uncontrolled hypertension with systolic blood pressure >170 mmHg and diastolic blood pressure >100 mmHg (EC 10)			
Severe renal insufficiency (i.e. with GFR <30 mL/min/1.73m ²) (EC 12)			
Serum albumin measurement <3.4 g/dL (EC 13)			
Liver disease of grades B and C according to the Child Pugh classification (EC 14)			
Significant electrolyte abnormalities, (EC 16)			
Other clinically significant hematological parameters including coagulation profile at screening (EC 17)			
Clinically relevant findings on physical examination based on the investigator's judgment (EC 21)			
H/O drug or alcohol abuse within the 12 months prior to dosing (EC 22)			
Cognitively impaired, debilitated, or fragile Patients (EC 24)			
Did not have enough blood samples available for assessment			
Hemolyzed blood samples			
Did not have an ECG taken at Visit 1			

Table 18: Study MORA-Non-compliance with inclusion/exclusion criteria

Inclusion/exclusion criteria	NER1006, 2-Day split dosing (N=18)	NER1006, 1-Day morning split dosing (N=17)	MOVIPREP 2-Day split dosing (N=21)
Abnormal activated partial thromboplastin time value at Visit 1			(b) (6)
Incomplete or absent coagulation tests at screening.			
Some laboratory samples not taken or measured at Visit 1			
Unverifiable or absent magnesium levels			
EC=Exclusion criteria; ICF=Informed consent form			

source: reviewer's table created from information provided in clinical study reports

Reviewer comment:

Very few of these violations would have biased the efficacy assessment. The numbers of patients with those types of violations (for example, use of prohibited stimulant laxatives that may have an effect on bowel cleansing) were very low and were comparable across treatment arms.

6.1.4 Analysis of Primary Efficacy Endpoint(s)

The efficacy analyses were based on the mFAS population. As stated above (see Sections 5.3.1 and 5.3.2), the primary, secondary, and supportive endpoints were the same for Studies NOCT and MORA. As stated above, the Applicant proposed the following “alternative primary efficacy endpoints” for both NOCT and MORA studies:

- Cleansing success rate in overall colon based on HCS
- Cleansing success rate in ascending colon

The primary efficacy evaluation in this review is based on the cleansing success rate in the overall colon for both studies. This is based on the Division's previous communication to the applicant that the cleansing success rate in the ascending colon is not acceptable as a stand-alone efficacy endpoint. The “alternative” primary endpoint based on cleansing success rate in the ascending colon is considered supportive.

6.1.4.1 Primary Efficacy: Cleansing Success Rate (Responder Rate) in Overall Colon (mFAS)

6.1.4.1.1 Study NOCT

The responder rates were identical (85%) between the two treatment groups (Table 19). Non-inferiority of NER1006 to Trisulfate was demonstrated; the difference in the responder rate was 0.14% with a 97.5% 1-sided lower CI of -8.15%. However, superiority of NER1006 to Trisulfate solution was not demonstrated statistically (1-sided p value 0.528).

Table 19: Study NOCT-Primary efficacy analysis (mFAS population)

	NER1006 (N=276)	Trisulfate (N=280)
Responders ^a (%)	235 (85.1)	238 (85.0)
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 Responders were defined as patients who achieved cleansing Grades of A and B by the colonoscopist based on HCS assessment criteria.

^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 mFAS, 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: Adapted from the Applicant's Clinical Study Report (NOCT) Table 11-4.

6.1.4.1.2 Study MORA

The responder rates for both the NER 2-Day split dosing and 1-Day split dosing regimens were numerically higher compared to Moviprep 2-Day split dosing regimen (Table 20). Numerically, a slightly higher proportion of patients in the NER1006, 2-Day split dosing group achieved efficacy (92%) compared to the NER1006, 1-Day morning split dosing regimen (89%) and the Moviprep 2-Day split dosing regimen (87.5%). However, the proportion of patients in the 1-Day morning split dosing were comparable compared to the Moviprep 2-Day split dosing regimen.

Both the NER1006 regimens groups met the NI margin; however, neither of the two NER-1006 groups demonstrated superiority.

- NI: For NER1006 2-Day split dosing, the difference in the treatment effect compared to Moviprep was 4.50%, with a 97.5% 1-sided lower confidence limit of -4.00%, and for NER1006 1-Day morning split dosing, the difference in the treatment effect compared to Moviprep was 1.59, with a 97.5% 1-sided lower confidence limit of -6.91%.
- Superiority: Superiority of the NER1006 2-Day split dosing and 1-Day morning split dosing regimens compared to MOVIPREP 2-Day split dosing was not demonstrated (1-sided p values of 0.055 and 0.328 for 2-Day and 1-Day split dosing groups, respectively).

Table 20: Study MORA-Primary efficacy analysis (mFAS population)

	NER1006 2-Day Split dosing (N=275)	NER1006 1-Day morning Split dosing (N=275)	MOVIPREP (N=272)
Responders ^a (%)	253 (92)	245 (89)	238 (87.5)
Difference in Harefield Cleansing Scale success rate^b	4.5	1.5	
97.5% 1-sided lower confidence limit	-4.00	-6.9	
98.75% 1-sided lower confidence limit	-5.22	-8.1	
99.5% 1-sided lower confidence limit	-6.62	-9.5	
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 mFAS 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: Adapted from the Applicant's Clinical Study Report (MORA) Table 11-4 and reviewer's results.

Reviewer comments:

The efficacy of the NER1006 2-Day regimen was slightly different in the two trials. In NOCT, the proportion of responders was 85% and in MORA, it was 92%. This likely represents normal variation that can occur between trials. The magnitude of the difference in the responder rate for NER1006-treated patients between the 2 trials was not so different as to raise a concern regarding the validity of the result.

In Study MORA, both treatment regimens were non-inferior to comparator (Moviprep). As indicated in the regulatory history above, the Agency had previously stated that the results for the same day (NER1 day) dosing regimen would need to be highly statistically persuasive to be included in the label, as this regimen was tested in only 1 of the 2 trials. Although the rate of success was numerically slightly lower for the NER 1-day regimen, compared to the NER 2-day, the rate of success for the NER 1-day regimen exceeded that of the comparator (which is administered as a 2-day split-dose). Furthermore, non-inferiority was shown at a higher bar of significance because the lower limit of the 99.5% 1-sided confidence interval (CI; which corresponds to the 99% 2-sided CI) was non-inferior to the NI margin of -10%. Thus, these results support including both regimens in the product label.

6.1.4.1.3 Sensitivity Analyses Supportive of the Primary Efficacy Analysis

The following sensitivity analyses were planned; however, the information was not provided in the initial NDA submission.

- Comparison of total fluids intake across grades of efficacy
- Comparison of success rate in reaching the IC valve and time to reach the IC valve across grades of efficacy
- Cleansing rates across all grades of efficacy
- Evaluation of success criterion Grade B based on score of 2 for several colonic segments
- Consistency/inconsistency of endoscopic evaluation across readers

- Efficacy comparison based on time elapsed between completion of bowel preparation and start of colonoscopy

An information request was sent to the Applicant on August 11, 2017 seeking these analyses. The Applicant provided all the information except for the first two analyses, as that information was not collected during the trials. The other sensitivity analyses are summarized below. Some limited information on cecal intubation and time to reach IC valve was later provided in a subsequent response to IR received January 17, 2018. Results of the key sensitivity analyses are described below.

Sensitivity analyses: Cleansing rates across all grades of efficacy

The colon cleansing scores of excellent (Grade A) and good (Grade B) or similar scores have been used for the approval of bowel preparations by the Division. The excellent cleansing rate (Grade A) is appropriate for evaluating the responder criteria. However, the assessment in the mid-range of cleansing scores/criteria/categorization i.e., Grades B and C, may contribute some bias towards efficacy in either treatment group due to subjectivity of the assessment. It would be important to evaluate if the efficacy remains consistent between the two treatment groups at each Grades of cleansing.

Table 21 and Table 22 show comparison between the two treatment groups at each grade of cleansing for the two studies, Study NOCT and Study MORA, respectively

Table 21: Study NOCT - Comparison of number of patients (%) in each grade of cleansing between the treatment groups

Colon Cleansing Grades	Treatment Group	
	NER1006 (N=276) n (%)	Trisulfate (N=280) n (%)
A	54 (19.6)	46 (16.4)
B	181 (65.6)	192 (68.6)
C	13 (4.7)	16 (5.7)
D - Failed	7 (2.5)	6 (2.1)
D - Missing	21 (7.6)	20 (7.1)

source: Applicant's response to IR, received 11/15/2017, page 5/8

Table 22: Study MORA - Comparison of number of patients (%) in each grade of cleansing between the treatment groups

Colon Cleansing Grades	Treatment Group		
	NER1006 2-Day split dosing (N=275) n (%)	NER1006 1-Day morning split dosing (N=275) n (%)	MOVIPREP (N=272) n (%)
A	56 (20.4)	59 (21.5)	27 (9.9)
B	197 (71.6)	186 (67.6)	211 (77.6)
C	4 (1.5)	20 (7.3)	12 (4.4)
D - Failed	5 (1.8)	5 (1.8)	10 (3.7)
D - Missing	13 (4.7)	5 (1.8)	12 (4.4)

source: Applicant's response to IR, received 11/15/2017, page 5/8

Reviewer comment:

In general, this analysis is supportive of the primary analysis. The proportion of patients achieving a Grade A overall score is was numerically greater for NER1006 than the comparator in both studies. Arguably, the proportion of patients achieving a Grade A rating is the most clinically meaningful assessment, as ideally, the product should produce an excellent view of the colon.

Sensitivity analysis: Evaluation of subjectivity in the success criteria Grade B based on HCS

The success criteria for overall bowel cleansing are defined as achieving Grade A or Grade B of the HCS (see Table 7 and Table 8). It is noted that Grade B is defined as 1 or more segments with a score of 2, with the remaining segments with a score of 3 or 4. Evaluation was carried out to determine the number of colonic segments having a score of 2. This was to determine if several colonic segments had scores of 2 that contributed to the Grade B success.

Table 23 and Table 24 show the overall proportion of patients with ≥ 1 colon segment having a score of 2 who were considered to have achieved success by being scored as Grade B in the two studies (Study NOCT and Study MORA). The results show that up to 20% patients had scores of 2 in all the segments, suggesting that lower cleansing was included as success in these patients.

Table 23: Study NOCT-Number of patients with score of 2 in each colon segment among patients in Grade B

Number of Patients with Grade B		Number (%) of Patients with different segments and Score 2									
NER1006 N	Trisulfate N	1 segment		2 segments		3 segments		4 segments		5 segments	
		NER n (%)	Trisulfate n (%)	NER n (%)	Trisulfate n (%)	NER n (%)	Trisulfate n (%)	NER n (%)	Trisulfate n (%)	NER n (%)	Trisulfate n (%)
181	192	32/181 (18)	28/192 (15)	36/181 (20)	24/192 (13)	30/181 (17)	36/192 (19)	46/181 (25)	59/192 (31)	37/181 (20)	45/192 (23)

Source: *Source: Adapted from the Applicant's response to information request table 1.1a (NOCT trial)*

Table 24: Study MORA - Number of patients with scores of 2 in each colon segment among patients in Grade B

No of patients in Grade B			Number (%) of Patients with Different Segments and Score 2														
NER-2 N	NER-1 N	MOVI N	1 segment			2 segments			3 segments			4 segments			5 segments		
			NER-2 (%)	NER-1 (%)	MOVI (%)	NER-2 (%)	NER-1 (%)	MOV I (%)	NER-2 (%)	NER-1 (%)	MOV I (%)	NER-2 (%)	NER-1 (%)	MOVI (%)	NER-2 (%)	NER-1 (%)	MOVI (%)
197	186	211	31/197 (16)	29/186 (16)	19/211 (9)	28/197 (14)	42/186 (23)	20/211 (10)	54/197 (27)	35/186 (19)	39/211 (19)	46/197 (23)	37/186 (20)	44/211 (21)	38/197 (19)	43/186 (23)	89/211 (42)

** NER-2: NER1006 2-Day split dosing regimen, NER-1: NER1006 1-Day morning split dosing regimen, MOVI: MOVIPREP 2-Day split dosing regimen.
source: *Adapted from the Applicant's response to information request table 1.2a (MORA trial)*

Reviewer's comments:

The Grade B criterion for efficacy is defined as having 1 or more segments with a score of 2, with the remaining scored as 3 or 4. For optimal efficacy, scores of 3 and 4 are desirable for all colon segments, and a score of 2 may be acceptable for 1-2 segments. However, it is concerning that in both studies up to 20% of patients had score of 2 in all the segments, suggesting that a lower level of cleansing was included as success. Nevertheless, this pattern was seen for all treatment arms, so it does not appear to bias the results in favor of either NER1006 regimen. For future efficacy endpoints, it should be stated that only 1 or 2 segments with a score of 2 should be included to define success.

Sensitivity analysis: Consistency/inconsistency of endoscopic evaluation

Efficacy assessment rates for each grade for the site colonoscopist and the first and second readers were evaluated to ascertain the degree/extent of agreement/disagreement in colon cleansing grading between the evaluators.

Table 25 and Table 26 show the cleansing rates assigned by the site colonoscopist and the first reader for Study NOCT and MORA, respectively. The site colonoscopist had numerically much higher responder rates and proportions of patients with Grade A compared to the first reader, whereas the first reader graded a higher proportion of patients in Grade B. The proportion of patients with combined Grade A and B, however, was similar for the site colonoscopist and first reader.

Table 25: Study NOCT - Assessment of efficacy rates for colonoscopist and first reader

Grades	Colonoscopist grading (%)		First reader grading (%)	
	NER1006 (N=276) n (%)	Trisulfate (N=280) n (%)	NER1006 (N=276) n (%)	Trisulfate (N=276) n (%)
A	193 (70)	179 (64)	53 (19)	45 (16)
B	48 (17)	69 (25)	171 (62)	185 (66)
C	11 (4)	13 (5)	23 (8)	24 (9)
D	7 (2.5)	3 (1)	8 (3)	6 (2)
Missing	17 (6)	16 (6)	21 (7)	20 (7)

source: Adapted from the Applicant's submission to information request Table 2.1 (NOCT trial)

Table 26: Study MORA - Assessment of efficacy rates for colonoscopist and first reader

Grades	Colonoscopist grading (%)			First reader grading (%)		
	NER-2 (N=275) n (%)	NER-1 (N=276) n (%)	MOVI (N=272) n (%)	NER-2 (N=275) n (%)	NER-1 (N=275) n (%)	MOVI (N=272) n (%)
A	187 (68)	176 (64)	138 (51)	57 (20)	56 (20)	27 (10)
B	68 (25)	70 (25)	101 (37)	191 (70)	177 (64)	204 (75)
C	7 (2.5)	12 (4)	17 (6)	11 (4)	31 (11)	18 (7)
D	1 (0.4)	5 (2)	9 (3)	13 (5)	5 (2)	12(4)
Missing	12 (4)	5 (2)	9 (3)	13 (5)	5 (2)	12 (4)

** NER- 2: NER1006 2-Day split dosing regimen, NER-1: NER1006 1-Day morning split dosing regimen, MOVI: MOVIPREP 2-Day split dosing regimen

source: Adapted from the Applicant's submission to information request Table 2.2 (MORA trial)

Table 27 and Table 28 show the assessments by the second reader for the patients, in the two studies, for those situations where there was non-agreement between the site colonoscopist and first reader.

Table 27: Study NOCT-Assessment of efficacy rates for colonoscopist, first and second reader (among patients with second reader)

Grades	Colonoscopist grading (%)		First reader grading (%)		Second reader grading (%)	
	NER1006 (N=23) n (%)	Trisulfate (N=24) n (%)	NER1006 (N=23) n (%)	Trisulfate (N=24) n (%)	NER1006 (N=23) n (%)	Trisulfate (N=24) n (%)
A	7 (30)	3 (12)	0	0	1 (4)	1 (4)
B	11 (48)	16 (67)	5 (21)	5 (21)	15 (65)	12 (50)
C	3 (13)	5 (21)	15 (65)	16 (67)	5 (21)	8 (33)
D	2 (9)	0	3 (13)	3 (12)	2 (9)	3 (12)
Missing	23 (100)	24 (100)	23 (100)	24 (100)	23 (100)	24 (100)

source: Adapted from the Applicant's submission to information request Table 3.1 (NOCT trial)

Table 28: Study MORA - Assessment of efficacy rates for colonoscopist, first and second reader (among patients with second reader)

Grades	Colonoscopist grading (%)			First reader grading (%)			Second reader grading (%)		
	NER-2 (N=18) n (%)	NER-1 (N=27) n (%)	MOVI (N=34) n (%)	NER-2 (N=18) n (%)	NER-1 (N=27) n (%)	MOVI (N=34) n (%)	NER-2 (N=18) n (%)	NER-1 (N=27) n (%)	MOVI (N=34) n (%)
A	2 (11)	8 (30)	9 (26)	1 (6)	0	1 (3)	0	3 (11)	1 (3)
B	10 (56)	12 (44)	11 (32)	5 (28)	7 (26)	13 (38)	11 (61)	16 (59)	20 (59)
C	5 (28)	6 (22)	12 (35)	9 (50)	18 (67)	16 (47)	2 (11)	7 (26)	10 (29)
D	1 (6)	1 (4)	2 (6)	3 (17)	2 (7)	4 (12)	5 (28)	1 (4)	3 (9)
Total	18 (100)	27 (100)	34 (100)	18 (100)	27 (100)	34 (100)	18 (100)	27 (100)	34 (100)

** NER-2: NER1006 2-Day split dosing regimen, NER-1: NER1006 1-Day morning split dosing regimen, MOVI: MOVIPREP 2-Day split dosing regimen.

source: Adapted from the Applicant's submission to information request Table 3.2a (MORA trial)

Reviewer comment:

There is large variation in assessment of efficacy (inter-observer variability) among the local and central reader, and even between the 2 central readers, when a second central reading was requested. This suggests the need for careful training and standardization of procedures for colonoscopy central readers. Further, this may suggest that the scoring system and algorithm need to be further refined, as it was not consistently understood and applied in the same way by different experts.

Sensitivity analysis: Efficacy comparison based on time elapsed between completion of bowel preparation and start of colonoscopy

Optimal colon cleansing is expected to occur when all of the bowel contents, including fluid and feces, are excreted. Assessing the colon cleansing before complete evacuation is expected to be sub-optimal. Therefore, analysis of the efficacy at several time periods helps in deciding the ideal time between finishing bowel preparation and start of colonoscopy.

The results in Table 29 and Table 30 show the efficacy comparison between different treatment groups and time periods. The majority of patients in both studies had colonoscopy between 3 and less than 6 hours after the completion of bowel preparation. As expected, longer delays (>9 hours post completion of dose) were associated with numerically lower rates of efficacy, although the numbers were very small.

Table 29: Study NOCT- Efficacy comparison based on time elapsed between completion of bowel preparation and start of colonoscopy

Elapsed time	NER1006 (N=276)		Trisulfate solution (N=280)	
	Completers m (Y%)	Efficacy n (Z%)	Completers m (Y%)	Efficacy n (Z%)
≤3 hours	45 (16)	39 (87)	35 (12.5)	34 (97)
>3-≤ 6 hours	176 (64)	161 (91)	188 (67)	173 (92)
>6-≤ 9 hours	35 (12.7)	32 (91)	35 (12.5)	26 (74)
>9-≤ 12 hours	3 (1.1)	2 (67)	2 (0.7)	2 (100)
> 12 hours	1 (0.4)	1 (100)	4 (1.4)	3 (75)
Missing	16 (5.8)	0	16 (5.7)	0
Total	276 (100)	235 (85)	280	238 (85)

N = the number of patients in the analysis set. m = the number of patients within the elapsed time band. n = the number of patients with overall bowel cleansing success for the respective treatment. (Y%) = $m/N \times 100$. (Z%) = $n/m \times 100$.

source: Adapted from the Applicant's response to information request table 6.1 (NOCT trial)

Table 30: Study MORA - Efficacy comparison based on time elapsed between completion of bowel preparation and start of colonoscopy

Elapsed time	NER1006, 2-Day split dosing		NER1006, 1-Day split dosing		MOVIPREP	
	Completers m (Y%)	Efficacy n (Z%)	Completers m (Y%)	Efficacy n (Z%)	Completers m (Y%)	Efficacy n (Z%)
≤3 hours	22 (8)	19 (86)	39 (14)	35 (90)	44 (16)	38 (86)
>3-≤ 6 hours	144 (52)	142 (99)	169 (62)	154 (91)	157 (58)	146 (93)
>6-≤ 9 hours	80 (29)	77 (96)	56 (20)	53 (95)	51 (19)	44 (86)
>9-≤ 12 hours	14 (5)	2 (14)	7 (2.5)	0	2 (0.7)	2 (100)
> 12 hours	1 (0.4)	1 (100)	3 (1.1)	2 (67)	2 (0.7)	2 (100)
Missing	14 (5)	2 (14)	7 (2.5)	0	12 (4)	3 (2.5)
Total	275 (100)	253 (92)	275 (100)	245 (89)	272 (100)	238 (87)

N = the number of patients in the analysis set. m = the number of patients within the elapsed time band. n = the number of patients with overall bowel cleansing success for the respective treatment. (Y%) = $m/N \times 100$. (Z%) = $n/m \times 100$.

source: Adapted from the Applicant's response to information request table 6.2 (MORA trial)

Reviewer comment:

This sensitivity analysis explores efficacy differences by the amount of time that elapsed after completion of ingestion of the prep. The results were consistent across time periods ranging from ≤3 hours through 9 hours post-ingestion, and generally supportive of the primary efficacy

results. The exception was patients who underwent the procedure >9 hours after preparation completion, where efficacy was notably reduced. This is expected, as the colon will continue to produce feces that will accumulate, if a long time period elapses from completion of the preparation and the procedure. The product label does encourage patients to take fluids until 2 hours before colonoscopy.

Sensitivity analysis: Cecal Intubation Time

Given that the Applicant chose a scoring system that assessed on withdrawal rather than on insertion of the colonoscope, the time to cecal intubation could be assessed as an additional supportive assessment of the adequacy of cleansing. The time to reach the cecum would be expected to be greater in a colon where a greater degree of washing/suctioning was required due to inadequate preparation. This analysis is limited by the fact that not all patients had video recording on insertion. However, a *post hoc* analysis to address the Agency's request for this information, based on patients with available video recordings on insertion, is shown below.

Table 31: Cecal Intubation Time - NOCT

HCS Grade	Summary Statistic (min:sec)	NER1006 2-Day N=255		Trisulfate N=260	
		n	Time	n	Time
All Grades	Mean (SD)	246	05:53 (05:08)	250	05:44 (05:13)
	Median (Min; Max)		04:17 (00:59; 38:36)		04:05 (01:19; 39:36)
A	Mean (SD)	54	04:56 (04:03)	43	04:18 (02:48)
	Median (Min; Max)		03:54 (01:14; 27:18)		03:45 (01:26; 17:33)
B	Mean (SD)	176	05:53 (05:08)	187	05:39 (05:10)
	Median (Min; Max)		04:20 (00:59; 38:36)		04:04 (01:19; 39:36)
C/D	Mean (SD)	16	09:00 (07:15)	20	09:42 (07:33)
	Median (Min; Max)		04:50 (03:13; 28:20)		07:01 (02:09; 27:18)

N=number of patients with videos scored on withdrawal; n=number of patient in analysis;
min:sec= minutes:seconds; SD=standard deviation; Min=minimum; Max=maximum

source: Applicant's response to information request dated 1/17/18

Table 32: Cecal Intubation Time (MORA)

HCS Grade	Summary Statistic (min:sec)	NER1006 2-Day N=262		NER1006 1-Day N=270		MOVIPREP N=260	
		n	Time	n	Time	n	Time
All Grades	Mean (SD)	222	09:47 (07:21)	215	09:39 (06:33)	199	09:28 (07:10)
	Median (Min; Max)		07:41 (01:19; 56:19)		08:09 (01:21; 41:25)		07:28 (01:42; 55:19)
A	Mean (SD)	49	08:35 (06:31)	49	08:36 (05:40)	25	09:19 (05:25)
	Median (Min; Max)		06:57 (02:15; 38:26)		06:47 (02:28; 26:13)		08:28 (03:13; 21:48)
B	Mean (SD)	167	09:57 (06:46)	149	10:11 (06:54)	164	09:31 (07:32)
	Median (Min; Max)		07:55 (01:19; 40:23)		08:33 (01:21; 41:25)		07:27 (01:42; 55:19)
C/D	Mean (SD)	6	15:16 (20:15)	17	07:52 (05:16)	10	08:58 (04:56)
	Median (Min; Max)		07:11 (04:24; 56:19)		07:40 (02:28; 25:42)		07:39 (03:44; 19:28)

N=number of patients with videos scored on withdrawal; n=number of patient in analysis; min:sec= minutes:seconds; SD=standard deviation; Min=minimum; Max=maximum

source: Applicant's response to information request dated 1/17/18

Reviewer comment:

In the overall assessment, cecal intubation times (where available) appear comparable across the NER1006 and comparator arms. As anticipated, mean times were generally longer in the failure group (C/D) compared to successful patients, but this was not replicated in the median times, which may suggest that the mean was altered by a small number of outliers. Also, the number of patients with "failure" grade C or D was so small, that meaningful conclusions cannot be drawn from this analysis.

6.1.4.2 Supportive Analyses (Per Protocol)

The following supportive analyses are considered exploratory.

• **Efficacy Analysis Based on Per Protocol Population**

Study NOCT

Table 33 shows the success rate per the responder definition based on the per protocol population. The proportion of patients was comparable (92%) in the NER1006 and Trisulfate 2-Day split dosing treatment groups.

Table 33: Study NOCT - Primary efficacy analysis (per-protocol set)

	NER1006 (N=233)	Trisulfate (N=239)
Responders ^a (%)	215 (92)	221 (92)
Difference in Harefield Cleansing Scale success rate^b	0.19	
97.5% 1-sided lower confidence limit	-9.26	
98.75% 1-sided lower confidence limit	-10.54	
<i>P</i> value ^c	0..6	

^a Grades A and B were classified as successful cleansing and grades C and D were classified as failure.

^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 PP 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: Adapted from the Applicant's Clinical Study Report (NOCT) Table 11-6.

Study MORA

Table 34 shows a higher success rate (97%) in the NER1006, 2-Day split dosing group compared to the NER1006, 1-Day split dosing (92%) and MOVIPREP, 2-Day split dosing (92%) groups.

Table 34: Study MORA - Primary efficacy analysis (per-protocol set)

	NER1006 2-Day Split dosing (N=220)	NER1006 1-Day morning Split dosing (N=218)	MOVIPREP (N=232)
Responders ^a (%)	214 (97.3)	202 (92.7)	214 (92.2)
Difference in Harefield Cleansing Scale success rate^b	5	0.42	
97.5% 1-sided lower confidence limit	-4.21	-8.82	
98.75% 1-sided lower confidence limit	-5.53	-10.14	
<i>P</i> value ^c	0.014	0.505	

^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 PP 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: Adapted from the Applicant's Clinical Study Report (MORA) Table 11-6.

Consistent with the results of the primary efficacy in the mFAS population in the MORA study, a higher proportion of patients in the NER1006, 2-Day split doing treatment group achieved efficacy (97.3%) compared to the NER1006, 1-Day morning split dosing regimen (92.7%) and MOVIPREP, 2-Day split dosing regimen (92.2%). However, the proportion of patients in the NER1006, 1-Day morning split dosing are comparable (92%) to the 2-Day split dosing regimen with MOVIPREP.

- **Exploratory Efficacy: Cleansing Success Rate in the Ascending Colon**

As discussed above, efficacy based on cleansing of the ascending colon was not accepted as a primary endpoint by the Division. The efficacy rates in the ascending colon are presented briefly for completeness (for more details, see Sections 5.3.1 and 5.3.2, Discussion of individual studies/clinical trials).

Study NOCT

The cleansing rates in the ascending colon for mFAS are shown in Table 35. The results show higher responder rates in the NER1006 group compared to the Trisulfate group.

Table 35: Study NOCT - Cleansing rates in ascending colon (mFAS)

	NER1006 (N=276)	Trisulfate (N=280)
Responders (Excellent plus good) ^a n (%)	99 (36)	82 (29)
Difference in Harefield Cleansing Scale success rate^b	6	
97.5% 1-sided lower confidence limit	-1.7	
98.75% 1-sided lower confidence limit	-2.8	
<i>P</i> value ^c	0.06	

^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 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 mFAS 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: Adapted from the Applicant's Clinical Study Report (NOCT) Table 11-7.

Study MORA

The cleansing rates in the ascending colon for mFAS are shown in Table 36. The results show higher responder rates in the NER1006 groups compared to the MOVIPREP group.

Table 36: Study MORA - Cleansing rates in ascending colon (mFAS)

	NER1006 2-Day Split dosing (N=275)	NER1006 1-Day morning Split dosing (N=275)	MOVIPREP (N=272)
Responders (Excellent plus good) ^a n (%)	87 (32)	93 (34)	41 (15)
Difference in Harefield Cleansing Scale success rate^b	16.56	18.7	
97.5% 1-sided lower confidence limit	8.1	10.32	
98.75% 1-sided lower confidence limit	6.9	9.12	
<i>P</i> 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 mFAS 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: Adapted from the Applicant's Clinical Study Report (MORA) Table 11-7.

Reviewer comment:

Please refer to the statistical review by Dr. Shala Farr for further details of this analysis and why the Agency does not consider this appropriate to support a claim of efficacy.

6.1.5 Analysis of Secondary Endpoints(s)

The secondary endpoints evaluated in the two phase 3 studies (NOCT and MORA) were:

- Adenoma Detection Rate (ADR): overall and ascending colon
- Polyp Detection Rate (PDR): overall and ascending colon

6.1.5.1 Adenoma Detection Rate in Overall and Ascending Colon

The ADR is one of the important quality indicators of adequate colonoscopy per American Society of Gastrointestinal Endoscopy and American College of Gastroenterology guidelines.²⁰ ADRs are typically calculated based upon screening colonoscopies in asymptomatic patients ≥ 50 years of age who are at average risk for colon polyps and colon cancer. Colonoscopists performing the colonoscopy should have ADRs of at least 25 percent.

The ADRs in the overall colon and ascending colon are summarized based on the mFAS set. The ADR was defined as the number of patients with at least one adenoma, divided by the number of patients in the mFAS.

Per the statistical reviewer, because superiority was not demonstrated for both proposed “co-primary endpoints,” formal statistical testing was stopped, and ADR should not be formally

²⁰ Quality indicators for colonoscopy. Rex DK *et al.* Gastrointest Endosc. 2015 Jan; 81(1):31-53.

tested. However, the clinical reviewer notes that ADR is clinically important, and so these results are presented descriptively.

- **Study NOCT**

In the overall colon, the ADR was similar in the NER1006 and Trisulfate treatment groups, i.e., 34% and 35%, respectively. The ADR in the ascending colon was numerically higher in the Trisulfate (17%) compared to NER1006 (14%) treatment group (Table 37), but again, limitations of any assessment conducted on only one segment are noted, as previously described. No carcinomas were detected in the overall colon in patients in either of the treatment groups.

Table 37: Study NOCT - Adenoma detection rate in overall and ascending colon (mFAS)

	NER1006 (N=276)		Trisulfate solution (N=280)	
	Ascending colon	Overall colon	Ascending colon	Overall colon
Number of adenomas, n (%)				
0	237 (86)	183 (66)	232 (83)	182 (65)
1	29 (10.5)	45 (16.3)	34 (12)	56 (20)
2	8 (3)	21 (7.6)	11 (4)	17 (6)
>2	2 (0.7)	27 (10)	3 (1)	25 (9)
ADR^a	14	33.7	17	35

^a ADR was defined as the number of patients with at least one adenoma divided by the number of patients in the mFAS.

source: Adapted from the Applicant's Clinical Study Report Table (NOCT) 11-10.

- **Study MORA**

In the overall colon, the ADR was comparable (27%) in the three treatment groups (Table 38). The ADR in the ascending colon was numerically higher in the NER1006 treatment groups (12% each) compared to Moviprep (8%). No carcinomas were detected in the overall colon in patients of either treatment group.

Table 38: Study MORA - Adenoma detection rate in overall and ascending colon (mFAS)

	NER1006 2-Day Split-Dosing (N=275)		NER1006 1-Day Morning Split-Dosing (N=275)		MOVIPREP (N=272)	
	Ascending colon	Overall colon	Ascending colon	Overall colon	Ascending colon	Overall colon
Number of adenomas, n (%)						
0	243 (88.4)	202 (73.5)	243 (88.4)	199 (72.4)	250 (91.9)	199 (73.2)
1	21 (7.6)	38 (13.8)	22 (8.0)	43 (15.6)	13 (4.8)	44 (16.2)
2	7 (2.5)	16 (5.8)	7 (2.5)	19 (6.9)	13 (4.8)	15 (5.5)
>2	4 (1.5)	19 (6.9)	3 (1.1)	14 (5.1)	4 (1.5)	14 (5.1)
ADR^a	11.6	26.6	11.6	27.6	8.1	26.8

^a ADR was defined as the number of patients with at least one adenoma divided by the number of patients in the mFAS.

source: Adapted from the Applicant's Clinical Study Report Table (MORA) 11-10.

Reviewer comment:

The ADR was numerically similar across treatment arms in both studies, which is reassuring and

supportive of the overall study findings demonstrating that efficacy was similar between NER1006 and comparators.

6.1.5.2 Polyp Detection Rate in Overall and Ascending Colon

The PDR in the overall and ascending colon are summarized based on the mFAS set.

- Study NOCT**

In the overall colon PDR was numerically similar in the NER1006 and Trisulfate treatment groups; 46% and 48%, respectively. The PDR in the ascending colon was numerically higher in the Trisulfate (24%) compared to the NER1006 (19%) treatment group (Table 39).

Table 39: Study NOCT - Polyp detection rate in overall and ascending colon (mFAS)

	NER1006 (N=276)		Trisulfate solution (N=280)	
	Ascending colon	Overall colon	Ascending colon	Overall colon
Number of polyps, n (%)				
0	225 (81.5)	150 (54)	213 (76)	144 (51.5)
1	36 (13)	61 (22)	51 (18)	70 (25)
2	11 (4)	24 (8.7)	11 (4)	26 (9.3)
>2	4 (1.4)	41 (15)	5 (2)	40 (14.3)
PDR^a	18.5	45.7	24	48.5

^a PDR was defined as the number of patients with at least one polyp divided by the number of patients in the mFAS.
Source: Adapted from the Applicant's Clinical Study Report (NOCT) Table 11-11.

- Study MORA**

In the overall colon, the PDR was comparable (44-45%) in all the three treatment groups. The PDR in the ascending colon was numerically higher in the NER1006, 2-Day split dosing (23%), and NER1006, 1-Day split dosing (19%) compared to MOVIPREP (16%) treatment group (Table 40).

Table 40: Study MORA-Polyp detection rate in overall and ascending colon (mFAS)

	NER1006 2-Day Split-Dosing (N=275)		NER1006 1-Day Morning Split-Dosing (N=275)		MOVIPREP (N=272)	
	Ascending colon	Overall colon	Ascending colon	Overall colon	Ascending colon	Overall colon
Number of polyps, n (%)						
0	211 (76.7)	154 (56.0)	224 (81.5)	151 (54.9)	228 (83.8)	151 (55.5)
1	42 (15.3)	55 (20.0)	31 (11.3)	51 (18.5)	28 (10.3)	52 (19.1)
2	15 (5.5)	21 (7.6)	12 (4.4)	32 (11.6)	9 (3.3)	29 (10.7)
>2	7 (2.5)	45 (16.4)	8 (2.9)	41 (14.9)	7 (2.6)	40 (14.7)
PDR^a	23.3	44.0	18.6	45.1	16.2	44.5

^a PDR was defined as the number of patients with at least one polyp divided by the number of patients in the mFAS.
source: Adapted from the Applicant's Clinical Study Report Table (MORA) 11-11.

Reviewer comment:

In summary, ADR and PDR rates were generally comparable between NER1006 and comparators. The ADR rates differ from those expected based on published guidelines, because

the population assessed here includes the full mFAS, whereas published benchmark ADR rates are based on a specific subset of patients >50 years undergoing first screening colonoscopy. Nonetheless, the numerically comparable rates seen here across treatment arms are generally reassuring and are consistent with the primary efficacy results.

6.1.6 Other Endpoints (Supportive Secondary Endpoints)

Multiple exploratory endpoints were included by the Applicant. This review will briefly summarize those the reviewer finds to be most informative, including:

- Bowel cleansing success rates using the BBPS
- Compliance with recommended administration
- *Post hoc* efficacy analysis based on insertion (per video recordings)

6.1.6.1 Bowel Cleansing Success Rates Using the Boston Bowel Preparation Scale (BBPS)

As described above, the BBPS is another commonly utilized cleansing scale to assess bowel preparation effectiveness. The bowel cleansing success rates using BBPS for the overall colon and for three colon segments (right, transverse and left colon) were evaluated based on the mFAS for the two studies. The overall responder rates (score of ≥ 6 overall and at least a score of 2 in each segment) and segmental cleansing rates for each of the three colon segments based on the scores of 2 and 3 are summarized for NER1006 treatment and active comparators in the two studies.

- **Study NOCT**

The proportion of responders for the overall colon cleansing were comparable between NER1006 (82%) and Trisulfate (81%) treatment groups (Table 41). The proportion of patients with segmental cleansing rates for each of the three colon segments, based on scores of 2 and 3 (see Table 10), were also comparable between the NER1006 and Trisulfate treatment groups.

Table 41: Study NOCT-Overall and segmental efficacy based on Boston Bowel Preparation Scale (mFAS)

	NER1006 (N=276) n (%)	Trisulfate solution (N=280) n (%)
Overall (responder criteria) ^a	228/276 (82.6)	227/280 (81)
Right colon		
• 3	56 (20.3)	56 (20)
• 2	184 (66.7)	180 (64.3)
Transverse colon		
• 3	63 (22.8)	68 (24.3)
• 2	178 (64.5)	175 (62.5)
Left colon		
• 3	51 (18.5)	55 (19.6)
• 2	185 (67%)	188 (67)

^a Score of ≥ 6 overall and at least a score of 2 in each segment corresponded to success.

source: Adapted from the Applicant's Clinical Study Report (NOCT) Table 11-14

• Study MORA

The proportion of responders for the overall colon cleansing were numerically higher in the two NER1006 treatment regimens (88-90%) compared to the Moviprep treatment group (85%) (Table 42). The proportion of patients with segmental cleansing rates for each of the three colon segments with a score of 3 were higher in the two NER1006 treatment groups (23-29%) compared to the MOVIPREP (13-18%).

Table 42: Study MORA-Overall and segmental efficacy based on Boston Bowel Preparation Scale (mFAS)

	NER1006 2-Day split dosing (N=275) n (%)	NER1006 1-Day split dosing (N=275) n (%)	MOVIPREP (N=272) n (%)
Overall (responder criteria) ^a	249 (90)	243 (88)	232(85)
Right colon			
• 3	66 (24)	63 (23)	36 (13)
• 2	188 (68)	190 (69)	206 (75)
Transverse colon			
• 3	77 (28)	81 (29)	49 (18)
• 2	183 (66)	179 (65)	201 (74)
Left colon			
• 3	66 (24)	65 (24)	50 (18)
• 2	190 (69)	185 (67)	199 (73)

^a Score of ≥ 6 overall and at least a score of 2 in each segment corresponded to success.

source: Adapted from the Applicant's Clinical Study Report (MORA) Table 11-14

Reviewer comments:

These results are consistent with the primary endpoint results.

6.1.6.2 Compliance (Assessed Using Patient Diary)

The overall compliance was based on the patient taking at least three quarters of each dose and mandatory fluids with each dose.

• Study NOCT

The overall compliance was comparable in both treatment groups 92% in NER1006 and 91 % in Trisulfate group (Table 43).

Table 43: Study NOCT-Bowel Preparation Compliance According to Patient Diary

	NER1006 (N=276) n (%)	Trisulfate (N=280) n (%)
Overall compliance	255 (92)	256 (92)

Note: The compliance results are based on the mFAS and therefore do not total to 100%. The missing percentages are mostly due to those patients in the mFAS who did not receive the study drug and therefore did not complete the patient diary.

source: Compiled from the Applicant's CSR (NOCT) Table 11-16.

- **Study MORA**

The overall compliance was comparable in all treatment groups (Table 44).

Table 44: Study MORA-Bowel Preparation Compliance According to Patient Diary

	NER1006		MOVIPREP 1-Day (N=275) n (%)
	2-Day (N=275) n (%)	1-Day (N=275) n (%)	
Overall compliance	235 (85.5)	245 (89)	246 (90)

Note: The compliance results are based on the mFAS and therefore do not total to 100%. The missing percentages are mostly due to those patients in the mFAS who did not receive the study drug and therefore did not complete the patient diary.

source: Compiled from the Applicant's CSR (MORA) Table 11-16.

6.1.6.34 Tolerance and acceptability:

Additional measures of tolerance and acceptability were collected via questionnaire. These were not submitted for review or agreed upon as fit-for-purpose in advance of phase 3, and so results are not discussed further here.

6.1.6.3 Post Hoc Efficacy Analysis During Advancement Phase Based on the Prerecorded Videos Taken During the Colonoscopy

Each video was reviewed by one of the central assessors. A *post hoc* analysis of efficacy based on advancement (video recording-captured) was conducted at the Agency's request. This analysis was conducted on the revised mFAS, described below.

Patient disposition

- **Study NOCT (NER1006-01/2016; ADV)**

There were 276 and 280 patients in the NER1006 and Trisulfate treatment groups respectively in the mFAS. In total, 21 patients (7.6%) in the NER1006 and 22 patients (7.9%) in the Trisulfate treatment group did not have the videos available. Therefore, there were 255 patients in

NER1006 and 258 patients in the revised mFAS. The number of patients included in the mFAS and revised mFAS are summarized in Table 45.

Table 45: Study NOCT-Patient disposition

	NER1006 (N=276) n (%)	Trisulfate (N=280) n (%)
Modified full analysis set (mFAS)	276 (100)	280 (100)
Patients did not have videos available	21 (7.6%)	22 (7.9%)
Revised mFAS	255 (92.4)	258 (92.1)

source: Adapted from the Applicant's clinical study report NER1006-01/2016 (ADV)

• **Study MORA (NER1006-02/2016; ADV2)**

There were 275 patients each in the two NER1006 treatment groups and 272 in the Moviprep group in the mFAS. In total, 51(18.5%) patients in the NER1006 2-Day treatment group, 55 (20%) patients in the NER1006 1-Day treatment group and 66 (24.3%) patients in the Moviprep treatment group did not have their videos available during advancement phase; Sites 203 and 402 did not record video during the advancement phase. Therefore, there were 224 patients in the NER1006 2-Day treatment group, 220 patients in the NER1006 1-Day treatment group and 206 patients in the Moviprep group in the revised mFAS (Table 46).

Table 46: Study MORA-Patient disposition

	NER1006 2-Day split dosing (N=275) n (%)	NER1006 1-Day split dosing (N=275) n (%)	MOVIPREP 2-Day split dosing (N=272) n (%)
Modified full analysis set (mFAS)	275 (100)	275(100)	272 (100%)
Patients did not have videos available	51 (18.5%)	55 (20%)	66 (24.3%)
Revised mFAS	224 (81.5)	220 (80)	206 (75.7)

source: Adapted from the Applicant's clinical study report NER1006-02/2016 (ADV2)

Post-hoc Efficacy Evaluation during Advancement

The efficacy evaluation was performed for the following:

Primary:

- Cleansing success rate in overall colon on advancement based on HCS

Supportive

- “Worst score” analyses of alternative primary endpoints
- Cleansing success rate in overall colon on advancement based on BBPS
- Total washing events and total washing time during advancement phase.

For more details see Section 5.3.3- Discussion of individual studies/clinical trials.

Cleansing success rate in overall colon on advancement

Efficacy evaluation was conducted on advancement for the overall colon cleansing. Results are described based on mFAS as well as revised mFAS populations.

- **Study NOCT**

mFAS: The success rates during the advancement phase (84-87%) are comparable to the primary efficacy rates (85%) during the withdrawal phase of colonoscopy in the mFAS. Non-inferiority of NER1006 to the Trisulfate treatment was demonstrated. However, because this analysis population imputed patients who did not have video recordings available as non-responders, the revised mFAS analysis is more reflective of the outcomes.

Revised mFAS: A higher success rates were achieved in the revised mFAS (91-94%) compared to mFAS (84-86%) (Table 47). Non-inferiority of NER1006 to the Trisulfate treatment was demonstrated.

Table 47: Study NOCT (ADV)-Cleansing success rate in overall colon on advancement (Revised mFAS)

	NER1006 2-Day Split dosing (N=255)	Trisulfate (N=258)
Responders n (%)	239 (93.7)	236 (91.5)
Treatment difference	2.5	
1-sided P value [1]	0.211	
97.5% 1-sided lower confidence limit [2]	- 6.32	
98.75% 1-sided lower confidence limit [2]	-7.56	

[1] p-value from Fisher's Exact test. [2] Exact Clopper-Pearson confidence limit. N = the number of patients in the revised mFAS.

n = the number of patients meeting the criterion. (%) = $n/N \times 100$.

source: Adapted from the Applicant's clinical study report NER1006-01/2016 (ADV) Tables 2 and 2.1.2

- **Study MORA**

mFAS: The success rates in the advancement phase in NER1006, 2-day split dosing group were numerically higher (75.3%) compared to the NER1006, 1-Day morning split dosing (69.1%) and Moviprep (68.4%) in the mFAS. The success rates were similar in between the NER1006, 1-Day morning split dosing and Moviprep 2-Day split dosing groups. Non-inferiority of both NER1006 treatment groups to the Moviprep treatment was demonstrated. The same limitations of this analysis population discussed for Study NOCT apply to these results.

Revised mFAS: Higher success rates were achieved in the revised mFAS compared to mFAS for all treatment groups (Table 48).

Table 48: Study MORA (ADV2)-Cleansing success rate in overall colon on advancement (Revised mFAS)

	NER1006 2-Day Split dosing (N=224)	NER1006 1-Day morning Split dosing (N=220)	MOVIPREP (N=206)
Responders n (%)	207 (92.4)	190 (86.4)	186 (90.3)
Treatment difference	2.12	-3.93	
1-sided P value [1]	0.271	0.921	
97.5% 1-sided lower confidence limit [2]	-7.32	-13.395	
98.75% 1-sided lower confidence limit [2]	-8.67	-14.73	

[1] p-value from Fisher's Exact test. [2] Exact confidence limit. N = the number of patients in the revised mFAS.
n = the number of patients meeting the criterion.
(%) = $n/N \times 100$.

source: Adapted from the Applicant's clinical study report NER1006-01/2016 (ADV2) Tables 3 and 2.1.2

Reviewer comment:

In the revised mFAS, the efficacy was similar between the advancement and withdrawal phases in both studies. However, the limitations of post hoc analyses include the fact that the two scales used for efficacy analysis (HCS and BBPS) are validated only for assessment during the withdrawal phase of the procedure. Also, there were missing video recordings of the colonoscopy in one study (Study MORA) in a large number of patients (17.9%), which makes the mFAS analysis less relevant. This was primarily due to the fact that 2 sites only captured video-recordings on withdrawal. Additionally, the primary efficacy results are based on colonoscopy by one observer and validation by two readers; whereas in the post hoc analysis, the results are based on a single reader reviewing the video recording. Nevertheless, this analysis is supportive of the primary efficacy results for the program.

Additional Efficacy Analyses (exploratory):

• **Cleansing success rate in overall colon - Worst score results**

Exploratory analysis was conducted comparing the scores obtained from both advancement phase and withdrawal phase, and assigning the worst of the 2 scores to each subject, within the mFAS population.

o **Study NOCT**

The proportion of patients that achieved successful colon cleansing were comparable in the NER1006 (82%) and Trisulfate (80%) groups, using worst assigned score during the advancement or withdrawal phases (Table 49).

Table 49: Study NOCT (ADV)-Cleansing success rate in overall colon based on worst score results (mFAS)

	NER1006 2-Day Split dosing (N=276)	Trisulfate (N=280)
Responders n (%)	227 (82.2)	224 (80.0)
Treatment difference		2.25
1-sided P value [1]		0.285
97.5% 1-sided lower confidence limit [2]		- 6.05
98.75% 1-sided lower confidence limit [2]		-7.22

[1] p-value from Fisher's Exact test. [2] Exact Clopper-Pearson confidence limit. N = the number of patients in the mFAS.

n = the number of patients meeting the criterion. (%) = n/N*100.

source: Adapted from the Applicant's clinical study report NER1006-01/2016 (ADV) Tables 5 and 2.3.1

o Study MORA

Based on worst scores, a higher proportion of patients achieved successful colon cleansing in the NER1006, 2-Day split dosing (74%) compared to NER, 1-Day split dosing (67%) and MOVIPREP (65%) during the advancement and withdrawal phases (Table 50).

Table 50: Study MORA (ADV2)-Cleansing success rate in overall colon on advancement based on worst score results (mFAS)

	NER1006 2-Day Split dosing (N=275)	NER1006 1-Day morning Split dosing (N=275)	MOVIPREP (N=272)
Responders n (%)	203 (73.8)	185 (67.3)	176 (64.7)
Treatment difference	9.11	2.57	
1-sided P value [1]	0.013	0.294	
97.5% 1-sided lower confidence limit [2]	0.75	-5.83	
98.75% 1-sided lower confidence limit [2]	-0.45	-7.03	

[1] p-value from Fisher's Exact test. [2] Exact confidence limit. N = the number of patients in the revised mFAS.

n = the number of patients meeting the criterion.

(%) = n/N*100.

source: Adapted from the Applicant's clinical study report NER1006-01/2016 (ADV2) Tables 6 and 2.3.1

Reviewer comment:

In both NOCT and MORA, the efficacy rates for all the treatment groups, based on the worst results for advancement/withdrawal, were supportive of the primary efficacy analysis results.

• Bowel cleansing success rate using BBPS on advancement

o Study NOCT

Cleansing success rate during advancement was numerically higher in the NER1006 group (83.7%) compared to the Trisulfate group (80.7%) (Table 51). However, the success rate of NER1006 during advancement phase was comparable to the efficacy success rate during withdrawal (85%).

Table 51: Study NOCT (ADV)-Cleansing success rate in overall colon on advancement using BBPS (mFAS)

	NER1006 2-Day Split dosing (N=276)	Trisulfate (N=280)
Responders n (%)	231 (83.7%)	226 (80.7)

N = the number of patients in the mFAS.

n = the number of patients meeting the criterion. (%) = $n/N \times 100$.

source: Adapted from the Applicant's clinical study report NER1006-01/2016 (ADV) Tables 2.4

o Study MORA

Cleansing success rates during advancement were much lower compared to the primary efficacy success rate during the withdrawal phase for all the three treatment groups (Table 52). The difference between withdrawal phase and advancement phase success rates was 19% for NER1006 2-Day split dosing, and 23% each for NER1006 1-Day split dosing and Moviprep treatment groups (Table 20). The limitation for the results is that several of the patients did not have their video recording for the advancement phase and were imputed as failure.

Table 52: Study MORA (ADV2)-Cleansing success rate in overall colon on advancement using BBPS (mFAS)

	NER1006 2-Day Split dosing (N=275)	NER1006 1-Day morning Split dosing (N=275)	MOVIPREP (N=272)
Responders n (%)	200 (73)	183 (66.5)	175 (64.3)

N = the number of patients in the revised mFAS. n = the number of patients meeting the criterion. (%) = $n/N \times 100$.

source: Adapted from the Applicant's clinical study report NER1006-02/2016 (ADV2) Table 2.4

- *Washing during advancement*

The contribution towards cleansing of washing during advancement phase was assessed by evaluating the number of washing events and total washing time in the different treatment groups in the revised mFAS.

o Study NOCT

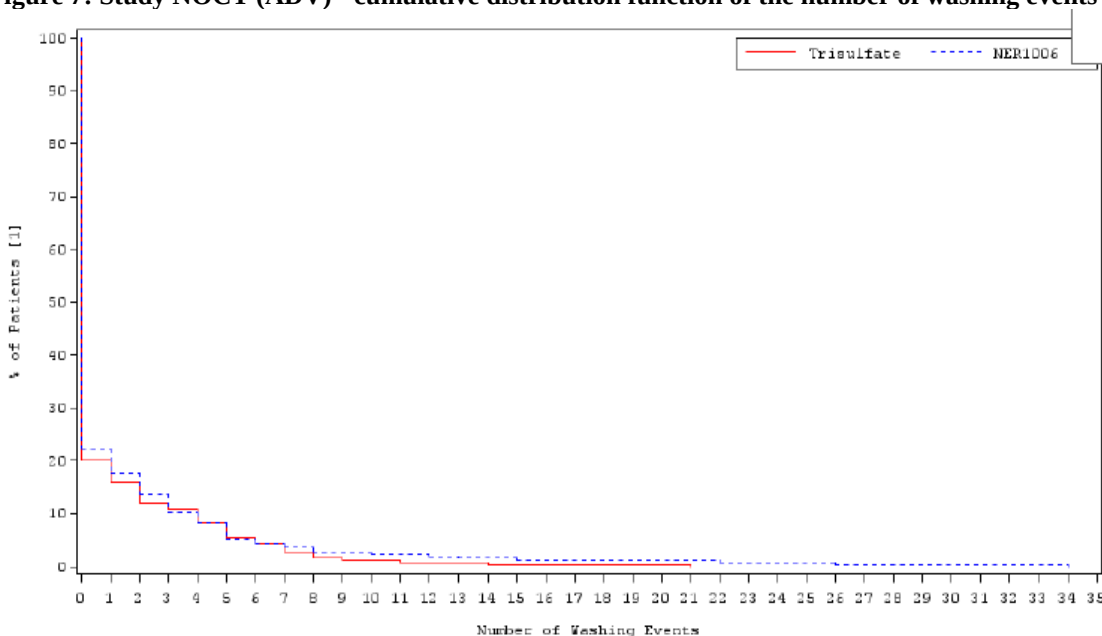
Washing event: The majority of patients did not require washing (had no washing events), and the proportion of patients who did not require washing was comparable between the NER1006 and Trisulfate group, 78% and 80%, respectively. Where washing was required, the numbers of washing events in the two treatment groups were comparable (Table 53 and Figure 7).

Table 53: Study NOCT (ADV)-Washing Events (Revised mFAS)

Number of washing events	NER1006 2-Day Split dosing (N=255)	Trisulfate (N=258)
0	198 (77.6)	206 (80)
1	12 (4.7)	11 (4.3)
2	10 (4)	10 (4)
3-5	22 (8.6)	17 (6.6)
6-10	7 (2.7)	11 (4.3)
11-20	3 (1.2)	2 (0.8)
>20	3 (1.2)	1 (0.4)

N = the number of patients in the analysis set, n = the number of patients meeting the criterion. (%) = n/N*100.
source: Adapted from the Applicant's clinical study report NER1006-01/2016 (ADV) Table 7 and 2.5

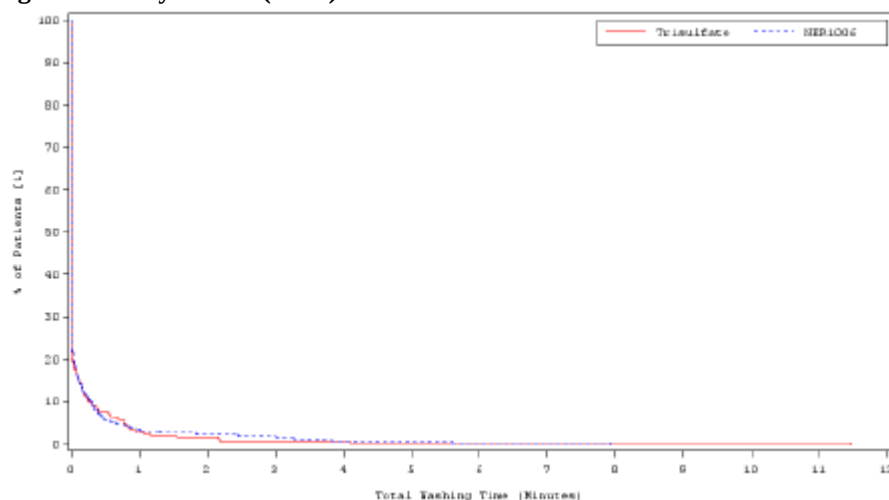
Figure 7: Study NOCT (ADV) - cumulative distribution function of the number of washing events



Source: Adapted from the Applicant's clinical study report NER1006-01/2016 (ADV) Figure 2.1

Washing time: The cumulative distribution function of the total washing time based on the revised mFAS, for the two treatment groups was comparable (Figure 8).

Figure 8: Study NOCT (ADV)-cumulative distribution function of the total washing time



source: Adapted from the Applicant's clinical study report NER1006-0/2016 (ADV) Figure 2.2

Reviewer comment:

The cumulative distribution functions for number of washing events and total washing time are closely overlaid for the two treatment groups; the total number of washing events and the total washing times were similar for the two treatment groups.

o Study MORA

Washing event: A higher proportion of patients in the two NER1006 treatment arms (89-90%) did not require washing (had no washing events) compared to Moviprep (83%). A majority of patients were reported to have 1-2 washing events; the proportion of patients with 1-2 washing events were higher in the Moviprep group (15%) compared to the NER 2-Day and 1-Day split dosing groups (8% each) (Table 54 and Figure 9).

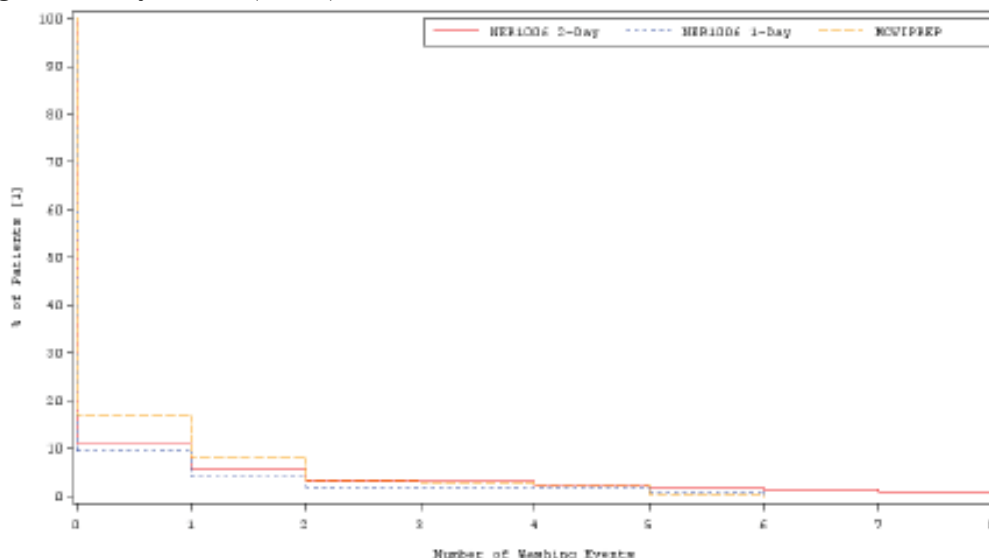
Table 54: Study MORA (ADV2)-Washing Events (Revised mFAS)

Number of washing events	NER1006 2-Day Split dosing (N=224)	NER1006 1-Day Split dosing (N=220)	MOVIPREP (N=206)
0	199 (88.8)	199 (90.5)	171 (83)
1	12 (5.4)	12 (5.5)	18 (8.7)
2	6 (2.7)	5 (2.7)	10 (6)
3-5	3 (1.3)	2 (1)	6 (3)
6-10	4 (1.8)	2 (1)	1 (0.5)

N = the number of patients in the analysis set, n = the number of patients meeting the criterion. (%) = $n/N \times 100$.

source: Adapted from the Applicant's clinical study report NER1006-02/2016 (ADV2) Table 8 and 2.5

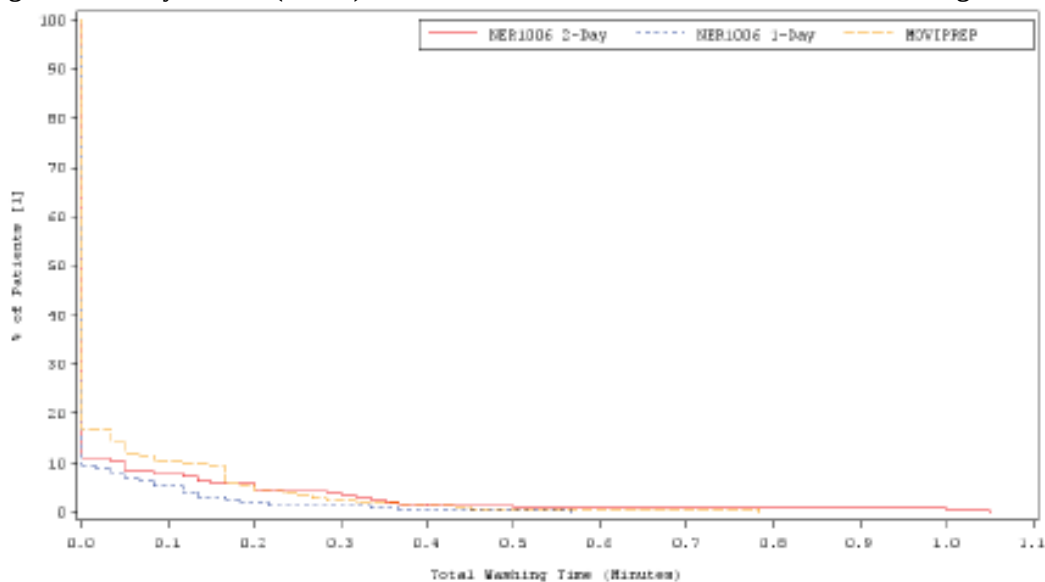
Figure 9: Study MORA (ADV2)-cumulative distribution function of the number of washing events



source: Adapted from the Applicant's clinical study report NER1006-02/2016 (ADV2) Figure 2.2

Washing time: The cumulative distribution function of the total washing time based on the revised mFAS, for the three treatment groups is shown in Figure 10. The proportion of patients in the Moviprep group is numerically higher compared to the two NER1006 treatment groups in the 0 to 0.2 minutes washing time category; the proportion of patients requiring > 0.2 minutes of washing appears to be comparable in the three treatment groups.

Figure 10: Study MORA (ADV2)-cumulative distribution function of the total washing time



source: Adapted from the Applicant's clinical study report NER1006-02/2016 (ADV2) Figure 2.3

Reviewer comment:

In NOCT study, the number of washing events and total time for washing were similar in the NER1006 and Trisulfate treatment. However, the washing events and total time for washing were numerically higher in the Moviprep group compared to the two NER1006 treatment groups. The observed small differences do not appear to contribute to the efficacy evaluation.

6.1.7 Subpopulations

6.1.7.1 Efficacy by Age

The primary efficacy results for the overall colon cleansing rate in the mFAS were analyzed as age groups of ≤ 65 years and > 65 years in the two studies.

- Study NOCT**

In patients ≤ 65 years, the overall colon cleansing rates were similar in the two treatment groups (NER1006 85% and Trisulfate 86%). However, in patients >65 years, overall colon cleansing rate were numerically higher in the NER1006 group (86%) compared to the Trisulfate group (80%) (Table 55).

Table 55: Overall HCS by age groups (mFAS)

	NER1006		Trisulfate solution	
	≤ 65 years (N=226)	>65 years (N=50)	≤ 65 years (N=229)	>65 years (N=51)
Successful ^a HCS, n (%)	192 (85)	43 (86)	197 (86)	41 (80.4)

^a Grades A and B were classified as successful cleansing and grades C and D were classified as failures.

source: Adapted from the Applicant's Clinical Study Report (NOCT) Table 11-19.

- Study MORA**

In patients ≤ 65 years as well as > 65 years, the overall colon cleansing rates were numerically higher in the two NER1006 treatment groups compared to Moviprep (Table 56).

Table 56: Overall HCS by age groups (mFAS)

	NER1006, 2-Day split dosing		NER1006, 1-Day split dosing		MOVIPREP	
	≤ 65 years (N=203)	>65 years (N=72)	≤ 65 years (N=215)	>65 years (N=60)	≤ 65 years (N=226)	>65 years (N=46)
HCS, n (%)						
Successful ^a	184 (91)	69 (96)	191 (89)	54 (90)	198 (87)	40 (87)

^a Grades A and B were classified as successful cleansing and grades C and D were classified as failures.

source: Adapted from the Applicant's Clinical Study Report (MORA) Table 11-19.

Reviewer comment:

In the NOCT study, the primary efficacy rates in patients with ages ≤ 65 years were comparable in the NER1006 and Trisulfate treatment groups; however, numerically higher success rates were observed in the NER1006 treatment group in patients > 65 years. In the MORA study, the

efficacy rates were higher in both age groups in the two NER1006 treatment regimens compared to Moviprep. The efficacy in the elderly population appears to be comparable to the younger population.

6.7.1.2 Efficacy by Gender, NOCT

Table 57: Efficacy analysis by Gender, 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: statistical review by Shala Farr, Ph.D.

Table 58: Efficacy analysis by Gender, 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: statistical review by Shala Farr, PhD.

Reviewer comment:

Overall the efficacy by gender was comparable to that seen for the population overall.

6.1.7.3: Other subgroups:

Reviewer comment:

Efficacy was not assessed by race, given that the vast majority of patients were Caucasian. Other planned subgroups of interest included Inflammatory Bowel Disease, and necessary use of motility-decreasing medications, but numbers were too small to make meaningful conclusions. The Applicant also analyzed efficacy by reason for colonoscopy, renal insufficiency (none vs. mild/moderate) and time from end of preparation to start of colonoscopy. There were major limitations to these analyses, so the results are not presented here in detail. For example, majority of the renal impairment patients (RI) were “mild,” so it is not possible to draw conclusion about patients with more significant RI (see also 7.5.4 for discussion about Renal Impairment patients). None of the Applicant-analyzed subgroups appear to suggest that NER1006 was less effective than comparators in these subgroups, with the limitations noted.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Table 59 shows the efficacy results of the NER1006 given as a 2-day split dosing regimen in the NOCT and MORA studies and a 1-Day morning split dosing regimen in the MORA study. The success rate of the 2-day NER1006 regimen (2-Day split dosing regimen) was numerically higher in the MORA study compared to the NOCT study (92% and 85%, respectively). The

success rate of the 2-day split dosing regimen of NER1006 was numerically higher compared to the 1-Day split dosing regimen of NER1006 (92% vs 89%) in the MORA study.

The success rate of NER1006, 1-Day split dosing was comparable (and non-inferior) to the 2-Day split dosing regimen of Moviprep (89% vs 87%) in the MORA study. The efficacy of 2-Day NER1006 was comparable (and non-inferior) to the Trisulfate 2-Day split dosing in NOCT study (Table 59).

Table 59: Efficacy comparison between 2-Day split-dose and 1-Day morning split dose regimens of NER1006

	NOCT		MORA		
	NER1006 2-day split-dosing	Trisulfate 2-day split-dosing	NER1006 2-day split-dosing	NER1006 1-Day split dosing	MOVIPREP 2-day split-dosing
% Success (responder) ^a	85	85	92	89	87

^a Responders were defined as patients who achieved cleansing Grades of A and B by the colonoscopist based on HCS assessment criteria.

source: Compiled from the primary efficacy tables (20 and 21) of this review document (NOCT) and (MORA)

Reviewer comment:

Limitations of cross-study comparisons limit the utility of directly comparing results from NOCT against MORA. Within the MORA study, it appears that the NER1006 2-day split dosing regimen (consistent with US standard of care practice for bowel preps) has a numerically higher rate of success compared to the 1-day split dosing regimen. However, the difference is small and may be due to chance. Given that NER 1-day regimen was associated with a numerically higher rate of success compared to the comparator (which was given as 2-day split dose prep) and that the results of this analysis of the 1-day regimen compared to Moviprep were considered statistically persuasive, the Division opted to permit both dosing regimens to be included in the labeling, to give patients and providers maximal flexibility in dosing.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Bowel cleansing preparations are given only occasionally, as split dosing, using same day or 2-day regimens, prior to a colonoscopic procedure. The therapeutic effect does not last more than 1-2 days beyond the procedure. Therefore, discussion of the persistent effect and or tolerance is not applicable for this application.

7 Review of Safety

Safety Summary

The safety of Plenvu (NER1006) was primarily ascertained through the evaluation of adverse events, physical examination findings, and laboratory data collected from patients in the two primary clinical trials, NOCT and MORA. Safety data from a third trial, DAYB, that used an active comparator that is not approved in the U.S. was supportive for assessing the safety of the proposed product. Safety information for each trial was assessed independently and not pooled across trials. Adverse events by SOC and PT were compared against the approved comparator within each trial (NOCT and MORA). In MORA, the trial design allowed for comparison of the

safety for the 1-day (same-day) split-dose regimen against the 2-day split-dose regimen of Plenvu.

In addition, blood pressure, ECG parameters, and laboratory values including for electrolytes, renal and liver functions labs were assessed for identifying any significant deviations from normal ranges, to evaluate safety of the drug product. Individual patient data and narratives were evaluated as needed when adverse events or laboratory findings warranted closer scrutiny. Trials included patients who were 18-86 years of age, with a majority in the 45-65 years' age group. There was a slightly higher number of females than males, and the population was predominantly White. Safety across subgroups of interest including age, race, gender, and disease was also compared.

The safety review did not raise any specific concerns outside of what is known for this drug class. Dehydration and electrolyte abnormalities are the main adverse events of interest associated with use of bowel preparations. In general, the percentage of patients with TEAEs across trials indicated a higher incidence of adverse events occurring with Plenvu compared to the approved comparator drugs: 27.3% vs. 18.1% (NER2 vs. Trisulfate solution; NOCT), and 18.5%, 17.7% vs. 11.5% (NER1, NER2 vs. PEG + electrolytes; MORA). The incidence of severe TEAEs or those leading to trial or treatment discontinuation was low and similar in the test and comparator treatments. AEs leading to treatment/trial discontinuation in the NER1006 group included GI intolerance (vomiting), and one event of hypersensitivity reaction, and were considered probably related to the study drug. Serious AEs (SAEs) were few and were all unrelated to the study treatment, based on review of patient narratives. There were no deaths in the clinical trials for Plenvu.

The commonly observed TEAEs in the clinical trials for Plenvu are summarized in the table below. All trials demonstrated that the incidence of nausea and vomiting with Plenvu was greater than with the active comparators. In trial MORA, the TEAEs of signs and symptoms of dehydration and vomiting were greater for the 1-day (same-day) dosing regimen of Plenvu relative to the 2-day split dose regimen. While, the overall incidence of electrolyte abnormalities was small, it was higher with the 1-day regimen compared to the 2-day split dose regimen or the active comparator in MORA.

Table 60: Treatment-emergent adverse events observed in at least 1% of patients in clinical trials NOCT, MORA and DAYB

Symptoms	NOCT 2-Day split dosing n (%)		MORA n (%)			DAYB 1-day split dosing on day prior to colonoscopy n (%)	
	NER1006 (N = 275)	Trisulfate (N = 271)	NER-2 (N = 265)	NER-1 (N = 271)	MOVIPREP (N = 269)	NER1006 (N = 243)	SP+MS (N = 247)
Vomiting	17 (6.2)	7 (2.6)	11 (4.2)	18 (6.6)	3 (1.1)	11 (4.5)	0
Nausea	18 (6.6)	5 (1.9)	16 (6.0)	15 (5.5)	9 (3.4)	6 (2.5)	2 (0.8)
Headache	5 (1.8)	2 (0.7)	4 (1.5)	2 (0.7)	4 (1.5)	4 (1.7)	4 (1.6)
Abdominal Pain/Discomfort	6 (2.2)	4 (1.5)	5 (1.9)	8 (3.0)	8 (3.0)	10 (4.1)	3 (1.2)
Signs and Symptoms of Dehydration	11 (4.0)	6 (2.2)	7 (2.6)	11 (4.1)	6 (2.2)	5 (2.1)	1 (0.4)
Electrolyte Abnormalities	4 (1.5)	3 (1.1)	2 (0.8)	3 (1.1)	1 (0.4)	2 (0.8)	1 (0.4)

Note: NER-2: 2-Day split dosing, NER-1: 1-Day split dosing morning of the colonoscopy, MOVIPREP, 2-Day split dosing.

source: Reviewer compilation of TEAEs in datasets ADAE2 (Safety set 2) provided in addenda for trials NOCT, MORA and DAYB; only one unique TEAE is counted for each patient in the categories presented here, including the grouped/re-coded AEs of abdominal pain/discomfort, signs and symptoms of dehydration and electrolyte abnormalities.

A small number of adverse events were graded as “severe” in study NOCT and these occurred with approximately equal frequency in study drug vs. active comparator groups. Of the severe TEAEs observed, GI symptoms such as nausea, vomiting, abdominal pain are known to be associated with the class, while the worsening of migraine, fatigue, and gout attack all could possibly be related to study drug. There was only one severe TEAE that was unrelated to the study drug in trial MORA.

Results of the shift analyses suggested that most of the measured laboratory parameters showed a peak shift outside the normal ranges at Visit 2, at post-dose and pre-colonoscopy. This proportion of patients with a shift outside normal values was greater in the NER1006 treatment groups compared to the active controls. For most parameters, the proportion of patients with extreme values decreased at follow-up Visits 3 and 4, suggesting a reversibility of the effects. The shift in sodium was primarily that of hyponatremia, with very few patients demonstrating hypernatremia. The majority of the hypernatremia cases were of CTCAE grade 1 in both trials.

Shifts in potassium occurred at a low frequency in trials. Overall, laboratory abnormalities persisted in only a small number of individuals beyond Visit 2 prior to the colonoscopy, where most abnormalities were noted. For many clinical trial patients with persisting laboratory abnormalities following Visit 2, the changes in lab values do not appear to be clinically meaningful, either because they normalized, or trended towards normalization by the subsequent Visits 3 or 4, or because the changes were only marginally out of range.

Decreased GFR, possibly due to inadequate fluid intake, was noted in few patients in the clinical trials and occurred in both the test and comparator treatment groups. It is difficult to draw any conclusions regarding the causality, as the cases were few and the volume of *ad libitum* fluid intake was not documented during these trials. Furthermore, most of these patients were on concomitant antihypertensive and diuretic medications. The percentage of patients with systolic or diastolic blood pressure below 90 mmHg was $\leq 0.8\%$, with no evidence of a statistically significant difference between treatment arms. For both trials, the percentage of patients with diastolic or systolic orthostatic changes of > 20 mmHg was $\leq 6.3\%$. The Division of Biostatistics VII (DB7) reviewers note that while there was no evidence of statistical significance between treatment arms for orthostatic changes, NER1006 treatment groups consistently demonstrated greater ranges for orthostatic changes than the comparator. No new cardiovascular safety signal was identified through evaluation of EKG data, signs/symptoms, or reported AEs.

Overall, there was no trend in clinical trials NOCT and MORA for any demographic subgroup regarding the incidence of significant TEAEs, serious AEs, study drug withdrawals or trial discontinuations. Common TEAEs were seen to have a trend for higher incidence in females in the NER1006 clinical trials. Overall, no consistent trends could be discerned regarding drug-disease interactions. The number of patients with diabetes, inflammatory bowel disease (IBD) and cardiac disease in the clinical trials appears too small to make a reasonable conclusion about the drug-disease relationship as it relates to safety. The incidence of TEAEs in patients with mild RI was generally comparable to that of patients who had normal renal function. While there does not appear to be a signal for acute renal injury following administration of PLENVU, data from patients with moderate RI is very limited and patients with severe RI were not studied. Thus, the vulnerability of a population with moderate to severely impaired renal function at baseline to experience further deterioration of renal function cannot be ruled out conclusively. In general, because patients with any level of RI (due to an already “low reserve” vs. those with normal renal function) may be more predisposed to the clinical consequences of dehydration due to bowel cleansing agents, caution is recommended when using PLENVU in patients with any degree of RI (e.g., advise patients about the importance of adequate hydration and consider monitoring laboratory tests at baseline and post-colonoscopy) .

In general, the safety profile of PLENVU appears consistent with other drugs in this class, and is generally acceptable to recommend approval.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety evaluation was conducted primarily on the two trials (i.e., NOCT and MORA) that were used for the efficacy evaluation. The third trial (DAYB) was used only for supportive safety evaluation, as the active comparator (SP+MS) used in this trial is not approved in the United States. The safety analyses were based on the Safety Analysis set 2 (SAF2), which included all randomized patients for whom it could not be ruled out (from their patient diary and drug reconciliation record) that they had received investigational drug at least once.

7.1.2 Categorization of Adverse Events

An adverse event (AE) was defined as the development of an undesirable and unintended medical condition or the deterioration of a pre-existing medical condition in a patient administered study medication, whether or not considered causally related to the study drug. An AE could be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or abnormal laboratory results. This definition included events occurring from the time of informed consent until 28 days after the last dose for each patient. Cases of diarrhea or detection of lesions during colonoscopy (polyps, adenomas, cancer, etc.) were not considered as AEs. Any AEs observed or reported by a patient and/or staff was recorded in the e-CRF. Laboratory abnormalities were recorded as AEs only if deemed clinically significant by the Investigator. All AEs were followed up until the outcome resolved or stabilized at a level acceptable to the Investigator or until 14 days after the last dose for each patient.

A serious AE (SAE) was defined as any AE that resulted in any of the following: death, a life-threatening reaction that placed the patient at an immediate risk of death, in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant disability that caused a substantial disruption of a person's ability to conduct normal life functions, congenital anomaly or birth defect in the offspring of a patient who received the study drug or an important medical event that based upon medical judgment might have jeopardized the patient and may have required medical or surgical intervention to prevent one of the outcomes listed above. All SAEs were followed until the outcome was resolved or stabilized at a level acceptable to the Investigator or up to 3 months after the last dose for each patient. All SAEs, regardless of suspected relationship to NER1006, were reported immediately (within 24 hours of the Investigator's first knowledge of the event) to the Pharmacovigilance Group by fax using the SAE report form or by telephone.

The intensity of the AEs was rated by the investigators according to the following definition:

Intensity	Criteria
Mild	Does not alter the patient's normal functioning.
Moderate	Produces some degree of impairment to function, but are not hazardous, uncomfortable or embarrassing to the patient.
Severe	Is definitely hazardous to well-being, significant impairment of function or incapacitation.

The causal relationship of each AE was classified per the following criteria:

Causality	Criteria
Probable	A reaction that follows a reasonable temporal sequence from administration of the drug, follows a known or expected response pattern to the suspected drug; this was confirmed by improvement on stopping or reducing the dosage of the drug or could not be reasonably explained by the known characteristics of the patient's clinical state.
Possible	A reaction that follows a reasonable temporal sequence from administration of the drug and that follows a known or expected response pattern to the suspected drug but that could readily have been produced by a number of other factors.
Unrelated	Any event for which there is sufficient and conclusive information that the event is not related to the investigational product.

Adverse Events Definition and Presentation

All AEs were classified by system organ class (SOC) and preferred term (PT) according to Medical Directory of Regulatory Activities (MedDRA) Version 18.0.

A treatment-emergent AE (TEAE) is defined as an AE that met any of the following conditions:

- begins on or after the first dose of study drug and before the end of study drug + 14 days;
- begins before the first dose of study drug and worsens in severity on or after the first dose of study drug and before the end of study drug + 14 days;
- is completely missing an onset date and end date;
- is completely missing an onset date and the end date is on or after the first dose of study drug.

Patients who reported more than one event were only counted once for each level of system organ class (SOC) and preferred term (PT).

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

No pooling of the safety data was done. Safety data from the three trials were evaluated separately because of different dosing regimens and active comparators.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The safety monitoring and follow-up, including the laboratory measurement for the assessment of possible renal function/electrolytes abnormalities, for the two dosing regimens was adequate.

Overall, clinical trials of NER1006 included an adequate number of patients who were exposed to the study drug at the planned dosing regimens and for the recommended duration of use (single use prior to scheduled colonoscopy). The overall demographic characteristics of the clinical trial population were well balanced with regard to gender and were representative of the target population with respect to the age (median: ~58 years in NOCT, ~55 years in MORA for NER1006 and active controls). The population enrolled was predominantly Caucasian (~81-83 % in NOCT and ~98 % in MORA for NER1006 and active controls), with a smaller percentage of blacks (12-14.5 % in NOCT and ~0.5-2 % in MORA for NER1006 and active controls), and little to no representation of other races. While it is ideal for clinical trial populations to provide adequate representation of all races, in this case, given the screening/diagnostic nature of the indication (bowel cleansing prior to colonoscopy), local mechanism of action within the GI tract, absence of genetic variability in the disease or enzyme polymorphism issues as well as the acute use of the drug product (single use prior to colonoscopy), it is not anticipated that the safety profile would be different across races. The demographic characteristics were also well balanced among the treatment groups within the trials.

7.2.2 Explorations for Dose Response

All patients in the NER1006 group received the same dose in the three phase 3 studies, however, in different dosing regimens, i.e., 2-day split dosing or 1-Day split dosing (either the day before colonoscopy or the same day of colonoscopy). Phase 1/phase 2 studies evaluated dosing regimen response; however, exploration of the dose-response was not done. Overall, the doses and regimens evaluated in the clinical trial program for NER1006 appear reasonable.

7.2.3 Special Animal and/or In Vitro Testing

None

7.2.4 Routine Clinical Testing

Patients underwent routine physical examination and laboratory testing at baseline, on the day of colonoscopy (Visit 2; Day 2), and on follow-up Visits 3 and 4 (Day 4 and 9).

7.2.5 Metabolic, Clearance, and Interaction Workup

Please refer to review by Dr. Dilara Jappara for a summary of the reviewed data.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Studies NOCT and MORA were acceptable to assess general safety of the NER1006. The trials included appropriate safety and laboratory monitoring for detecting common adverse events related to this drug class, including gastrointestinal symptoms, and AEs of interest such as electrolyte abnormalities, and signs and symptoms of dehydration.

7.3 Major Safety Results

Table 61 summarizes the TEAE for the three phase 3 trials; this includes TEAEs, severe TEAEs (STEAEs), and TEAEs leading to discontinuation and or death. There was no death in any study. A greater proportion of patients in the NER treatment groups reported TEAEs compared to comparators in the three trials. Serious TEAEs were rare across the 3 studies and occurred with similar frequency across treatment arms.

Table 61: Summary of TEAEs in clinical trials NOCT, MORA, and DAYB

	NOCT 2-Day split dosing		MORA			DAYB 1-day split dosing on day prior to colonoscopy	
Number of patients with	NER (N=275) n (%)	Trisulfate (N=271) n (%)	NER-2 (N=265) n (%)	NER-1 (N=271) n (%)	MOVIPREP-2 (N=269) n (%)	NER (N=243) n (%)	SP+MS (N=247) n (%)
Any TEAE	75 (27.3)	49 (18.1)	47 (17.7)	50 (18.5)	31 (11.5)	41 (16.9)	24 (9.7)
Any STEAE	1 (0.4)	1 (0.4)	2 (0.8)	0	0	1 (0.4)	0
Any TEAE leading to discontinuation	1 (0.4)	1 (0.4)	0	1 (0.4)	1 (0.4)	1 (0.4)	0
Any TEAE leading to death	0	0	0	0	0	0	0

Note: NER-2: 2-Day split dosing, NER-1: 1-Day split dosing morning of the colonoscopy, MOVIPREP-2: 2-Day split dosing.

Source: Table 12-1A- Overall Treatment-Emergent Adverse Events (Safety Set 2) from CSR Addenda for clinical trials NOCT, MORA, and DAYB

7.3.1 Deaths

No deaths were reported in clinical trials NOCT, MORA, and DAYB.

7.3.2 Nonfatal Serious Adverse Events

7.3.2.1 Trial NOCT

One patient each in the NER1006 and Trisulfate solution treatment groups experienced a treatment-emergent SAE. Brief narratives are provided for each patient:

- Patient (b) (6) (Trisulfate group):

A 63 year old white male with past medical history (PMH) of hypertension, hypercholesterolemia, osteoarthritis of the knees, and bleeding peptic ulcer (b) (6) underwent diagnostic colonoscopy and polypectomy (tubular adenoma in the cecum) on (b) (6). He was taking antihypertensive medications (nifedipine, HCTZ, lisinopril, and lovastatin). The patient developed intermittent GI bleed associated with syncope, orthostasis and drop in hemoglobin (10.2 gm/dL). Patient was admitted to the hospital, treated conservatively and discharged 2 days later, on (b) (6). The GI bleed seems to be related to the complication of polypectomy and not related to the investigational drug.

o Patient (b) (6) (NER1006 group):

A 59 year old white male with PMH of diabetes mellitus (Type 2), hypertension, and hypercholesterolemia underwent colonoscopy and polypectomy (tubular adenoma hepatic flexure) on (b) (6). He was taking antihypertensive medications (Benazepril) and lovastatin. The patient developed abdominal distension associated with distended air-filled colon, diagnosed as ileus and was admitted to the hospital for 1 day and made a spontaneous recovery. The relevant abnormal laboratory test results reported were: anion gap 19 mmol/L (reference range 8-16 mmol/L), bicarbonate 21 mmol/L (reference range 22-32 mmol/L), potassium 3.4 mmol/L (range 3.6-5.0 mmol/L), and glucose 61 mg/dL (reference range 70-99 mg/dL). In view of the complete resolution within 24 hours, the development of symptoms is more likely to be related to the procedure (air inflation used during the procedure or not suctioned before finishing colonoscopy).

Note that Patient (b) (6) in the Trisulfate solution treatment group experienced an SAE of vasovagal syncope, which occurred prior to any drug administration and therefore will not be discussed further.

Reviewer comment:

The reviewer agrees with the Applicant's assessment that these SAEs were unrelated to the investigational drug intake.

7.3.2.2 Trial MORA

Two patients in the NER1006 2-Day Split-Dosing treatment group experienced treatment-emergent SAEs. Brief narratives are provided for each patient:

- o Patient (b) (6): A 56 year old white female with PMH of hysterectomy, asthma, and ureteral stent underwent colonoscopy and polypectomy for villous high grade dysplasia on (b) (6), i.e., the day study drug was administered. The patient developed an SAE of perforation in the ascending colon associated with mediastinal and retroperitoneal air after the polypectomy, requiring hospitalization and was discharged on (b) (6). The SAE is related to the polypectomy procedure and unrelated to the investigational drug.
- o Patient (b) (6): A 34 year old white male with PMH of depression and alcohol abuse underwent screening colonoscopy on (b) (6). Patient developed relapse of alcohol abuse on (b) (6) and was admitted in the hospital from (b) (6) for detoxification and psychiatric assessment. The SAE seems unrelated to the investigational drug.

Two other patients (Patients (b) (6)) who received NER1006 2-day split dosing, were reported to have SAEs. However, these events occurred outside the predefined window period to qualify as treatment-emergent SAEs. Brief narratives are provided for each patient:

- Patient (b) (6): A 81 year old white male patient with PMH of bladder cancer, chronic kidney disease, celiac disease, dermatitis herpetiformis, essential hypertension, pernicious anemia, and prostate cancer received the first and second doses of study drug on (b) (6) respectively, and completed the study on (b) (6). After the completion of the study, the patient underwent polypectomy on (b) (6) and was hospitalized two days later for a severe SAE of rectal hemorrhage. Patient received 2 units of blood and was discharged from the hospital on (b) (6). The event is not a treatment-emergent SAE as it occurred > 14 days from the end of the dose, and seems to be related to the polypectomy procedure.
- Patient (b) (6): A 50 year old white male received the first dose of study drug on (b) (6) and completed the study on (b) (6). The study colonoscopy detected 4 polyps, one of which was determined on histology to be a carcinoma. The patient later was hospitalized for surgical treatment of the rectal carcinoma, which was the recorded SAE. This occurred outside the treatment-emergent window. Also, given the fact that it takes many years for adenoma to develop into carcinoma, the occurrence of this cancer cannot be considered related to study drug.

Two other patients with SAEs did not receive the study drug and therefore will not be discussed further (Patient (b) (6) on NER1006 randomized to 2-Day split dosing and Patient (b) (6) randomized to NER1006, 1-Day split dosing).

Reviewer Comment:

The SAEs observed in these 6 patients seem unrelated to the investigational drug.

7.3.2.3 Trial DAYB

One patient in the NER1006 group was reported to have an SAE. A brief narrative is provided for the patient:

- Patient (b) (6) (NER1006 1 day split-dosing): A 54 year old white female with PMH of ulcerative colitis (UC), DM, hypertension, and osteoporosis, received study drug on (b) (6). On (b) (6) patient was found to have severe pain on compression in the lower abdomen bilaterally. Patient developed abdominal cramps on (b) (6) and in due course was diagnosed with tubo-ovarian abscesses and admitted in the hospital from (b) (6). Laparoscopic drainage of the abscess and adnexectomy performed on (b) (6). Her blood tests on (b) (6) showed elevated leucocyte count and ANC, increased urea/creatinine from baseline and low potassium. The abnormal labs seem to be related to the underlying septic process (tubo-ovarian abscess) and unlikely to be related to the investigational drug.

Reviewer Comment:

The SAE appears to be unrelated to the study drug. Overall, the rate of occurrence of treatment emergent SAEs in the clinical trials for NER1006 was small and all reported SAEs appear to be unrelated to the study drug.

7.3.3 Dropouts and/or Discontinuations

The patients who dropped out and/or discontinued treatment in the three studies are summarized below.

7.3.3.1 Trial NOCT

One patient discontinued study drug treatment:

- Patient (b) (6): A 60 year old white female in the Trisulfate group with PMH of non-Hodgkin's lymphoma (s/p chemotherapy), hypercholesterolemia, irritable bowel syndrome, and dysphagia taking atorvastatin, valacyclovir, omeprazole, calcium and vitamin supplements developed severe AE (pain in her abdomen) after she received the first dose of study drug on (b) (6). On (b) (6) the patient experienced severe abdominal pain. Study treatment was permanently discontinued. The abdominal pain recovered/resolved on (b) (6). The patient completed the study on (b) (6).

Reviewer Comment:

The event appears probably related to the study drug.

Two patients discontinued from the clinical trial due to an AE:

1. Patient (b) (6): A 46 year old white male received trisulfate solution 2-Day split doses on (b) (6). Patient discontinued from the trial due to an adverse event. The patient was reported to have a diffuse upper chest rash (mild AE) that lasted for 14 days (start date of the AE appears to occur prior to the intake of investigational drug - from (b) (6)). The event was categorized to have a 'probable' relationship to the drug treatment.
2. Patient (b) (6): A 31 year old white female patient received NER1006 2-Day split doses on 23 November, and 24 November, 2014, and was discontinued from the trial after developing a drug hypersensitivity reaction (moderate AE) which began on (b) (6) lasting till (b) (6) (Day 7 of the study).

Reviewer comment:

Both patients (one on trisulfate, and the other on NER1006) who discontinued from the trial appear to have experienced delayed allergic reactions that are probably related to the study drug. This will be included in the product label as a less common adverse event.

7.3.3.2 Trial MORA

One patient in the NER1006, 1-Day split dosing discontinued the treatment due to an AE:

- o Patient (b) (6) (NER1006, 1-Day split dosing): A 42 year old white female patient with no ongoing medical condition developed moderate AE (vomiting) after taking the first dose of study drug on (b) (6). Further study treatment was discontinued. However, the patient had colonoscopy because the investigator considered that the patient had ingested adequate drug. The event was considered probably related to the study drug.

One patient in the Moviprep group discontinued from the trial due to an AE:

- o Patient (b) (6) (Moviprep): A 54 year old white female patient with PMH of caesarean section, colon operation, multiple allergies, and malignant neoplasm developed moderate AEs of nausea and vomiting after taking the first dose of the study drug on (b) (6). Study treatment was discontinued permanently. Nausea and vomiting were considered recovered/resolved on (b) (6).

Reviewer Comments:

Both events appear probably related to treatment.

Two more patients, one in each Moviprep (Patient (b) (6)) and NER1006, 2-day split dosing group (Patient (b) (6)), had drug interrupted (not withdrawn) for symptom of nausea. Both patients took about three-quarters of the first dose and the full second dose and could complete the trial.

7.3.3.3 Trial DAYB

One patient discontinued study treatment due to an AE.

- o Patient (b) (6): A 36 year old white female in the NER1006 group with PMH of hypothyroidism developed a moderate AE of vomiting after taking the first dose of the drug on (b) (6). The study treatment was permanently discontinued and vomiting resolved/recovered on the same day. The investigator considered that the patient has ingested an adequate volume of the study drug and proceeded with the colonoscopy. The event was considered probably related to the study drug.

One patient discontinued from the clinical trial due to an AE.

- o Patient (b) (6): A 65 year old white female in the NER1006 group experienced spinal pain and discontinued from the trial on (b) (6). AE appears to be unrelated to the study drug.

Reviewer Comment:

Overall, the incidence of trial/treatment discontinuations was small and included patients from both the study drug and comparator groups, limiting the ability to draw any definitive conclusions. The AEs leading to treatment/trial discontinuation in the NER1006 group included GI intolerance (vomiting), and one event of hypersensitivity reaction. AEs that led to treatment

or trial discontinuation for the most part appeared probably related to study drug.

7.3.4 Significant Adverse Events

The significant AEs in the three studies are summarized below.

7.3.4.1 Trial NOCT

Four patients in NER1006 and 3 patients in the Trisulfate group experienced adverse events that were graded as “Severe” based on the Applicant’s datasets.

Table 62: Trial NOCT- "Severe" AEs

Patient ID (age, race, sex)	Preferred Term	AE onset, duration and resolution	Investigator Assessment of Relatedness to treatment	Reviewer’s Assessment of Relatedness to Treatment
Trisulfate				
(b) (6) (52 y/o, other, F)	Worsening of Migraine	AE on day 2 of dosing; resolved after 8 days	Unrelated	Possible
(b) (6) (60 y/o, W, F)	Abdominal Pain (drug withdrawn)	AE on day 2 of dosing; resolved same day;	Probable	Probable
(b) (6) (52 y/o, B, F)	Abdominal Pain, lower; Bursitis, elbow	Abd pain on study day 3 for 3 days; Bursitis on study day 5, for 5 days	Abd pain: Unrelated Bursitis: unrelated	Abdominal pain: Probable Bursitis: unrelated
NER1006				
(b) (6) (57 y/o, W, M)	Rectal Hemorrhage	AE on study day 14 and resolved the following day	Unrelated	Unrelated
(b) (6) (55 y/o, W, F)	Fatigue	AE on study day 4 and resolved the following day	Possible	Possible
(b) (6) (73 y/o, W, M)	Worsening of gout symptoms	AE on study day 9 and was unresolved	Possible	Possible
(b) (6) (61 y/o, W, M)	Nausea	AE occurred and resolved on day 2	Probable	Probable

Source: Reviewer’s compilation of information from patient listings of demographics, disposition and adverse events (severe).

Reviewer's comment:

There were a small number of adverse events graded as "severe" and they occurred with approximately equal frequency in study drug vs. active comparator groups. GI symptoms such as nausea, vomiting, and abdominal pain are known to be associated with the class. Migraine worsening, fatigue, and gout attack all could possibly be related to study drug, in the opinion of this reviewer, as dehydration as a result of bowel preparation, or the drug itself could possibly trigger these conditions.

7.3.4.2 Trial MORA

One patient ((b) (6)) in NER1006, 2-Day split dosing regimen was considered to have a "Severe" AE of 'relapse of alcohol abuse' that was unrelated to the study drug. This patient was also reported to have a nonfatal serious adverse event and discussed in Section 7.3.2.2.

7.3.4.3 Trial DAYB

Three patients were considered to have "Severe" AEs in the AE data sets.

Table 63: Trial DAYB- "Severe" AEs

Patient ID (age, race, sex)	Preferred Term	AE onset, duration and resolution	Investigator's Assessment of Relatedness to treatment	Reviewer's Assessment of Relatedness to treatment
NER1006				
((b) (6)) (33 y/o, W, F)	Abdominal Pain	AE on day 2 of study; not resolved	Possible	Possible; Patient also has UC
((b) (6)) (54 y/o, W, F)	Abdominal Pain (cramps) Dry Mouth	Abdominal Pain on study day 2 that lasted for 20 days; Dry mouth on study day 3 that lasted for 6 days	Abdominal Pain: unrelated Dry Mouth: Possible	Abdominal pain: unrelated; patient had an SAE of tubo-ovarian abscess, as noted in Section 7.3.2.3; Dry mouth: Possible
SP + MS				
((b) (6)) (53 y/o, W, F)	Muscle spasms (cramps in both calves)	AE on day 3 of study and resolved on the following day	Probable	Probable; patient has no significant medical history

source: Reviewer's compilation of information from patient listings of demographics, disposition and adverse events (severe).

Reviewer's comment:

There were a small number of adverse events graded as "severe" and they occurred with comparable frequency in study drug vs. active comparator groups. In the opinion of this

reviewer, muscle cramps may have occurred as a result of dehydration from the ingestion of low-volume bowel preparation.

7.3.5 Submission Specific Primary Safety Concerns

The safety review did not raise any specific safety concerns outside of what is known for this drug class.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Treatment-emergent AEs reported for patients in the three studies are summarized below.

7.4.1.1 Trial NOCT

A total of 116 TEAEs were reported in 74 (27%) patients of the NER1006 group, compared to 65 TEAEs reported in 49 (18.1%) patients of the Trisulfate group. Table 67 summarizes the incidence of TEAEs occurring in at least 1% of patients in the NER1006 and Trisulfate treatment groups. The most common events in the NER1006 treatment group included nausea, vomiting, signs and symptoms of dehydration, abdominal pain/discomfort, and headache. These events occurred at a greater frequency in the NER1006 group compared to the Trisulfate solution. Electrolyte abnormalities occurred at a comparable rate between the two treatments.

Table 64: NOCT; Treatment-Emergent Adverse Events occurring in ≥ 1 % of patients by Preferred Term (safety set 2)

Preferred Term	NER1006 [2-day Split] (N = 275) n (%)	Trisulfate (N = 271) n (%)
Abdominal distension	3 (1.1)	2 (0.7)
Abdominal pain/discomfort ^a	6 (2.2)	4 (1.5)
Gastritis	3 (1.1)	3 (1.1)
Hiatus hernia	3 (1.1)	1 (0.4)
Nausea	18 (6.6)	5 (1.9)
Vomiting	17 (6.2)	7 (2.6)
Fatigue	4 (1.5)	3 (1.1)
Headache	5 (1.8)	2 (0.7)
Nasopharyngitis	3 (1.1)	2 (0.7)
Signs and symptoms of dehydration ^b	11 (4.0)	6 (2.2)
Electrolyte abnormalities ^c	4 (1.5)	3 (1.1)
Decline in GFR ^d	5 (1.8)	5 (1.9)

^a Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and abdominal tenderness

^b Includes dehydration, dizziness, dry mouth, orthostatic hypotension, presyncope, syncope, and thirst

^c Includes anion gap increased, blood bicarbonate decreased, blood magnesium decreased, blood osmolality increased, blood potassium decreased, blood potassium increased, hypercalcemia, hyperkalemia, hyponatremia, hyperosmolar state, hyperuricemia, hypocalcemia, and hypophosphatemia

^d Includes GFR decreased, GFR abnormal
source: Reviewer compilation using ADAE2 dataset

7.4.1.2 Trial MORA

A total of 53 TEAEs from 31 patients (11.5%) in the Moviprep group, 92 TEAEs from 50 patients (18.5%) in the NER1006 1-day split dosing, and 80 TEAEs from 47 patients (17.7%) in the NER1006 2-day split dosing were reported in this trial. Table 68 summarizes the incidence of TEAEs occurring in at least 1% of patients in the NER1006 and Moviprep treatment groups. The most commonly reported TEAEs that also occurred at a greater frequency in the NER1006 treatment groups were abdominal pain/discomfort, nausea, vomiting, hypertension and signs and symptoms of dehydration. Except for nausea, these AEs occurred more frequently in the 1-day dosing regimen, compared to the 2-day split dose regimen of NER1006. The incidence of electrolyte abnormalities was in general low, but occurred at somewhat higher rate in the NER1006 treatment groups.

Table 65: MORA-Treatment-emergent adverse events occurring in ≥ 1 % of patients by preferred term (Safety set 2)

Preferred Term	NER1006 [1-day; AM] [N = 271] n (%)	NER1006 [2-day Split] [N = 265] n (%)	Moviprep [N = 269] n (%)
Abdominal pain/discomfort ^a	8 (3.0)	5 (1.9)	8 (3.0)
Nausea	15 (5.5)	16 (6.0)	9 (3.4)
Vomiting	18 (6.6)	11 (4.2)	3 (1.1)
Headache	2 (0.7)	4 (1.5)	4 (1.5)
Hypertension	4 (1.6)	2 (0.8)	0
Signs and symptoms of dehydration ^b	11 (4.1)	7 (2.6)	6 (2.2)
Electrolyte Abnormalities ^c	3 (1.1)	2 (0.8)	1 (0.4)

^a Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and abdominal tenderness

^b Includes dehydration, dizziness, dry mouth, orthostatic hypotension, presyncope, syncope, and thirst

^c Includes anion gap increased, blood bicarbonate decreased, blood magnesium decreased, blood osmolality increased, blood potassium decreased, blood potassium increased, hypercalcemia, hyperkalemia, hyponatremia, hyperosmolar state, hyperuricemia, hypocalcemia, and hypophosphatemia

source: Reviewer compilation from ADAE2 dataset in MORA addendum

7.4.1.3 Trial DAYB

A total of 65 TEAEs were reported from 41 patients (16.8%) in the NER1006 day-before dosing group, versus a total of 30 TEAEs from 24 patients (9.7%) in the comparator group. Table 69 summarizes the incidence of TEAEs occurring in at least 1% of patients in the NER1006 and comparator groups. The most common TEAEs that occurred at a greater frequency in the NER1006 group included abdominal pain/discomfort, nausea, vomiting and signs & symptoms of dehydration.

Table 66: DAYB-Treatment-emergent adverse events occurring in ≥ 1 % of patients by preferred term (Safety set 2)

Preferred Term	NER1006 [Day-before] (N = 243) n (%)	SP + MS (N = 247) n (%)
Abdominal pain/discomfort ^a	10 (4.1)	3 (1.2)
Nausea	6 (2.5)	2 (0.8)
Vomiting	11 (4.5)	0
Headache	4 (1.7)	4 (1.6)
Signs and symptoms of dehydration ^b	5 (2.1)	1 (0.4)

^a Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and abdominal tenderness

^b Includes dehydration, dizziness, dry mouth, orthostatic hypotension, presyncope, syncope, and thirst
source: Reviewer compilation using ADAE2 dataset in DAYB addendum

Reviewer comments:

Overall, the incidence of TEAEs was greater in the NER1006 treatment groups relative to the comparator drugs in all three trials. Generally, common AEs were mild and transient in nature. In MORA, the incidence of common TEAEs such as abdominal pain, vomiting, signs and symptoms of dehydration appeared numerically higher with the NER1006 1-day (morning of colonoscopy) regimen, as compared with the 2-day split dosing regimen. Given this difference, as well as the fact that split-dose administration of bowel preparations is recommended as standard of care in the US due to improved visualization as compared to single day administration, consideration should be given to limiting the use of the same day (morning of colonoscopy) preparation to rare situations where a 2-day split-dose prep is not feasible or indicated.

TEAEs were predominantly related to GI disorders and signs and symptoms of dehydration. A greater incidence of nausea and vomiting and signs and symptoms of dehydration associated with NER1006 treatment compared to the active controls was observed in all the three trials.

CDTL comment:

Although the limitations of the NER1006 1-day group are noted above, the decision was made to permit the 1-day dosing regimen to be included in the label without further clarification or limitations was based on the following:

- Efficacy was demonstrated against an approved split-dose comparator and was considered a robust result from a statistical standpoint (described in efficacy section above).

- *While the numerically higher rate of some common AEs is acknowledged, the patient numbers were small, and it cannot be definitively concluded that this dosing regimen is “less safe” in comparison to the 2-day split-dose regimen. Further, the majority of common AEs were mild and transient. There was no imbalance in the rates of serious adverse events between the two dosing regimens. Providing an alternate dosing regimen gives patients and providers additional flexibility, which may promote greater degree of compliance, and as a result, improved rates of successful colon cleansing.*

7.4.2 Laboratory Findings

In all trials, the laboratory tests were performed at baseline (Visit 1), day of colonoscopy (Visit 2), and follow-up Visits 3 (Day 4 ± 1) and 4 (Day 9 ± 1) in most of the patients except the patients enrolled in the first protocol Version 3. Laboratory evaluations on the day of colonoscopy were conducted between 1 to 2 hours (±30 minutes) before the colonoscopy procedure. In patients enrolled under the first version of the protocol for the three studies, blood samples at visit 4 were collected only if the results at Visit 3 were out of range. The following laboratory tests were obtained:

Clinical chemistry:	Sodium, potassium, bicarbonate, urea (or blood urea nitrogen), creatinine, chloride, calcium, phosphate, magnesium, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), alkaline phosphatase, albumin, total protein, bilirubin, urate, osmolality, anion gap, creatinine clearance (GFR)
Hematology:	Basophils, erythrocytes (red blood cells), eosinophils, hemoglobin, hematocrit, lymphocytes, leukocytes (white blood cells), mean corpuscular hemoglobin, mean corpuscular volume, monocytes, neutrophils, platelets, prothrombin time, international normalized ratio, activated partial thromboplastin time, hemoglobin, nitrite, ketones, pH, protein.
Pregnancy test (urine)	In women of child-bearing potential
Urinalysis	Hemoglobin, nitrite, ketones, pH, protein

Laboratory parameter analyses:

DB7 assessed the safety laboratory parameters of interest (Na, K, Cl, ALT, urea, and creatinine) for extreme values post-dose (shift analysis), as well as for changes that persisted post-colonoscopy (persistence analysis). Laboratory data from the three clinical trials (NOCT, MORA and DAYB) were assessed at Visit 1 (prior to colonoscopy), Visit 2 (day of colonoscopy), Visit 3 (follow-up visit at 4 days after colonoscopy) and Visit 4 (follow-up visit 9 days after colonoscopy). The DB7 reviewers noted that a major limitation of laboratory analyses was that the proportion of patients with data at Visit 1 and a subsequent visit decreases with follow-up time. Reviewers suggest caution in the interpretation of differences between the arms for the shift and persistence analyses due to missing data. Please refer to the safety statistical review by Thanh Van Tran, Ph.D, dated 3/5/2018 for details of these analyses.

Shift analyses:

For this analysis, DB7 considered 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 DB7 reviewers note that their results are different from the Applicant's value (Module 2.7.4 Tables 2.7.4-26 and 2.7.4-27) due to different laboratory range values and the number of subjects considered. Specifically, regarding the reference lab ranges used, for their analyses, DB7 used the Applicant-provided normal laboratory ranges included with each dataset. Thus, the lower and upper limits of reference ranges were not fixed, but rather varied by the laboratory that generated the data. In addition, for shift analysis, while the Applicant used values above the normal range, DB7 considered lab values that were either above or below the range for some parameters (Na, K), and values above the reference range for others (Cl, ALT, urea and creatinine). In addition, the Applicant used the subjects with normal baseline values (Visit 1) as the denominator for all subsequent visits. DB7 used data from subjects who had both normal baseline values at Visit 1 and data at the visit of interest as the denominator.

The proportion and percentage (%) of patients who had normal values at baseline (Visit 1), and demonstrated a shift at later visits are summarized below for the two pivotal studies, NOCT and MORA.

Table 67: Incidence of shifts in laboratory measures from normal at baseline (Visit 1) to abnormal at post-baseline visits (Clinical trials NOCT and MORA) (DB7 Analysis)

Laboratory parameter	Visit #	NOCT		MORA		
		n/N (%) - TRI	n/N (%) - NER2	n/N (%) - MOVIPREP	n/N (%) - NER1	n/N (%) - NER2
Sodium	Visit 2	14/246 (5.7)	103/246 (42.0)	5/246 (2.0)	48/246 (19.5)	35/235 (15.0)
	Visit 3	7/239 (3.0)	11/243 (4.5)	7/251 (2.8)	10/252 (4.0)	1/243 (0.4)
	Visit 4	10/205 (4.9)	6/193 (3.1)	3/203 (1.5)	5/207 (2.4)	10/190 (5.3)
Chloride	Visit 2	4/237 (1.7)	54/229 (23.5)	6/224 (2.7)	58/225 (26.0)	45/226 (20.0)
	Visit 3	3/229 (1.3)	8/226 (3.5)	9/228 (4.0)	9/230 (3.9)	8/233 (3.4)
	Visit 4	3/194 (1.5)	9/178 (5.1)	4/184 (2.2)	4/190 (2.1)	4/178 (2.2)
Potassium	Visit 2	11/255 (4.3)	7/253 (2.8)	13/238 (5.5)	7/238 (2.9)	8/232 (3.4)
	Visit 3	4/251 (1.6)	6/251 (2.4)	12/245 (4.9)	9/245 (3.7)	8/242 (3.3)
	Visit 4	4/214 (1.9)	3/202 (1.5)	7/198 (3.5)	9/202 (4.5)	8/187 (4.3)
Urea	Visit 2	2/240 (0.8)	5/243 (2.0)	4/237 (1.7)	8/231 (3.5)	9/232 (3.9)
	Visit 3	2/232 (0.9)	10/239 (4.2)	8/238 (3.4)	10/233 (4.3)	8/235 (3.4)
	Visit 4	11/196 (5.6)	9/192 (4.7)	6/194 (3.1)	7/190 (3.7)	7/183 (3.8)
Creatinine	Visit 2	8/248 (3.2)	18/244 (7.4)	4/233 (1.7)	11/235 (4.7)	5/222 (2.3)
	Visit 3	7/240 (2.9)	3/241 (1.2)	3/234 (1.3)	6/238 (2.5)	4/226 (1.8)
	Visit 4	10/205 (4.9)	5/194 (2.6)	8/191 (4.2)	4/194 (2.1)	4/182 (2.2)

NER1: NER1006 1-day regimen; NER2: NER1006 2-day regimen

N = number of patients normal at visit 1 with data at indicated visit

n = number of patients normal at visit 1 and abnormal at the indicated visit

source: Compiled from Tables 9 and 10 of statistical review by Thanh Van Tran, dated 3/5/18.

Reviewer comments:

Results of the shift analyses suggest that most of the measured laboratory parameters showed a shift outside the normal ranges at Visit 2, which occurred post-dose on the day of colonoscopy. This is not unexpected, given that the drug is associated with production of copious watery diarrhea, and some electrolyte abnormalities are unavoidable.

The proportion of patients with a shift outside normal values was greater in the NER1006 treatment groups compared to the active controls, except for potassium, which had comparable shifts in the test and comparator groups. For most parameters, except urea, the proportion of patients with extreme values decreased at follow up Visits 3 and 4, suggesting a reversibility of the effects. For urea, the proportion of patients demonstrating values outside the normal range was greatest at follow-up Visit 3, which occurred up to 4 days after colonoscopy. Please refer to the DB7 review for details of the shift analyses, including the statistical significance of the differences observed. In general electrolyte abnormalities that were noted were mild and not clinically significant- further details are provided below.

In addition to the above, the reviewer requested the Applicant to conduct additional analysis of shift from normal baseline parameters (separated by increase vs. decrease) for key parameters of interest. This included anion gap, bicarbonate, bilirubin, calcium, chloride, creatinine, creatinine clearance, glucose, magnesium, osmolality, phosphate, potassium, sodium, urate, and urea. From these data, the reviewer identified the following parameters that were noted to be abnormal in a greater proportion of patients receiving either regimen of NER1006, compared to the active comparator (Clinical Trials NOCT or MORA).

Table 68: Shift analysis of selected laboratory parameters (seen in greater frequency on NER1006 than comparator at Visit 2) (Applicant's analysis)

		NOCT		MORA		
Laboratory parameter	Visit #	n/N (%) - TRI	n/N (%) - NER2	n/N (%) - MOVIPREP	n/N (%) - NER1	n/N (%) - NER2
Bicarbonate (low)	Visit 2	6/255 (2.4)	16/253 (6.3)	35/199 (17.6)	51/197 (25.9)	35/182 (19.2)
	Visit 3	5/247 (2.0)	4/249 (1.6)	12/202 (5.9)	21/196 (10.7)	15/184 (8.2)
	Visit 4	4/210 (1.9)	3/199 (1.5)	3/162 (1.9)	11/160 (6.9)	6/132 (4.5)
Calcium (high)	Visit 2	12/251 (4.8)	15/247 (6.1)	4/241 (1.7)	23/244 (9.4)	17/237 (7.2)
	Visit 3	1/243 (0.4)	4/245 (1.6)	4/243 (1.6)	5/248 (2.0)	6/239 (2.5)
	Visit 4	2/208 (1.0)	3/197(1.5)	7/199 (3.5)	7/200 (3.5)	3/180 (1.7)
Chloride (high)	Visit 2	4/237 (1.7)	54/229 (23.6)	6/226 (2.7)	58/226 (25.7)	45/227 (19.8)
	Visit 3	3/229 (1.3)	8/226 (3.5)	9/229 (3.9)	9/231 (3.9)	8/234 (3.4)
	Visit 4	3/194 (1.5)	9/178 (5.1)	4/186 (2.2)	4/191 (2.1)	4/179 (2.2)

<i>Creatinine (high)</i>	<i>Visit 2</i>	8/249 (3.2)	18/244 (7.4)	4/235 (1.7)	11/236 (4.7)	5/223 (2.2)
	<i>Visit 3</i>	7/240 (2.9)	3/241 (1.2)	3/236 (1.3)	6/239 (2.5)	4/227 (1.8)
	<i>Visit 4</i>	10/205 (4.9)	5/195 (2.6)	8/193 (4.1)	4/195 (2.1)	4/183 (2.2)
<i>Creatinine Clearance (low)</i>	<i>Visit 2</i>	12/220 (5.5)	34/212 (16.0)	6/179 (3.4)	19/186 (10.2)	11/187 (5.9)
	<i>Visit 3</i>	15/213 (7.0)	18/208 (8.7)	9/178 (5.1)	10/183 (5.5)	8/186 (4.3)
	<i>Visit 4</i>	17/183 (9.3)	11/173 (6.4)	8/135 (5.9)	9/140 (6.4)	6/133 (4.5)
<i>Magnesium (High)</i>	<i>Visit 2</i>	2/250 (0.8)	0/253	1/242 (0.4)	7/235 (3.0)	2/236 (0.8)
	<i>Visit 3</i>	1/243 (0.4)	1/252 (0.4)	0/245	2/240 (0.8)	0/240
	<i>Visit 4</i>	0/202	0/197	3/202 (1.5)	1/193 (0.5)	0/185
<i>Phosphate (high)</i>	<i>Visit 2</i>	5/244 (2.0)	17/239 (7.1)	2/236 (0.8)	10/230 (4.3)	16/231 (6.9)
	<i>Visit 3</i>	3/237 (1.3)	3/238 (1.3)	4/239 (1.7)	2/234 (0.9)	8/239 (3.3)
	<i>Visit 4</i>	6/194 (3.1)	2/185 (1.1)	2/198 (1.0)	6/192 (3.1)	4/182 (2.2)
<i>Sodium (high)</i>	<i>Visit 2</i>	11/247 (4.5)	103/246 (41.9)	0/248	47/247 (19.0)	35/236 (14.8)
	<i>Visit 3</i>	7/239 (2.9)	9/243 (3.7)	5/252 (2.0)	6/253 (2.4)	1/244 (0.4)
	<i>Visit 4</i>	6/205 (2.9)	6/194 (3.1)	1/205 (0.5)	2/208 (1.0)	7/191 (3.7)
<i>Osmolality (high)</i>	<i>Visit 2</i>	11/163 (6.7)	99/170 (58.2)	7/145 (4.8)	48/154 (31.2)	42/150 (28.0)
	<i>Visit 3</i>	13/150 (8.7)	16/165 (9.7)	18/143 (12.6)	23/155 (14.8)	12/151 (7.9)
	<i>Visit 4</i>	22/122 (18.0)	15/130 (11.5)	9/120 (7.5)	11/122 (9.0)	11/120 (9.2)
<i>Urate (High)</i>	<i>Visit 2</i>	22/226 (9.7)	27/240 (11.3)	13/219 (5.9)	22/220 (10.0)	31/206 (15.0)
	<i>Visit 3</i>	10/215 (4.7)	5/235 (2.1)	10/223 (4.5)	11/224 (4.9)	9/208 (4.3)
	<i>Visit 4</i>	7/176 (4.0)	8/183 (4.4)	8/182 (4.4)	9/183 (4.9)	7/161 (4.3)
<i>Urea (High)</i>	<i>Visit 2</i>	2/241 (0.8)	5/243 (2.1)	4/239 (1.7)	9/232 (3.9)	9/233 (3.9)

	Visit 3	2/232 (0.9)	10/239 (4.2)	8/240 (3.3)	10/234 (4.3)	8/236 (3.4)
	Visit 4	11/196 (5.6)	9/193 (4.7)	6/196 (3.1)	7/191 (3.7)	7/184 (3.8)

N= number of patients with normal value at Visit 1, and with data at indicated visit

n= number of patients with normal value at Visit 1 and with abnormal data at indicated visit

source: reviewer's table, compiled from data from applicant's response to information request received 3/27/18, appendix 1.

Reviewer comments:

Similar to the analysis above (Table 67), this more detailed analysis of shifts in individual parameters showed similar trends. In the majority of cases, the differences in the proportion of patients with a shift from baseline were comparable between the 2 groups by Visit 3, suggesting that where abnormalities were related to study drug, they were mostly temporary and resolved without intervention. The difference in proportion of patients experiencing abnormal values was greatest between NER1006 and comparator for hyponatremia, hyperosmolality, and hyperchloremia. Given that serum sodium is an important component driving serum osmolality, this correlation is expected. Hyperchloremia on its own is unlikely to be clinically important. The other two parameters that are clearly correlated are serum creatinine, and calculated creatinine clearance. It was anticipated that when higher rates of elevations of creatinine are noted, higher proportions of patients with reduced creatinine clearance would also be noted. Both events occurred at Visit 2 with greater frequency in NER1006-treated patients compared to those who received comparator. Reassuringly, the proportions of patients with these events were comparable by Visit 3 and Visit 4- suggesting that the differences seen at the first visit were transient.

To further assess potential clinical relevance of these findings, in particular, the high proportion of patients experiencing abnormal serum sodium and/or chloride on the day of colonoscopy in the NER-treated groups, additional information was requested from the Applicant, to better assess the severity/clinical implication of these changes.

In IRs dated January 3 and January 5, 2018, the Applicant was asked to compile the number and proportion of patients who developed hyponatremia and hypernatremia at Visit 2 (by CTCAE grade), of those who had normal sodium at baseline Visit 1. The following information is compiled from the Applicant's response dated 01/17/2018:

Table 69: Hyper- and hyponatremia incidence at Visit 2 by CTCAE criteria (NOCT and MORA)

	NOCT - n/N (%)		MORA - n/N (%)		
	Trisulfate	NER2	MOVIPREP	NER1	NER2
Hypernatremia at Visit 2					
All hypernatremia	11/246 (4.5)	103/246 (42.0)	0.00	47/246 (19.0)	35/235 (15.0)
CTCAE Grade 1 >ULN - 150 mmol/L	11/246 (4.5)	102/246 (41.5)	0/246	43/246 (17.5)	30/235 (12.8)
CTCAE Grade 2 >150 - 155 mmol/L	0/246	1/246 (0.4)	0/246	4/246 (1.6)	5/235 (2.1)
CTCAE Grade 3 >155 - 160 mmol/L	0/246	0/246	0/246	0/246	0/235
CTCAE Grade 4 >160 mmol/L	0/246	0/246	0/246	0/246	0/235
Hyponatremia at Visit 2					
All Hyponatremia	3/246 (1.2)	0.00	5/246 (2.0)	1/246 (0.4)	0.00
CTCAE Grade 1 <LLN - 130 mmol/L	3/246 (1.2)	0/246	5/246 (2.0)	1/246 (0.4)	0/235
CTCAE Grade 3 <130 - 120 mmol/L	0/246	0/246	0/246	0/246	0/235
CTCAE Grade 4 <120 mmol/L	0/246	0/246	0/246	0/246	0/235

NER1: NER1006 1-day regimen; NER2: NER1006 2-day regimen

N = the number of patients in the analysis set where the baseline value was normal and a Visit 2 value was present.

n = the number of patients in the analysis set where the baseline value was normal and the Visit 2 value was abnormal according to the CTCAE Grade. (%) = n/N*100.

source: Compiled from applicant tables 2.1, 2.2 and 3.1, 3.2; clinical information amendment dated 01/17/2018

Reviewer comment:

Shift analyses showed that a large number of patients in both trials demonstrated abnormal sodium levels at Visit 2, especially in the NER1006 treatment groups of Trials NOCT and MORA. It is reassuring that the vast majority of these are considered CTCAE grade 1 abnormalities (unlikely to cause clinical symptoms/sequelae). This is consistent with the reported AEs, where there were very few occurrences of electrolyte abnormalities considered an Adverse Event by the Investigator and reported as an AE. Further, a majority of the shifts in sodium were above the normal reference range (hypernatremia), with very few patients demonstrating hyponatremia.

Table 70: Hyper- and hypokalemia incidence at visit 2 by CTCAE criteria (NOCT and MORA)

	NOCT - n/N (%)		MORA - n/N (%)		
	Trisulfate	NER2	MOVIPREP	NER1	NER2
Hyperkalemia at Visit 2					
All hyperkalemia	5/255 (2.0)	6/253 (2.4)	4/238 (1.7)	7/238 (1.9)	3/232 (1.3)
CTCAE Grade 1 >ULN – 5.5 mmol/L	2/255 (0.8)	4/253 (1.6)	3/238 (1.3)	7/238 (2.9)	3/232 (1.3)
CTCAE Grade 2 >5.5 - 6 mmol/L	3/255 (1.2)	2/253 (0.8)	1/238 (0.4)	0/238	0/232
CTCAE Grade 3 >6 - 7 mmol/L	0/255	0/253	0/238	0/238	0/232
CTCAE Grade 4 > 7 mmol/L	0/255	0/253	0/238	0/238	0/232
Hypokalemia at Visit 2					
All hypokalemia	6/255 (2.4)	1/253 (0.4)	9/238 (3.8)	0.0	5/232 (2.2)
CTCAE Grade 1/ 2 <LLN – 3.0 mmol/L	6/255 (2.4)	1/253 (0.4)	9/238 (3.8)	0/238	5/232 (2.2)
CTCAE Grade 3 < 3 – 2.5 mmol/L	0/255	0/253	0/238	0/238	0/232
CTCAE Grade 4 < 2.5 mmol/L	0/255	0/253	0/238	0/238	0/232

NER1: NER1006 1-day regimen; NER2: NER1006 2-day regimen

N = the number of patients in the analysis set where the baseline value was normal and a Visit 2 value was present.
n = the number of patients in the analysis set where the baseline value was normal and the Visit 2 value was abnormal according to the CTCAE Grade. (%) = n/N*100.

source: Compiled from applicant tables 4.1, 4.2; 5.1, 5.2 clinical information amendment dated 01/17/2018

Reviewer comments:

Rates of hyper- and hypokalemia were much lower as compared to changes in serum sodium. A shift to abnormal potassium from baseline Visit 1 to post-dose Visit 2 occurred at low frequency with NER1006 treatment, with no marked difference between the incidence of hypokalemia and hyperkalemia (CTCAE grade 1/2), or between the test drug and active controls. Most the shifts were to a CTCAE grade 1 change, unlikely to have clinical consequence, and consistent with low reported rates of potassium change as a reported AE.

Other Parameters:

All occurrences of decreased bicarbonate, hypercalcemia, hypomagnesemia, hyperphosphatemia, hyperuricemia in the above described shift analysis were of CTCAE Grade 1 only – suggesting that these shifts were unlikely to be clinically significant.

For the remaining parameters, the number of patients with any abnormality greater than CTCAE Grade 1 were very low – limiting the ability to draw any specific conclusions, but nevertheless, reassuring that shifts in laboratory parameters with NER1006 were very rarely found to be severe.

Specifically:

- For hypocalcemia, only 1 NER1006 treated patient was noted to have CTCAE Grade 2 elevation, and none had Grade 3 or higher.

-
- For hypermagnesemia, only 1 NER1006 treated patient had a CTCAE Grade 3 elevation, the rest were Grade 1.
 - For hypophosphatemia, the majority of the patients who did have a CTCAE Grade 2 or greater elevation were in the comparator arm (both comparators caused a greater proportion of hypophosphatemia of any grade, compared to NER1006).
 - For bilirubin, the majority of the patients who did have a CTCAE Grade 2 or greater elevation in bilirubin were in the comparator arm (both comparators included a greater proportion of patients with elevated bilirubin, compared with NER1006).

Reviewer comment:

In summary, although shifts in chemistry parameters were seen commonly, and in some cases with greater frequency in NER1006 patients than those treated with comparators, the vast majority of these abnormalities were considered not clinically significant (both by the investigator assessment, and also based upon objectively defined CTCAE criteria).

Changes in Renal Function parameters by CTCAE grade:

Creatinine and creatinine clearance were assessed for severity by CTCAE grade at Visit 3, rather than Visit 2. The rationale for this was that changes in these parameters, if present, are likely due to a pre-renal cause (i.e., dehydration secondary to bowel preparation) and may not be evident immediately as renal injury. In such cases, it may take 24-48 hours to be evident on laboratory test results. As a result, change in creatinine clearance and rise in serum creatinine are presented below, by CTCAE grade at Visit 3.

Table 71: Changes in Renal Function Parameters by CTCAE grade (Visit 3)

	NOCT - n/N (%)		MORA - n/N (%)		
	Trisulfate	NER2	MOVIPREP	NER1	NER2
Creatinine Clearance Decreased (Visit 3)					
Creatinine Clearance Decreased	M=271 n/N (%)	M=275 n/N (%)	M=269 n/N (%)	M=271 n/N (%)	M=265 n/N (%)
CTCAE Grade 1 (LLN to 60ml/min/1.73 m ²)	5/213 (2.3)	11/208 (5.3)	6/178 (3.4)	7/183 (3.8)	6/186 (3.2)
CTCAE Grade 2 (59 to 30 ml/min/1.73m ²)	9/213 (4.2)	7/208 (3.4)	3/178 (1.7)	2/183 (1.1)	1/186 (0.5)
CTCAE Grade 3 or higher (<=29 ml/min/1.73 m ²)	1/213 (0.5)	0/208	0/178	1/183 (0.5)	1/186 (0.5)
Creatinine Increased (Visit 3)					
Creatinine Increased	M=271 n/N (%)	M=275 n/N (%)	M=269 n/N (%)	M=271 n/N (%)	M=265 n/N (%)
CTCAE Grade 1 >ULN to 1.5x ULN	7/240 (2.9)	3/241 (1.2)	3/236 (1.3%)	5/239 (2.1)	4/227 (1.8)
CTCAE Grade 2 1.5 X ULN to 3.0 x ULN	0/240	0/241	0/236	0/239	0/227
CTCAE Grade 3 or greater >3.0x ULN	0/240	0/241	0/236	1/239	0/227

M= number of patients in analysis set

N= number of patients normal at visit 1 with data at indicated visit

n= number of patients normal at visit 1 and abnormal based on the CTCAE grade at indicated visit

source: reviewer table compiled from analysis submitted by applicant in response to IR dated 3/27/18

Reviewer comment:

Across the 2 studies, the majority of changes in renal function parameters were of CTCAE Grade1 (small magnitude, unlikely to be clinically significant) and the changes occurred at similar frequencies across treatment groups. This is consistent with the analysis of renal safety presented in Section 7.5.4.1 below and does not suggest a signal of renal injury associated with NER1006.

Persistence analyses:

In addition to the overall shift analysis, an understanding of when electrolyte abnormalities persisted is of interest, as this situation could indicate a renal injury or other more serious problem than transient fluid/electrolyte shifts associated with bowel preparation administration. At the request of the review Division, DB7 reviewers also assessed the persistence of extreme laboratory values after colonoscopy. In a persistence analysis, 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 were considered. A persistence analysis evaluates the presence of sustained extreme laboratory values from Visit 2 to Visit 3. In this regard, the Applicant was also requested

to conduct additional analyses of patients in clinical trials NOCT and MORA who had persistence of abnormal laboratory values at Visit 3, after presenting with normal values at baseline (Visit 1) and abnormal values (post-dose/pre-colonoscopy) at Visit 2.

The following table summarizes the proportion and percentage (%) of patients who demonstrated extreme laboratory values at Visit 3 for various laboratory parameters assessed in clinical trials NOCT and MORA:

Table 72: Persistence analysis - Clinical Trials NOCT and MORA

	NOCT n/N (%)		MORA n/N (%)		
Visit 3	Trisulfate	NER2	MOVIPREP	NER1	NER2
Sodium	0/12	8/102 (8.0)	1/5 (20.0)	4/47 (8.5)	0/35
Potassium	0/10	0/6	1/13 (8.0)	1/6 (17)	0/6
Chloride	1/4 (25.0)	7/53 (13.0)	4/6 (67.0)	7/56 (12.5)	4/45 (9.0)
Urea	0/0	1/5 (20.0)	4/4 (100)	3/8 (38.0)	4/9 (44.4)
Creatinine	2/7 (29.0)	3/18 (17.0)	1/4 (25.0)	2/10 (20)	1/5 (20.0)

NER1: NER1006 1-day regimen; NER2: NER1006 2-day regimen

N = number of patients normal at visit 1, abnormal at visit 2, and data at visit 3 present n = number of patients normal at visit 1, abnormal at visit 2, and abnormal at visit 3

source: Compiled from tables 12 and 13 of statistical review by Drs. Thanh Tran and Clara Kim

Reviewer comments:

Overall, laboratory abnormalities persisted in only a small number of individuals beyond Visit 2 prior to the colonoscopy, where most abnormalities were noted. This persistence assessment is limited to Visit 3, which occurred 1-3 days (inclusive) after the colonoscopy. For sodium, there were a greater proportion of patients with persistent abnormalities in the NER group, compared to Trisulfate (NOCT) but the opposite trend was noted in MORA (more patients in the comparator group, compared to NER groups).

In general, the observation of very small numbers of patients with persistent abnormalities is both reassuring, and limits the ability to draw conclusions about the relative safety of the study drug with comparators.

A limitation of this analysis (particularly as it pertains to serum creatinine) is that it includes only patients who had normal values at baseline. To further assess for the potential occurrence of worsening renal function among those who had abnormal renal function at baseline, refer to additional discussion in section 7.5.4.1 below.

Narratives of select patients with persisting laboratory abnormality at Visit 3/4: For many clinical trial patients with persisting laboratory abnormalities following Visit 2, the changes in lab values do not appear to be clinically meaningful, either because they normalized, or trended towards normalization by the subsequent Visits 3 or 4, or changes were only marginally out of range. Narratives for a subset of patients in the clinical trials NOCT and MORA who were on NER1006 regimens, in whom there was evidence of persistence for one or more laboratory parameters outside of the normal reference range by the last visit are provided here. These cases

were selected by the clinical reviewers because one or more values did not appear to be trending back toward normal by the last available data point. In general, the Applicant claims ‘no evidence of renal injury’ for these patients:

Table 73: Narratives of select patients with persistent extreme laboratory values

Patient ID	Narrative	Lab abnormality	Other lab findings	Reviewer Comment
NOCT (NER2)				
(b) (6)	White, female, 50 y/o; Ongoing diseases: hypertension, cystitis, GERD, hypogonadism; Ongoing Meds: hydrochlorothiazide, estradiol, omeprazole, lotrel	Urea: Normal at baseline; raised to 3.33 mmol/L (0.33 > ULN) at visit 2; still rising at 3.5 mmol/L at visit 4 (day 16).	Serum albumin, ALT, AST, ALP, Bilirubin, GGT were normal; Serum creatinine, protein and urate were normal; urea increased over baseline at visits 2-4; Creatinine clearance fell gradually from screening (76) over visits 2,3,4 (64, 63, 56 mL/min); reference range for CLcr given as 60-130 mL/min	Isolated minimal rise in urea without corresponding changes in other parameters is unlikely to be of clinical consequence.
(b) (6)	Male; 50 y/o; Ongoing: Rectal hemorrhage; no medications	Creatinine rose to 114.9 (8.8 µmol/L > ULN) at V2, and still rising at 132.6 µmol/L at visit 4 (day 10); patient also had a raised anion gap at screening and at all visits; other labs were normal	Creatinine clearance was deemed normal at baseline (64 mL/min; lab ref normal range 60-200); CLcr then fell during visits 2, 3, 4 at 58, 54, 50 mL/min; serum urea, urate, protein and urinalysis were normal	Applicant had no additional information (notes, follow-up labs) on this patient. However, urinalysis was normal and no evidence of orthostatic hypotension to suggest renal injury or dehydration.

(b) (6)	Black, female, 64 y/o; Ongoing: chronic kidney disease, Hep C, hypokalemia, drug allergies; Ongoing Meds: cetirizine, ranitidine, cyclosporine, omeprazole, aspirin, fluoxetine, diltiazem, losartan, hydrochlorothiazide, potassium, Mg, baclofen	Creatinine: Normal at baseline, rose to 105.2 µmol/L (~17 > ULN), and still raised at V4 (98 µmol/L; day 10); V3 creatinine (95.5) was lower than V4 value.	Creatinine clearance decreased from baseline to visit 4 (73, 56, 63, 61 ml/min at baseline, v2, v3, v4); this was deemed low as the lab's ref range for CLcr was 88-128 ml/min; serum protein, urea, urate were normal; urinalysis was trace for proteins at screening and negative at V2;	Multiple confounding factors including the presence of kidney disease at baseline and nephrotoxic medications in use.
(b) (6)	Black, female, 64 y/o; Ongoing Hypertension; Ongoing meds include, hydrochlorothiazide, Lisinopril, amlodipine, fluticasone, loratadine	Creatinine: Normal at baseline; raised to ~95 µmol/L (6.2 > ULN) at visit 2; still raised at 99 µmol/L at visit 4 (day 9);	Creatinine clearance decreased from baseline to visit 4 (79, 63, 68, 60 at baseline, v2, v3, v4); this was deemed low as the lab's ref range for CLcr was 88-128 ml/min; serum protein, urea, urate were normal; urinalysis was negative for proteins;	Applicant notes that there could be factors not related to the bowel prep, such as hypertension and concomitant medications which could impact the renal findings. There was no evidence of orthostatic hypotension.
(b) (6)	Male; 68 y/o; Ongoing GERD, arthritis; ongoing meds: ibuprofen and fexofenadine	Chloride: Normal at baseline; raised to 111 mmol/L (4>ULN) and still raised at 112 mmol/L (5 > ULN) at visit 4 (day 9)	Serum creatinine, creatinine clearance, protein, and urea were normal	Isolated minimal increase in chloride without other changes in labs suggestive of decreased renal function is unlikely to be of clinical consequence.

MORA				
(b) (6) (NER1)	Male; 43 y/o; No concomitant diseases or drugs;	Chloride: Normal at baseline; raised to 115 mmol/L (7 > ULN); last record at visit 3 remaining at 114 mmol/L; anion gap was raised at baseline;	Creatinine was normal and Cr Cl was high at all visits; serum urea/urate, protein, urinalysis were all normal	Isolated minimal increase in chloride without other changes in labs suggestive of decreased renal function is unlikely to be of clinical consequence.
(b) (6) (NER2)	Female; 30 y/o; ongoing erosive gastritis; on Yasmin (contraceptive).	Urea: normal (2.84) at baseline; dropped below LLN (2.23 mmol/L) at visit 2 and remained low at visit 4 (day 8) at 2.21 mmol/L (0.55<LLN); osmolality was also low at V2	Serum Albumin, ALT, AST, ALP, GGT, bilirubin, were normal; Creatinine clearance was normal at all visits; serum urate and protein, urinalysis were normal;	Isolated mild decrease of urea not of clinical consequence.
(b) (6) (NER2)	Male; 73 y/o; ongoing hypercholesterolemia and Hx of angina pectoris; co-meds: Aspirin, simvastatin;	Urea: raised to 6.9 mmol/L (0.3 > ULN) at visit 2; higher at 8.3 at V3; and trending towards normal at 7.2 mmol/L at visit 4 (day 12);	Serum Albumin, ALT, AST, ALP, bilirubin, were normal; GGT was high at baseline, and remained high at visit 4; Serum creatinine, urate, urinalysis were normal; creatinine clearance was 61 mL/min and remained constant at all visits	Overall laboratory panel not suggestive of renal disease, urea trending back toward normal.
(b) (6) (NER2)	Female; 62 y/o; no medical conditions or concomitant meds to report;	Creatinine: lowered to 60.11 µmol/L at visit 2 (10.61<LLN) and still lower at 56.58 µmol/L at visit 3 (last record)	Creatinine clearance was in the normal range; urea and protein were normal;	Decreased Cr of no clinical importance.

sources: review table, based on results provided in Appendix 2 of Applicant's IR response dated 01/17/2018; internally generated listing of persistence data; and additional safety datasets for NOCT and MORA

Reviewer comments:

In the majority of these provided brief narratives, the overall picture of signs/symptoms and laboratory findings do not suggest a new-onset renal injury occurred.

For two of the patients ((b) (6)), additional details were requested to further clarify. Although the Applicant was unable to clearly rule out a renal injury due to the bowel preparation (seen as a decline in CrCl), the normal ranges of other chemistry parameters and safety findings including normal urinalysis, absence of orthostatic hypotension, etc., do not strongly indicate an acute renal injury in these subjects.

Additional evaluation of laboratory parameters:

The Applicant was requested to provide additional information for the patients in the three trials who were reported to have dehydration, hypotension, decreased GFR, altered liver enzymes, fatigue, or syncope/pre-syncope. This was to evaluate if there was any correlation of these AEs with orthostasis and electrolytes changes suggestive of intravascular volume depletion. The Applicant provided the information on September 1, 2017. Please see Appendix-D for the patients identified with different AEs in the three studies. The information for GFR and liver enzyme changes are summarized below:

Glomerular Filtration Rate (GFR): In clinical trial NOCT, the number of patients reported to have decreased GFR were comparable in the two treatment groups (NER1006 = 4, Trisulfate = 5). A change from baseline in creatinine (from +8 to 20 $\mu\text{mol/L}$) but below the upper limit of normal was observed in all of these patients in both treatment groups. In all patients except three, the values returned to normal within 3 to 8 days; in three patients, it took 15 to 61 days to return to normal. One patient in the NER1006 group had associated elevated Na (152 mmol/L) and potassium (5.5 mmol/L) levels and was on concomitant atenolol for hypertension. No patient had orthostasis.

In MORA, one patient in the NER1006 2-Day split dosing group compared to no patients in the Moviprep group, was reported to have a slight increase in creatinine from baseline. The patient had orthostasis (drop in the systolic BP > 20 mm Hg) and Na (148 mmol/L) and K (4.9 mmol/L) in the upper arrange of normal; these values returned to normal in 4 days.

In DayB, one patient in the SP+MS group reported a shift in creatinine from baseline of 67 to 80 $\mu\text{mol/L}$, which returned to normal in 6 days. No orthostasis or electrolytes abnormality was observed. The proportion of patients with reversible changes in GFR (or creatinine) were comparable in the treatment groups.

Reviewer's comments:

Decreased GFR is likely to occur due to inadequate fluid intake. The mandatory drug and water intake in the NER1006 groups is less (2 L with additional ad libitum fluids) compared to the Trisulfate and Moviprep groups (3 L with additional ad libitum fluids). There are several limitations to correlating symptoms/changes in laboratory parameters with the reduced volume

of the NER1006, as the volume of ad libitum fluids was not collected during the phase 3 trials. Furthermore, only small proportion of patients developed these symptoms and most of these patients were on concomitant antihypertensive and diuretics medications.

The currently approved bowel preparations are high volume (3L or 4L) bowel preparations, compared to NER1006 (2L). The high volume bowel preparations are likely to provide bowel cleansing fluids as well as water/fluids to minimize transfer of fluids/electrolytes from the vascular and extravascular compartments into the colonic lumen. Theoretically, the low volume bowel preparation, NER1006 (2L), is likely to sequester water and fluid from the intra- and/or extra-vascular space to generate additional fluid in the colon to obtain optimal volume for bowel cleansing. This process, along with nausea and vomiting, may lead to dehydration and electrolyte abnormalities.

Liver related laboratory parameters: Transient elevations in one or more liver enzymes (ALT, AST, ALP, GGT) and bilirubin levels were noted in some patients for both the study drug and the active control regimens in the clinical trials for NER1006. The Applicant considers that this could be related to transient dehydration. The following Applicant-submitted table summarizes the shift from a normal value at baseline to high (i.e., > ULN) at post-baseline visits for NOCT, MORA and DAYB.

Table 74: Incidence of Shifts in Liver Enzyme and Bilirubin Levels from Normal at Baseline to High (>ULN) at Post-Baseline Visits – NOCT, MORA and DAYB Trials

Parameter	Visit	Number (%) of patients						
		NOCT		MORA			DAYB	
		NER1006 (N=262)	Trisulfate (N=265)	NER1006 2-Day (N=262)	NER1006 1-Day (N=269)	MOVIPREP® (N=263)	NER1006 (N=235)	SP+MS (N=241)
ALT	V2	23 (8.8)	7 (2.6)	24 (9.2)	20 (7.4)	13 (4.9)	19 (8.1)	4 (1.7)
	V3	8 (3.1)	4 (1.5)	7 (2.7)	12 (4.5)	7 (2.7)	9 (3.8)	3 (1.2)
	V4	5 (1.9)	5 (1.9)	6 (2.3)	3 (1.1)	4 (1.5)	5 (2.1)	1 (0.4)
AST	V2	15 (5.7)	17 (6.4)	33 (12.6)	17 (6.3)	17 (6.5)	15 (6.4)	16 (6.6)
	V3	5 (1.9)	4 (1.5)	5 (1.9)	8 (3.0)	4 (1.5)	6 (2.6)	11 (4.6)
	V4	5 (1.9)	2 (0.8)	3 (1.1)	5 (1.9)	4 (1.5)	2 (0.9)	4 (1.7)
Bilirubin	V2	19 (7.3)	32 (12.1)	30 (11.5)	22 (8.2)	33 (12.5)	28 (11.9)	27 (11.2)
	V3	4 (1.5)	7 (2.6)	9 (3.4)	15 (5.6)	9 (3.4)	5 (2.1)	4 (1.7)
	V4	5 (1.9)	3 (1.1)	12 (4.6)	9 (3.3)	11 (4.2)	4 (1.7)	1 (0.4)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; N = total number of patients; SAF = safety analysis set; ULN = upper limit of normal; V = visit.

Source: ISS Table 3.2.2.1

source: Applicant Table 8-31, ISS; page 67 of 71;

Reviewer comments:

The Applicant's analysis suggests that an increase over normal baseline values in liver enzymes and bilirubin occurred in both the test drug and active comparator groups. For all liver parameters across all treatments in these trials, the peak proportion of patients with a change from baseline > ULN occurred at Visit 2, which is post-dose and pre-colonoscopy. The incidence of liver enzyme shifts reduced gradually at subsequent Visits 3 and 4 suggesting the

reversible/transient nature of these shifts. In particular, ALT shifts occurred in a greater proportion of patients treated with NER1006 than comparators, across all three trials. Further analysis of this is described below.

Upon request from the clinical division, DB7 reviewers conducted additional analyses on ALT. The proportion of patients who had normal ALT at baseline and had an abnormal value at one or more post-baseline visits (shift analysis) are summarized below for the two clinical trials of interest, NOCT and MORA:

Table 75: DB7 analysis of shift from a normal baseline in ALT at post-baseline visits

		NOCT		MORA		
Shift analysis	Visit #	n/N (%) - TRI	n/N (%) - NER2	n/N (%) - MOVIPREP	n/N (%) - NER1	n/N (%) - NER2
<i>ALT</i>	<i>Visit 2</i>	7/232 (3.0)	23/238 (9.7)	13/226 (5.8)	20/224 (8.9)	24/226 (11.0)
	<i>Visit 3</i>	4/227 (1.8)	8/233 (3.4)	7/228 (3.1)	12/231 (5.2)	7/231 (3.0)
	<i>Visit 4</i>	5/190 (2.6)	5/186 (2.7)	4/187 (2.1)	3/189 (1.6)	6/177 (3.4)

source: Compiled from Tables 9 and 10 of DB7 review

Reviewer comments:

The DB7 analysis of shift in ALT from baseline suggests similar trends as reported by the Applicant. The proportion of patients with a shift from a normal ALT at baseline to > ULN at post-baseline peaked at Visit 2 (post-dose and pre-colonoscopy), and reduced over time during the subsequent visits. For NOCT, the proportion of patients with a transient increase in ALT at Visit 2 was 3-fold relative to the active comparator (Trisulfate). By Visit 4, these proportions were comparable between the test and control groups. In MORA, both NER1006 dosing regimens (2-day and 1-day) showed a greater proportion of patients with a shift from normal ALT at Visit 2, with no marked difference between the two regimens. These proportions decreased over time and were comparable by Visit 4 across all treatments, suggesting the transient nature of the liver enzyme elevations. A possible explanation of the greater proportion of patients with acute ALT elevations on NER1006 compared to comparator may be related to the frequency of dehydration (which seemed to occur more commonly with the study drug than comparator, as discussed above under Common Adverse Events). It is reassuring that liver enzymes appeared to trend toward normal for most patients over time and also that the majority of shifts were of small magnitude (cases with >3X ULN elevation of liver enzymes, were rare and are discussed below).

Note: The denominator values in the Applicant and FDA tables pertaining to shift analysis of ALT are different. While the Applicant used all subjects with normal baseline values (Visit 1) as the denominator for all subsequent visits, DB7 used only those subjects who had both normal baseline values at Visit 1 and had data for the visit of interest as their denominator.

The Applicant also summarized the number and percentage of patients meeting the first two components of Hy's Law (as defined in the FDA *Guidance for Industry - Drug-Induced Liver Injury: Premarketing Clinical Evaluation*, 2009) at any post-baseline assessment, i.e., ALT or AST >3X ULN, elevation of serum total bilirubin (TBL) to > 2X ULN, and no other explanation for the combination of increased ALT/AST and TBL, such as viral hepatitis, preexisting or acute liver disease, or on a medication capable of causing the observed injury.

No cases met all three criteria for Hy's Law; one patient in the Moviprep (active control) group of MORA met the first two criteria but had a relevant hepatic medical history (chronic hepatitis, hyperlipidemia) and had baseline elevations in liver enzymes and bilirubin (ID (b) (6); 51 y/o, white male patient). The following table summarizes the proportion of patients in each treatment group that had AST, ALT elevations >3X ULN, or Bilirubin elevation >2X ULN.

Table 76: Patients meeting liver parameter outlier criteria of interest at any post-baseline visit

	NOCT		MORA		
	Trisulfate (N = 265) n (%)	NER1006 (N = 262) n (%)	Moviprep (N = 263) n (%)	NER-1 (N = 269) n (%)	NER-2 (N = 262) n (%)
ALT >3XULN	1 (0.4)	2 (0.8)	1 (0.4)	4 (1.5)	2 (0.8)
AST >3x ULN	0	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)
Bili >2x ULN	7 (2.6)	3 (1.1)	7 (2.7)	12 (4.5)	8 (3.1)

source: From applicant Table 3.4, ISS; N = number of patients in the analysis set; n = number meeting the criterion

Reviewer comment:

The number of patients meeting pre-specified criteria suggest that the incidence of significant post-baseline elevations was small and comparable across groups. These data are not limited to those with normal values at baseline.

One patient on the NER1006 2-day regimen in study MORA met the first two (laboratory) criteria for Hy's Law, but not the 3rd criteria of "no other explanation" due to underlying hepatic disease and/or elevated baseline values. Another MORA patient on the NER1006 1-day regimen met the first two criteria at the baseline visit, and experienced further increase in bilirubin only. Narratives of these patients are provided below:

Patient (b) (6): This 54 year old white male patient received NER1006, 2-day split dose regimen in Study MORA. The patient had increases in ALT and AST at Visit 2 (post-dose and pre-colonoscopy) and more pronounced elevations at the post-colonoscopy Visit 3 on Day 4. At a subsequent unscheduled follow up visit on Day 10, the values decreased to within normal range. The patient's bilirubin was high at all visits, including at baseline. The patient's relevant ongoing medical conditions included Gilbert's syndrome, hypercholesterolemia, gallbladder polyp and relevant concomitant medication includes rosuvastatin.

Patient (b) (6): This 61 year old white female patient received NER1006, 1-day split dosing regimen in Study MORA. The patient had elevated ALT, AST and bilirubin at the screening visit and both parameters showed progressively lower values over subsequent visits. Her bilirubin was 3-fold over ULN at baseline and was 5-fold higher relative to ULN at Visit 2; it

later showed a trend to decline toward baseline value with subsequent visits. This patient had a past medical history of previous appendectomy and current history of ulcerative colitis. Concomitant medications included; azathioprine 150 mg once daily; mesalazine 2g once daily; and eugynon once daily.

Lab values for both patients are summarized below:

Table 77: Liver-related laboratory values in Patient (b) (6) in MORA

# (b) (6) (2-day Split Dosing Regimen)	ALT (mU/mL) [NR: 1 -40]	AST (mU/mL) [NR: 1 -40]	Bilirubin (umol/L) [NR: 0.2-1.2]	GGT (mU/mL) [NR: 8-61]	Albumin (g/dL) [NR: 3.4-5]	ALP (mU/mL) [NR: 50-136]
Baseline V1	28	28	2.2	41	4.0	53
Visit 2; day 2	46	51	3.1	42	4.5	65
Visit 3; day 4	143	154	1.6	435	4.1	66
V3 f/u; day 10 (unscheduled)	40	22	2.3	139	NA	63
# (b) (6) (1-day AM Split Regimen)	ALT (μmol/L*s) [NR: 0-0.55]	AST (μmol/L*s) [NR: 0-0.51]	Bilirubin (μmol/L) [NR: 0-3]	GGT (μmol/L*s) [NR: 0-0.62]	Albumin (g/L) [NR: 34-48]	ALP (μmol/L*s) [NR: 0-1.99]
Baseline V1	1.78	1.57	9	0.35	37	1.04
Visit 2; day 1	0.93	0.97	15	0.27	39	0.92
Visit 3; day 4	0.85	0.76	11	0.25	35	0.86
Visit 4; day 15	0.67	0.56	10	0.34	35	0.87

source: reviewer's table based on data provided in CSR and narratives

Reviewer comments:

In Patient (b) (6), the lab values and medical history suggests that individual fits the first two criteria for Hy's Law, but not the third due to underlying hepatic disease and elevated baseline values for bilirubin. Further given that

- 1) AST and ALT normalized rapidly by unscheduled follow-up on Day 10
- 2) there was no persistently rising bilirubin that would suggest liver impairment
- 3) the patient had known Gilbert's, which is the most likely explanation of the rise in bilirubin,

this case is not consistent with acute liver injury.

In Patient (b) (6), the first two criteria for Hy's Law were met only at the baseline visit, with only bilirubin showing a further rise post-dose (Visit 2). Given the higher baseline values, lack of increase in AST and ALT enzymes post-treatment and a decreasing trend for bilirubin over subsequent (post-dose) visits, there is no clear evidence of drug-induced liver injury. The cause of the baseline elevations is not clear, although it could be related to ulcerative colitis, concomitant medications, undiagnosed liver disease, etc. An acute increase in bilirubin due to Plenvu cannot be ruled out, though this case is not strongly suggestive of drug-induced liver injury.

Overall, marked elevations in liver enzymes to >3L ULN occurred in few patients, appeared transient in nature, and were not markedly different across NER1006 and active control treatments or across the dosing regimens of NER1006. These findings do not suggest a signal of liver injury. Further, no patient met all three criteria for Hy's Law.

7.4.3 Vital Signs

In the two studies, weight, height, temperature, pulse and blood pressure were measured at clinical visits. The changes from baseline in vital signs do not appear to be clinically relevant, with no clinically meaningful difference between the two NER1006 treatment groups.

DB7 has assessed the proportion and percentages of patients with hypotension (systolic blood pressure < 90 mmHg), and orthostatic changes (a decrease of >20 mmHg in SBP and DBP, separately) in the clinical trials for NER1006. Key findings from their analyses are summarized below. Please refer to the statistical review by Drs. Thanh V. Tran and Clara Kim for details.

Hypotension analysis:

Table 78: Proportion and percentage (n/N (%)) of patients who have systolic blood pressure < 90 mmHg at visit 1 (baseline) or visit 2 (post-dose)

	NOCT		MORA		
	Trisulfate n/N (%)	NER2 n/N (%)	MOVIPREP n/N (%)	NER1 n/N (%)	NER2 n/N (%)
SYSBPO Visit 1	0/265 (0.0)	0/261 (0.0)	1/253 (0.4)	0/259 (0.0)	0/251 (0.0)
SYSBPO Visit 2	2/265 (0.8)	0/261 (0.0)	0/253 (0.0)	2/259 (0.8)	1/251 (0.4)
SYSBPS Visit 1	0/265 (0.0)	0/262 (0.0)	0/242 (0.0)	0/247 (0.0)	0/233 (0.0)
SYSBPS Visit 2	0/265 (0.0)	1/262 (0.4)	0/242 (0.0)	0/247 (0.0)	0/233 (0.0)

NER2=NER1006 2-day split dosing; SYSBPO: orthostatic systolic blood pressure; SYSBPS: supine systolic BP
N = number of patients with data at indicated visit; n = number of subjects with systolic blood pressure < 90 mmHg at indicated visit;

source: Table 15 and 16, DB7 statistical review for NDA 209381

Reviewer comment:

The percentage of patients with SYSBPO or SYSBPS < 90 mmHg was ≤ 0.8%, with no evidence of a statistically significant difference between treatment arms.

Orthostasis analysis:

Table 79: Proportion and percentage (n/N (%)) of patients who have orthostatic changes (systolic or diastolic) of > 20 mmHg

	NOCT		MORA		
	Trisulfate n/N (%)	NER2 n/N (%)	MOVIPREP n/N (%)	NER1 n/N (%)	NER2 n/N (%)
DIAORTHO	2/265 (0.8)	3/261 (1.1)	0/236 (0.0)	0/240 (0.0)	0/224 (0.0)
SYSORTHO	8/265 (3.0)	12/261 (4.6)	8/236 (3.4)	15/240 (6.3)	14/224 (6.3)

NER1=NER1006 1-day split dosing, NER2=NER1006 2-day split dosing

N = number of patients with data; n = number of patients with orthostatic change > 20 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

source: Table 18 and 19, DB7 statistical review for NDA 209381

Reviewer comment:

For both trials, the percentage of patients with diastolic or systolic orthostatic changes of > 20 mmHg were $\leq 6.3\%$. DB7 reviewers acknowledge that while there was no evidence of statistical significance between treatment arms for orthostatic changes, NER1006 treatment groups consistently demonstrated greater orthostatic ranges than the comparator. For example, for the NOCT trial, with the NER 2-day split regimen, the range for SYSORTHO was [21, 49] mmHg, compared to SYSORTHO [21, 38] mmHg for the active comparator, Trisulfate. In MORA, the SYSORTHO ranges for the three groups were [21, 42] mmHg for NER-1, [21, 35] mmHg for NER-2 regimens, compared to [21,30] mmHg for the active comparator, Moviprep.

7.4.4 Electrocardiograms (ECGs)

In general, the Applicant noted that in both NOCT and MORA, the changes from baseline ECG were not considered clinically significant, and there were no clinically significant differences between the two treatment groups.

QTcF outlier analysis: The incidence of QTcF outliers in NOCT and MORA are summarized for the post-dose Visit 2 in the following table. The number of patients with QTcF outlier data (> 450 ms, >480 ms, >500 ms) remained comparable to the baseline for the NER1006 treatment groups in both trials.

The proportion of patients with QTcF change > 30 msec was greater compared to those with QTcF change > 60 msec. Overall, a shift of > 60 msec from baseline occurred with low frequency in the NER1006 groups. While the proportion of patients with absolute changes of 30 msec or 60 msec over baseline was larger for the NER1006 2-day split regimen in Study MORA, compared to the 1-day regimen, this incidence was comparable to the comparator drug MoviPrep. The incidence for the 2-day split dose regimen in MORA was not comparable to the same regimen in NOCT, thus failing to demonstrate a consistent trend for ECG outliers with the regimen used.

Table 80: Incidence of ECG outliers by treatment and regimen in trials NOCT and MORA

	NOCT		MORA		
	NER1006 (N = 262) n (%)	Trisulfate (N= 265) n (%)	NER-1 (N = 269) n (%)	NER-2 (N = 262) n (%)	MOVIPREP (N = 263) n (%)
Baseline					
>450 msec	8 (3.1)	16 (6)	12 (4.5)	12 (4.6)	9 (3.4)
>480 msec	2 (0.8)	1 (0.4)	1 (0.4)	2 (0.8)	2 (0.8)
>500 msec	1 (0.4)	0	1 (0.4)	1 (0.4)	0
Visit 2 (post-dose & pre-colonoscopy)					
>450 msec	10 (3.8)	20 (7.5)	12 (4.5)	13 (5)	22 (8.4)
>480 msec	2 (0.8)	1 (0.4)	2 (0.7)	1 (0.4)	3 (1.1)
>500 msec	1 (0.4)	0	0	1 (0.4)	1 (0.4)
Change from baseline >30 ms	7 (2.7)	16 (6)	16 (5.9)	30 (11.5)	34 (12.9)
Change from baseline >60 ms	2 (0.8)	1 (0.4)	3 (1.1)	6 (2.3)	8 (3.0)

N = the number of patients in the analysis set; n = the number of patients meeting the criterion
source: Compiled from applicant's Table 5.2.1: Incidence of outliers in QTcF (Safety Analysis Set); ISS Collated Tables; Applicant clarified that additional patient data in the revised dataset SAF2 does not change the above results

Reviewer comment:

QTcF change over baseline of > 30 msec or > 60 msec was noted in all test and active comparator groups in Trials NOCT and MORA. The proportion of these outliers was small in the NER1006 groups, especially for a shift > 60 msec, and appears comparable or smaller relative to the active control groups. Results do not show consistent proportions of QTcF outliers with the 2-day split dose regimen of NER1006 across the two trials. Given that the drug product is for single use prior to colonoscopy, and the observed QTcF changes are potentially acute effects related to electrolyte changes caused by the bowel prep, this does not appear to pose a significant concern.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies or clinical trials were conducted.

7.4.6 Immunogenicity

Not applicable because NER1006 is not a protein.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

All the patients in the clinical trials received the same total dose. Therefore, dose dependency is not applicable.

7.5.2 Time Dependency for Adverse Events

NER1006 was administered once prior to the colonoscopy examination either as a 1-day split dosing regimen or a 2-day split dosing regimen. Therefore, time dependency for adverse event was not evaluated.

7.5.3 Drug-Demographic Interactions

The following is a summary of number of TEAEs and percentage of patients (%) with these events, in the various demographic subgroups of interest.

Table 81: Proportions and percentages of TEAEs by demographic subgroups

	NOCT (2-day Split)		MORA		
	NER1006 (N = 262)	Trisulfate (N = 265)	NER-1 (N = 269)	NER-2 (N = 262)	MoviPrep (N = 263)
Gender					
Male	28 (20.7)	23 (15.3)	11 (8.9)	15 (13.9)	15 (11)
Female	44 (34.6)	26 (22.6)	38 (26.2)	31 (20.1)	16 (12.6)
Age group					
< 45 years	7 (31.8)	6 (31.6)	9 (14.8)	6 (14)	6 (9.8)
45-65 years	48 (25)	32 (16.2)	30 (20.3)	28 (18.8)	19 (12.1)
>65 years	17 (35.4)	11 (22.9)	10 (16.7)	12 (17.1)	6 (13.3)
Race					
White	66 (29.9)	44 (20.1)	46 (17.3)	45 (17.6)	30 (11.5)
Black	3 (8.8)	3 (12)	3 (100)	0	1 (100)
Asian	3 (42.9)	0	0	0	0

source: Compiled from applicant's Table 8-27 [Integrated summary of safety, ISS; pages 59-60]

Reviewer comment:

There appears to be a trend for a higher incidence of TEAEs in females, particularly in the NER1006-treated patients. A consistent relationship of age vs. TEAE incidence was not observed. Because the population enrolled was predominantly Caucasian, it is difficult to discern a relationship of TEAE incidence with race. Overall, however, there was no trend in clinical trials NOCT, and MORA for any demographic subgroup regarding the incidence of significant TEAEs, serious AEs, study drug withdrawals or trial discontinuations.

7.5.4 Drug-Disease Interactions

Co-existing disease states in patients of clinical trials NOCT and MORA included diabetes, RI, cardiac diseases, IBD, and diverticular disease. The number of patients enrolled with these diseases in clinical trials was generally small, except for RI, where many patients in the key trials (NOCT and MORA) had mild RI; moderate RI was noted in a few patients and none had severe impairment. The following is a summary of number of TEAEs and percentage of patients (%) with these events, in the various disease subgroups:

Table 82: Proportions and percentages of TEAEs by disease subgroups

	NOCT (2-day Split)		MORA		
	NER1006 (N = 262)	Trisulfate (N = 265)	NER-1 (N = 269)	NER-2 (N = 262)	MoviPrep (N = 263)
Diabetes					
Yes	4 (14.8)	4 (11.4)	3 (15)	5 (33.3)	3 (50)
No	68 (28.9)	45 (19.6)	46 (18.5)	41 (16.6)	28 (10.9)
Renal Impairment					
Mild	48 (29.3)	27 (16.9)	28 (15.2)	29 (16.5)	19 (11)
Moderate	1 (50)	1 (100)	4 (28.6)	4 (33.3)	0
None	23 (24.2)	21 (20.4)	17 (25)	13 (18.3)	12 (15.6)
Cardiac Diseases					
Yes	3 (30)	2 (18.2)	17 (25)	13 (18.3)	12 (15.6)
No	69 (27.4)	47 (18.5)	47 (17.9)	45 (17.4)	28 (10.9)
IBD					
Yes	0	1 (20)	1 (20)	0	1 (25)
No	72 (27.8)	48 (18.5)	47 (17.9)	45 (17.4)	28 (10.9)
Diverticular Disease					
Yes	22 (22.7)	17 (16.2)	5 (25)	8 (33.3)	0
No	50 (30.3)	32 (20)	49 (18.2)	45 (17.3)	31 (11.9)

source: Compiled from applicant's Table 8-27 [Integrated summary of safety, ISS; pages 59-60]

Reviewer comments:

The number of patients with diabetes, moderate RI, IBD and cardiac disease in clinical trials is too small to make a reasonable conclusion about the drug-disease relationship as it relates to safety. The incidence of TEAEs in patients with mild RI was generally comparable to that of patients who had normal renal function. There were no patients with severe RI. There were a considerable number of patients with diverticular disease in the NER1006 and trisulfate groups of Study NOCT; the incidence of TEAEs appears generally comparable in patients in this study, regardless of disease state. Overall, no consistent trends could be discerned regarding drug-disease interactions.

7.5.4.1 Safety in Patients with Renal Impairment

In the development program, patients with mild to moderate RI were permitted to enroll. The majority of those enrolled with RI had mild impairment (NOCT and MORA; GFR $\geq$ 60 - 89 mL/min/1.73m²). The number of patients with moderate RI (MORA only; GFR $\geq$ 30 to 59 mL/min/1.73m²) was too low to draw meaningful conclusions about safety in this population.

The identified adverse events and laboratory abnormalities associated with treatment with NER1006 were mostly related to dehydration and electrolyte changes. In patients with baseline RI, these types of fluid shifts could put patients at risk of worsened renal function, or acute-on-chronic renal injury.

To assess this potential, the Applicant was asked to provide an assessment of patients who developed either of the following (derived from RIFLE criteria²¹): a rise in creatinine of > 0.3 mg/dL (compared to baseline) or a decrease in calculated creatinine clearance of >25% (compared to baseline).

The results of this analysis are summarized in the tables below. In Table 83 below, patients are grouped by renal function cohort, and the numbers of patients meeting either criteria for creatinine or creatinine clearance are noted by visit. The numbers of patients in any arm meeting either or both of these criteria are very low, limiting the ability to draw conclusions about comparative safety between drug and comparator; however, no evidence of signal of renal injury related to study drug is noted.

Table 83: Proportion of Patients with Change in Renal Function Parameters (Creatinine, and/or Creatinine Clearance) by Baseline Renal Function

Renal Function Cohort, based on Screening Status	Visit #	NOCT		MORA		
		Trisulfate n/N (%)	NER-2 n/N (%)	Moviprep n/N (%)	NER-1 n/N (%)	NER-2 n/N (%)
Normal	Visit 2	9/103 (8.7)	8/93 (8.6)	0/76	3/69 (4.3)	0/71
	Visit 3	6/99 (6.1)	3/92 (3.3)	0/74	1/69 (1.4)	1/71 (1.4)
	Visit 4	4/87 (4.6)	1/78 (1.3)	0/59	1/54 (1.9)	1/58 (1.7)
Mild RI	Visit 2	5/158 (3.2)	6/164 (3.7)	1/167 (0.6)	4/172 (2.3)	0/168
	Visit 3	6/154 (3.9)	0/161	3/170 (1.8)	2/175 (1.1)	0/172
	Visit 4	4/130 (3.1)	4/127 (3.1)	2/141 (1.4)	2/147 (1.4)	1/129 (0.8)
Moderate RI	Visit 2	0/1	0/2	0/11	0/15	1/13 (7.7)
	Visit 3	0/1	0/2	0/11	0/15	0/13
	Visit 4	0/0	0/1	0/10	0/11	0/11

RI= renal impairment

N= number of patients within each cohort with serum Cr and/or creatinine clearance data at baseline and at the indicated visit

n= the subset of N who had an abnormal value indicative of possible acute kidney injury (defined as either a rise in creatinine of >0.3mg/dL above baseline and/or a decrease in calculated creatinine clearance of >25% from baseline) at the indicated visit.

source: reviewer's table created from data submitted by applicant in response to IR received 3/27/18

Noting that 1) important changes in these parameters that might suggest acute renal injury (or acute-on-chronic injury) particularly if due to prerenal causes such as dehydration, may not be evident until 24-48 hrs post-procedure and 2) if the change was clinically important, it would persist, additional analysis of persistence of abnormalities was conducted. The analysis in Table 84 shows patients who met either of these criteria (rise in creatinine or decline in creatinine

²¹ Bellomo, et al. Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the second international consensus conference of the acute dialysis quality initiative (ADQI) group. Critical Care 2004. <https://doi.org/10.1186/cc2872>

clearance) at Visit 3, and in whom the abnormal parameter persisted to the subsequent follow-up visit (Visit 4).

Table 84: Proportion of Patients in whom Changes in Renal Function Parameters (Creatinine, and/or Creatinine Clearance) at Visit 3 also Persisted at Visit 4, by Baseline Renal Function

		NOCT n/N (%)		MORA n/N (%)		
	Visit 4	Trisulfate M=271 n/N (%)	NER2 M=275 n/N (%)	MOVIPREP M=269 n/N (%)	NER1 M=271 n/N (%)	NER2 M=265 n/N (%)
Normal Renal Function	Creatinine	1/88 (1.1)	0/81	0/59	0/54	0/58
	Creatinine Clearance	1/93 (1.1)	0/82	0/59	0/54	0/58
Mild Renal Impairment	Creatinine	0/131	0/131	0/143	0/147	0/130
	Creatinine Clearance	1/136 (0.7%)	0/138	1/143 (0.7)	1/147 (0.7)	0/130
Moderate Renal Impairment	Creatinine	0/0	0/1	0/10	0/11	0/11
	Creatinine Clearance	0/0	0/1	0/10	0/11	0/11

M= number of patients in analysis set

For creatinine:

N= number of patients in the renal function cohort with increase in creatinine of >0.3mg/dL from baseline at visit 3 and have data at visit 4 or decreased creatinine clearance of >25% at visit 3 and visit 4

n= number of patients in the renal function cohort with increase in creatinine of >0.3mg/dL at visit 3 and at visit 4.

For creatinine clearance:

N= number of patients in the renal function cohort who have a decrease relative to baseline in creatinine clearance of >25% at visit 3 and have data at visit 4

n= number of patients in the renal function cohort who have a decrease relative to baseline in creatinine clearance of >25% at visit 3 and at visit 4

source: reviewer's table adapted from applicant's response to IR dated 3/27/18, Table 4

Reviewer comment:

These data are reassuring in that even among patients with RI at baseline, any worsening in renal function parameters after treatment rarely persisted. Thus, this reviewer concludes that among patients with mild RI, the safety of Plenvu appears to be comparable to those with normal baseline renal function. The number of patients enrolled and with follow up data within the "moderate RI" cohort is too small to make any conclusion regarding safety in this sub-population.

Following a request from the Division, the Applicant identified and provided narratives on additional patients who received NER1006 in NOCT (n = 8) or MORA (n = 5) in whom a decline in creatinine clearance (CrCl) was noted relative to baseline and had not resolved by the final visit. A brief overview of the patient narratives is provided below (information from the Applicant's IR response dated 03/27/2018).

NOCT: All 8 patients with declining CrCl received the bowel preparation for screening/surveillance colonoscopy and had a successful study outcome. These patients also had a corresponding rise in serum creatinine. The CrCl change was deemed to be of CTCAE Grade 1

at the final visit in all patients. Only one patient was over 65 years of age. None of the patients experienced adverse events. Medical history included hypertension and/or hyperlipidemia in most, and patients were on medications for these conditions. The narratives for two of these patients included an investigator comment that further clinical evaluation was not considered necessary based on evaluation of all labs.

MORA: Of the 5 patients with declining renal function parameters at the final visit, 3 were elderly (> 65 years). Two elderly patients had baseline CrCl values that were indicative of moderate RI. All patients also exhibited a corresponding rise in serum creatinine. Urinalysis, EKG and physical exams were normal. All but 2 patients had co-existing medical conditions and were on concomitant medications. Three patients had no adverse events. The other two, both elderly with baseline moderate RI, experienced TEAEs including dizziness, thirst, and nausea. Follow-up investigator comments available for four patients, indicated that further clinical evaluations were either not found to be clinically necessary or were found to be normal, including improving values for renal parameters in one of the two elderly patients at 3-months post-study. Investigators relayed no concerns for acute renal injury/deterioration of renal function in any of the patients.

Reviewer comment:

Available data on renal function parameters, including in patients with baseline mild RI do not indicate a risk for acute renal injury after using NER1006. Data in patients with moderate (or worse) RI are either very limited or lacking, and therefore it is not possible to rule out a potential risk to renal function in this population.

7.5.5 Drug-Drug Interactions

No drug-drug interaction studies were performed.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No human carcinogenicity studies were performed.

7.6.2 Human Reproduction and Pregnancy Data

No formal studies with NER1006 were conducted in pregnant women.

7.6.3 Pediatrics and Assessment of Effects on Growth

In the agreed initial Pediatric Study Plan (iPSP) for NER1006 Powder for Oral Solution, dated 09/12/2016, the Applicant requested a waiver of studies in infants and toddlers aged less than 1 year, for the following reason: 'NER1006 does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group and is not likely to be used by a

substantial number of pediatric patients in that age group (Section 505B(a)(4)(B)(iii) of the Act).’

The Applicant requested a deferral for clinical trials in pediatric patients aged 12 to < 18 years, 2 to < 12 years and 1 to < 2 years of age, for the proposed indication of ‘cleansing of the colon in preparation for colonoscopy.’ The Applicant proposed to conduct randomized, active/standard of care comparator-controlled, pediatric clinical trials in each of these age cohorts, including dose determination and PK evaluation. It proposed to defer the initiation of all proposed pediatric studies until evaluation of the integrated safety and efficacy data following completion of the three phase 3 adult Clinical Study Reports.

This application triggered PREA and the following planned pediatric studies were discussed with the Pediatric Research Committee (PeRC) on 3/14/18:

3371-1: A study to evaluate safety, efficacy, tolerability, palatability and acceptability of PLENVU vs an approved comparator in patients 12 to < 18 years of age. The study will include dose determination and PK evaluation.

3371-2: A study to evaluate safety, efficacy, tolerability, palatability and acceptability of PLENVU vs an approved comparator in patients 2 to < 12 years of age. The study will include dose determination and PK evaluation.

3371-3: A study to evaluate safety, efficacy, tolerability, of PLENVU vs an approved comparator in patients 1 to < 2 years of age. The study will include dose determination and PK evaluation.

Refer to the approval letter for milestone dates.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no cases of overdose reported during the clinical trials; there does not appear to be any potential for abuse, withdrawal or rebound, based on the other osmotic bowel cleansing products.

7.7 Additional Submissions / Safety Issues

There are ongoing theoretical concerns related to products with contain PEG3350. Specifically, there is concern that while absorption of PEG3350 is minimal, what is absorbed systemically could potentially degrade to more toxic degradants, such as diethylene glycol, ethylene glycol, and its secondary metabolites including glycolic acid, diglycolic acid, oxalic acid and/or hydroxyethoxyacetic acid.

As a result, until sufficient data on this theoretical safety concern are available, the Division requires all new products containing PEG3350 to assess the PK of PEG3350 and its potential

metabolites. Because these issues were not adequately addressed pre-approval, the Division will issue a post-marketing required study to assess as follows:

3371-4: A phase 1 pharmacokinetic trial to adequately characterize the PK of PEG 3350 and its metabolites, diethylene glycol (DEG), and ethylene glycol (EG), and its secondary metabolites such as glycolic acid (GA), diglycolic acid (DGA), Oxalic acid (OA) and hydroxyethoxyacetic Acid (HEAA) in healthy subjects. Adequate bioanalytical assay methods with acceptable sensitivity should be developed for all analytes.

8 Postmarket Experience

NER1006 is not marketed in the US or other countries.

9 Other Information

9.1 Labeling Recommendations

Final labeling negotiation was ongoing at the time this review was finalized. Refer to the approval letter for the final label.

During the NDA review, several labeling changes were recommended by the Division to ensure accuracy, enhance flow and reduce redundancies.

Key changes included:

Section 6:

Section 6.1 of the Clinical Trial Experience section of the proposed prescribing information for Plenvu was revised to incorporate summary tables of TEAEs occurring in $\geq 1\%$ of patients with one or more treatments in clinical trials NOCT and MORA. The list of less common TEAEs was also updated. A summary of relevant changes in electrolytes was included.

Demographic information for the clinical trial population was also incorporated into Section 6.1 to clarify that the population studied included those with mild to moderate renal impairment. Section 6.2 was updated with post-marketing experience from a related product containing identical active ingredients to those in Plenvu.

Class language regarding caution in use in patients with renal impairment was retained. As described in the review above, while the safety of Plenvu appears to be comparable in patients with mild RI (compared to the general population), there were insufficient numbers of patients with moderate RI to draw any conclusion regarding safety in this population. Further, there is theoretical increased susceptibility to adverse events in patients with RI, and this warrants caution on behalf of providers and patients to ensure adequate hydration and attention to electrolyte balance.

Efficacy: Section 14: Efficacy results were limited to the primary endpoint of “success in the overall colon,” as the Division did not agree with the Applicant’s proposed co-primary endpoint of success in the colon ascendens (refer to detailed discussion in regulatory history section above).

Clinical Pharmacology: Changes were recommended to Section 12 to include PK data on the active ingredients.

PLLR: Changes were made to the label in collaboration with DPMH colleagues to ensure compliance with PLLR format.

Instructions for Use: Modifications to the Instructions for Use were recommended in consultation with patient labeling colleagues to ensure clear and concise instructions that patients can understand. Emphasis was placed on ensuring that the timing of the 2 doses and instructions for “additional fluid” requirements and recommendations were clear.

9.2 Advisory Committee Meeting

No advisory meeting was convened.

10 Appendices

Appendix-A: Studies supporting the combination rule

NER1006 is a combination product consisting of two drugs in Dose 1 and three drugs in Dose 2; therefore, the Fixed-Combination Drug Rule (21 CFR 300.50²²) is applicable.

Background:

The active ingredients (PEG 3350, sulfates and ascorbates) of NER1006 have been used alone or in combination in previously approved bowel preparations. The active ingredients in NER1006 are same as in MOVIPREP bowel preparation (this drug was previously owned by the Applicant) but with different concentrations. The studies conducted during the MOVIPREP development program, NER1006 program and supportive literature together support compliance with the Fixed-Combination Drug Rule, and are summarized below:

MOVIPREP Program:

The following two studies were conducted in healthy subjects to explore the contribution of Vitamin C (sodium ascorbate/ascorbic acid) and sodium sulfate on the stool output generated by PEG.

- Study N98002 (Report N98002): This proof-of-concept study showed that 210 g of PEG 3350 alone produced a stool weight of 1460 g (treatment group A); addition of 20 g Vitamin C (treatment group B), produced an additional ~400 g stool, i.e., a 25% increase of the stool weight. Further addition of (b) (4) sodium sulfate (treatment group C) increased the stool output by additional 873 g stool, which reached the target stool output level of >2.5 L (Table A-1).

Table A-1: MOVIPREP pharmacodynamic results – Study N98002

	A	B	C
	Reference solution (210 g PEG in 2 L)	PEG (210 g) + Vit C (20 g) solution (2 L)	PEG (210 g) + Vit C (b) (4) Sodium sulfate solution (2 L)
Stool weight, [g]	1465.2 ± 56.7	1862.0 ± 140.8	2735 ± 199
P-value (Treatment vs. Reference)		<0.002	<0.001

PEG = polyethylene glycol; Vit C = vitamin C.

source: Table 2.7.2.5 of the Applicant's submission, Module 2.7.2.: Clinical Summary – Summary of Clinical Pharmacology Studies

²² Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug. <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=300.50>

- Study N00/01 (Report N00/01, 2000): This study was conducted to evaluate the contribution of PEG 3350, sodium ascorbate and ascorbic acid (ASC), as well as sodium sulfate in a cross-over fashion in 30 healthy subjects. Different combinations of PEG 3350 (100 g), sodium sulfate (5 and 7.5 g) and ASC (0, 5, and 10 g) were tested and the stool volume measured (Table A-2 and Figure A-1). This study showed that the addition of 20 g ascorbate components (treatment groups C and D) to the 200 g PEG 3350/15 g sodium sulfate formulation (treatment group A) generated an additional 600-700 mL stool, slightly more than in study N98002. Also, the addition of 5 g sodium sulfate (treatment group C) to the 200 g PEG 3350/10 g sodium sulfate/20 g ascorbate components formulation (treatment group E) generated an additional ~410 mL stool, i.e., each gram of sodium sulfate generated about 82 g stool.

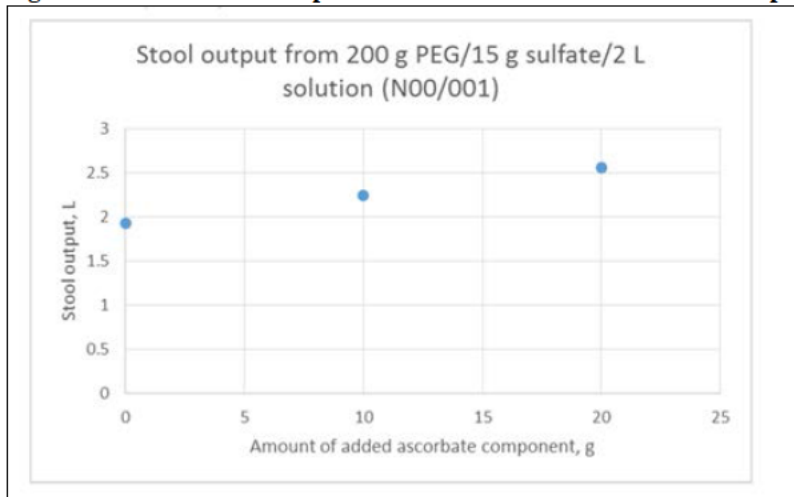
Table-A-2: Overall dose for 2 liter solution by treatment group and total stool volume - Study N00/01

Treatment groups	A	B	C	D	E
Formulation [g]	(b) (4)				
PEG 3350					
Sodium sulfate					
Ascorbic acid					
Sodium ascorbate					
Total stool volume [L]					
N	10	10	10	10	10
Mean (SD)	1.93 (0.598)	2.25 (0.437)	2.61 (0.538)	2.51 (0.442)	2.20 (0.369)
Range	0.65 - 2.62	1.58 - 2.84	1.80 - 3.40	1.44 - 3.08	1.49 - 2.60

N = number of subject in treatment group; PEG = poly ethylene glycol; SD = standard deviation.

source: Table 2.7.2.6 of the Applicant's submission, Module 2.7.2.: Clinical Summary – Summary of Clinical Pharmacology Studies

Figure A-1: Ascorbate component dose-related increase in stool output (N00/01)



source: Figure 2.7.2-3 of the Applicant's submission, Module 2.7.2.: Clinical summary – summary of clinical pharmacology studies

Reviewer comments:

The studies of the MOVIPREP program show that the addition of the 20 gm ascorbate component to PEG alone will not be effective to produce the targeted volume of stool output. The

combination of PEG 3350, ASC and sodium sulfate is effective in increasing the stool output compared to PEG 3350 alone. Also, the highest concentrations of ASC (20 g) and sodium sulfate (15 g) tested were more effective than the lower concentrations.

NER1006 Program:

The PD effects of different formulations of NER1006 were measured *in vitro* (osmolality) and *in vivo* (stool output). The basic principle of the studies is that there is no osmotic barrier between the colonic lumen and extracellular space; it is known that fecal water attains the osmolality of 350 mOsm/L, regardless of the concentration of PEG 3350 introduced into the gut. The introduction of a hyperosmotic load stimulates equalization of this osmolality via osmosis. The osmolality of a drug is generally calculated based on volume of deionized water to be added to powder formulation to reach an osmolality close to 350 mOsm/kg, i.e., the osmolality of fecal water (V350). The V350 represents the volume to which the osmotic component would expand in the human bowel, and thus the volume of stool that would be triggered.

In vitro studies:

The Applicant conducted a series of *in vitro* osmolality experiments to determine the V350 of different amounts of sodium sulfate (3, 6, and 9 g), PEG 3350 (20, 40, and 100 g) and ascorbate (30 and 50 g) using different formulations (A1-A3 and B1-B5). The evening dose and morning dose prototypes with formulations, volume of water added and osmolality are summarized in Table A-3. The A2, A3, and B3 formulations appear to be optimal, as they were associated with larger volumes of water added to achieve the osmolality of 350; these formulations were tested in a phase 1 study (OUT).

Table A-3: NER1006 prototype evening and morning dose: Formulation, volume of water added, and osmolality - *in vitro* experiments

Evening dose	A1	A2	A3
Formulation [g]			
PEG 3350	100	100	100
Sodium sulfate (b) (4)	3	6	9
Volume of water added [mL]	750	770	900
Osmolality [mOsm/L]	259	347	349

Morning dose	B1	B2	B3	B4	B5
Formulation [g]					
PEG 3350	20	20	40	20	40
Sodium ascorbate	50	30	30	30	30
Sodium sulfate (b) (4)	NA	NA	NA	6	NA
Ascorbic acid	NA	20	20	NA	NA
(b) (4)	NA	NA	NA	NA	20
Volume of water added [mL]	1425	1175	1250	1140	1263
Osmolality [mOsm/L]	335	338	335	345	354

NA = not applicable; PEG = polyethylene glycol.

source: Table 2.7.2.7 of the Applicant's submission, Module 2.7.2.: Clinical summary – summary of clinical pharmacology studies

• **NER1006-01/2011 [OUT] study**

Study design:

This was an open-label, randomized, single center, phase 1 study with two parts (A/B) to investigate the PD effects (stool weight) of various modified low volume PEG+ASC prototypes and MOVIPREP® (Table A-4).

Table A-4: Study NER1006 –OUT

Type of study	Study identifier	Objectives	Study design and type of control	Test/comparator product; dosage regimen; route of administration	Study subjects	Treatment duration	Study status
Phase I (PD and PK)	NER1006-01/2011 (OUT) (EudraCT 2011-000271-14, NCT01834742) (Romania)	To investigate PD, PK and safety of various modified low volume PEG 3350+ASC-based gut cleansing solutions	Open-label, randomized, single center study with two parts (A and B); active comparator drug: MOVIPREP®	Part A: NER1006 prototypes: three variable evening doses reconstituted with water up to 750 mL each and fixed morning dose reconstituted with water up to 500 mL; Oral. MOVIPREP®: fixed evening and fixed morning doses; Powder for oral solution, reconstituted with water up to 1 L Part B: NER1006 prototypes: Fixed evening dose and four variable morning doses; reconstituted each with water up to 500 mL; Oral All Products: 2-Day split-dosing regimen: in the evening of Day 1 (day before colonoscopy) and in the morning of Day 2	Healthy subjects Part A: 81 Part B: 80 18 - 45 years of age	2 days +2 days follow-up (4 days total)	Complete (CSR available; Module 5.3.4.1)

source: Applicant's submission, Module 2.7.2.: Clinical summary – summary of clinical pharmacology studies

Part A of the OUT study (NER1006-01/2011) explored three evening formulations; the active ingredients of the three evening formulations (E2, E3, and E-IP) and one morning formulation (M3) were tested; although the active ingredients of the E2, E3, and M3 formulations were same as the A2, A3 and B3 formulations, respectively, tested *in vitro*, the concentrations of the different ingredients varied (Tables A-3 and A5); E-IP was not tested *in vitro*. The volume of the evening dose of the three formulations (E2, E3, and E-IP) was 750 mL and that of the morning dose formulation (M3) was 500 mL. The volume of MOVIPREP evening and morning doses was 1,000 mL each.

In Part B, the morning M3 formulation was modified to 4 different formulations (M1, M4, M5, M-IP) and these were tested (Table A-6). The evening formulations tested, E2 and E3, were the same as in Part A (Table A-7).

Each of the evening and morning formulations were tested for osmolality *in vitro* as well as stool output.

Table A-5: Formulations of Part A of OUT study – quantities of osmotically active ingredient and electrolytes.

Ingredient [g]	Evening dose in 750 mL			Morning dose M3 in 500 mL	MOVIPREP® Even + Morn. in 2000 mL
	E2	E3	E-IP		
PEG 3350	100	100	75	40	200
Sodium sulfate	6.0	9.0	5.6	-	15.0
Sodium ascorbate	-	-	-	33.9	11.8
Ascorbic acid	-	-	-	20.1	9.4
Sodium chloride	1.6	2.0	2.0	2.8	5.4
Potassium chloride	0.7	1.0	0.8	1.3	2.0
Osmolality of powder dose					
Volume (mL) of water to be added to achieve osmolality of approx. 350 mOsm/kg	915	1080	795	1600	1235 + 1235

PEG = polyethylene glycol.

source: Table 2.7.2.11 of the Applicant's submission, Module 2.7.2.: Clinical summary – summary of clinical pharmacology studies

Table A-6: Formulations of Morning Doses in Part B of OUT Study – Quantities of Osmotically Active Ingredients and Electrolytes

Ingredient [g]	M1 in 500 mL	M4 in 500 mL	M5 in 500 mL	M-IP in 500 mL
PEG 3350	40	40	40	(b) (4)
Sodium sulfate	-	6.0	-	
Sodium ascorbate	56.6	33.9	33.9	
Ascorbic acid	-	-	-	
Sodium chloride	3.5	2.8	3.1	
Potassium chloride	2.2	2.0	1.3	
(b) (4)	-	-	-	
Osmolality of powder dose				
Volume (mL) of water to be added to achieve osmolality of 350 mOsm/kg	2000	1700	1700	950

PEG = polyethylene glycol.

source: Table 2.7.2.12 of the Applicant's submission, Module 2.7.2.: Clinical summary – summary of clinical pharmacology studies

Table A-7: NER1006 and MOVIPREP regimens used in OUT study

Part A				
Interval	E2 (in 750 mL)	E3 (in 750 mL)	E-IP (in 750 mL)	MOVIPREP® (in 1000 mL)
Evening				
Mandated additional clear fluid	+875 mL	+875 mL	+875 mL	+500 mL
Morning	M3 (in 500 mL)	M3 (in 500 mL)	M3 (in 500 mL)	MOVIPREP® (in 1000 mL)
Mandated additional clear fluid	+875 mL	+875 mL	+875 mL	+500 mL
Osmolality of total powder dose				
Volume (mL) of water to be added to achieve osmolality of 350 mOsm/kg	2515	2680	2395	2470
Part B				
Evening	E3 (in 750 mL)	E3 (in 750 mL)	E3 (in 750 mL)	E3 (in 750 mL)
Mandated additional clear fluid	+875 mL	+875 mL	+875 mL	+875 mL
Morning	M1 (in 500 mL)	M4 (in 500 mL)	M5 (in 500 mL)	M-IP (in 500 mL)
Mandated additional clear fluid	+875 mL	+875 mL	+875 mL	+875 mL
Osmolality of total powder dose				
Volume (mL) of water to be added to achieve osmolality of 350 mOsm/kg	3080	2780	2780	2030

E = evening dose; M = morning dose.

Note: Total intake volume for every formulation tested was 3 L.

source: Table 2.7.2.13 of the Applicant's submission, Module 2.7.2.: Clinical summary – summary of clinical pharmacology studies

Results:

- Effect of either evening and morning dose on osmolality:**

Evening formulation: In PART A of the study, the E3 formulation was osmotically more effective compared to E2 (Table A-5). Therefore, E3 was selected as the standard evening dose for PART B of the study.

Morning formulation: The results of the PART A and PART B of the study showed that the M1 formulation was osmotically more effective compared to M4 formulation (Table A-6). M1 formulation used in PART B had slightly higher amount of ascorbate compared to M3 used in PART A of the trial (56.6 g in M1 compared to 54 g in M3 formulation).

- Effect of a combination of evening and morning doses on osmolality**

The results show that the combination of E3/M1 resulted in optimal osmolality (Table A-6).

- Effect of a combination of evening and morning doses on stool output**

The results show that the combination of E3/M1 resulted in optimal stool output (Table A-8). This correlates with the *in vitro* findings discussed above.

Table A-8: Summary statistics for stool weights from the start of the intake to 24 hours after (OUT study)

Part A (variable E dose)	Sum of stool weight [g] (Median [Q1; Q3])			
	E2/M3 (N = 19)	E3/M3 (N = 19)	E-IP/M3 (N = 18)	MOVIPREP® (E and M) (N = 16)
	2981.30 [2741.55; 3435.55]	3493.20 [2982.40; 3804.30]	2796.80 [2641.00; 3296.25]	3145.95 [2643.95; 3280.65]
Part B (variable M dose)	E3/M1 (N = 20)	E3/M4 (N = 20)	E3/M5 (N = 19)	E3/M-IP (N = 20)
	3128.90 [2299.05; 3433.15]	2546.00 [1666.70; 3199.20]	2440.10 [1620.55; 3449.30]	2466.85 [2059.70; 2912.35]

E = evening dose; M = morning dose; N = number of subjects; SD = standard deviation; Q1 = 1st quartile; Q3 = 3rd quartile.

source: Table 2.7.2.15 of the Applicant's submission, Module 2.7.2.: Clinical summary – summary of clinical pharmacology studies

Reviewer comments:

The study shows that the active ingredients in E3/M1 formulations showed optimal osmolality and stool output. However, the volumes of E3 and M1 administered, with mandatory fluid intake, were in the range of 3 L compared to 2L in the clinical trial.

• **NER1006-01/2012 [OPT] study**

Study design

The E3 and M1 formulations were tested in a phase 2 (OPT) study (Table A-9) to evaluate the effect of reduced volume of E3 and low ascorbate concentration in the M1 dose. Also, the M1 formulations were optimized for electrolytes, taste and flavor. To improve the flavor of the M1 formulation, some of the sodium ascorbate was replaced by ascorbic acid (TF043); however, the amount of ascorbate was the same.

Table A-9: Study OPT

Type of study	Study identifier	Objectives	Study design and type of control	Test/comparator product; dosage regimen; route of administration	Study subjects	Treatment duration	Study status
Phase II (PD and clinical results)	NER1006-01/2012 (OPT) (EudraCT 2012-003052-37, NCT01714466) (Germany)	Part A: To investigate PD, safety and tolerability of dose and taste optimized, low volume PEG/ASC-based formulations in healthy subjects Part B: To investigate clinical efficacy, PD, PK, safety and tolerability in subjects undergoing colonoscopy	Open-label, randomized, single center study with two parts (A and B); active comparator drug: MOVIPREP®	Part A: NER1006: Various permutations of evening and morning doses; Reconstituted in 500-750 mL water; Oral MOVIPREP®: fixed evening and fixed morning doses; Powder for oral solution, reconstituted with water up to 1 L Part B: NER1006: Variations of Part A-selected regimen OPT003; Reconstituted in 500 mL water; Oral; MOVIPREP®, same as Part A Both products: 2-Day split-dosing regimen: in the evening of Day 1 (before colonoscopy) and in the morning of Day 2	Part A: 117 healthy subjects, 40 - 70 years of age Part B: 120 Subjects undergoing screening colonoscopy, 55 - 70 years or 40 - 70 years of age with known risk of colon neoplasia	2 days	Complete (CSR available; Module 5.3.4.2)

ASC = Ascorbic Acid/Ascorbate; CSR = clinical study report; PEG = poly ethylene glycol; PD = pharmacodynamics; PK = pharmacokinetic.
Source: Section 9.4, NER100601/2011 (OUT) CSR, Module 5.3.4.1; Section 9.4, NER100601/2012 (OPT) CSR, Module 5.3.4.2.

The effect of all the four formulations, alone and in combination as evening and morning dose, on osmolality was measured (Tables A-10 and A-11).

The effect of combination of the evening and morning doses and different volumes of the two doses on stool output and/or bowel cleansing was conducted in two parts. In Part A, stool output in healthy volunteers was evaluated, whereas in Part B, stool output and bowel cleansing was evaluated in patients undergoing colonoscopy.

Each of the evening and morning formulations were evaluated for osmolality *in vitro* as well as stool output.

Table A-10: NER1006 formulations in OPT study: Quantities of osmotically active ingredients and electrolytes.

Ingredient [g]	TF048 (in 750 mL) = E3	TF047 (in 500 mL) "Reduced reconstitution volume" version of TF048	TF043 (in 500 mL) = M1	TF044 (in 500 mL) "Low ascorbate" version of TF043
PEG 3350	100	100	(b) (4)	
Sodium sulfate	9.0	9.0		
Sodium ascorbate	-	-		
Ascorbic acid	-	-		
Sodium chloride	2.0	2.0		
Potassium chloride	1.0	1.0		
Osmolality of powder dose				
Volume (mL) of water to be added to achieve osmolality of 350 mOsm/kg	1100	1125	1850	1500

PEG = polyethylene glycol.

source: Table 2.7.2.33 of the Applicant's submission, Module 2.7.2.: Clinical summary – summary of clinical pharmacology studies

Table A-11: NER1006 and MOVIPREP (OPT004) regimens used in OPT study

Interval	Part A			
	OPT001	OPT002	OPT003	OPT004
Evening	TF048 (in 750 mL)	TF043 (in 500 mL)	TF047 (in 500 mL)	MOVIPREP® (in 1000 mL)
Mandated additional clear fluid	+875 mL	+875 mL	+1000 mL	+500 mL
Morning	TF043 (in 500 mL)	TF048 (in 750 mL)	TF043 (in 500 mL)	MOVIPREP® (in 1000 mL)
Mandated additional clear fluid	+875 mL	+875 mL	+1000 mL	+500 mL
Total intake volume	3000 mL	3000 mL	3000 mL	3000 mL
Osmolality of total powder dose				
Volume (mL) of water to be added to achieve osmolality of 350 mOsm/kg	2950	2950	2975	2470
	Part B			
	OPT003	OPT007	OPT006	OPT004
Evening	TF047 (in 500 mL)	TF047 (in 500 mL)	TF047 (in 500 mL)	MOVIPREP® (in 1000 mL)
Mandated additional clear fluid	+1000 mL	+500 mL	+1000 mL	+500 mL
Morning	TF043 (in 500 mL)	TF043 (in 500 mL)	TF044 (in 500 mL)	MOVIPREP® (in 1000 mL)
Mandated additional clear fluid	+1000 mL	+500 mL	+1000 mL	+500 mL
Total intake volume	3000 mL	2000 mL	3000 mL	3000 mL
Osmolality of total powder dose				
Volume (mL) of water to be added to achieve osmolality of 350 mOsm/kg	2975	2975	2625	2470

source: Table 2.7.2.34 of the Applicant's submission, Module 2.7.2.: Clinical summary – summary of clinical pharmacology studies

Results:

Effect on osmolality

The results in Table A-10 show that the new evening formulation (TF047) and the morning formulation (TF043) with reduced reconstitution volume (500 mL) achieved optimal osmolality.

The effect of a combination of the evening and morning doses on osmolality, with different fluid intake, was measured in two parts. Part A was a 4-arm study; NER1006 was reconstituted with different volumes of water for subjects in the three groups (OPT001, OPT002, and OPT003), and MOVIPREP was administered to subjects in OPT004. The results in Table A-11 show that the osmolality was optimal in the OPT003 group compared to other groups.

In Part B of the study, the effect of reduced total mandatory fluid intake (OPT007) on osmolality was compared with the OPT003 group. Also, OPT004 (MOVIPREP) was included as a comparator. The total volume intake for OPT007 was 2000 mL and for OPT004 and MOVIPREP 3000 mL. The results in Table A-11 show that the osmolality was the same in

OPT003 and OPT007 groups despite lower volume intake in the OPT007 group compared to OPT003.

• **Effect on stool output and bowel cleansing**

The results of the Part A of the study show that the stool output was optimal in the OPT003 group compared to other groups (Table A-12). In Part B of the study, the stool output was optimal in OPT007 group (Table A-12). The evening and morning doses and the total mandatory fluids required for NER1006 used in the clinical studies are same as in the OPT007 group.

Table A-12: shows summary statistics for the stool weights (OPT Study)

Statistic	Part A			
	OPT001 (N=30)	OPT002 (N=29)	OPT003 (N=30)	MOVIPREP® (N=30) ^a
Mean (SD) [g]	2951.0 (873.77)	3218.7 (809.89)	3399.3 (575.78)	2490.8 (879.24)
Median (range) [g]	2978.75 (729.2 - 4328.5)	3326.20 (912.0 - 4559.1)	3513.00 (2114.5 - 4216.9)	2597.40 (375.8 - 4505.0)
[90% CI]	[2679.99;3222.10]	[2962.85;3474.52]	[3220.65;3577.88]	[2213.02;2768.51]
p-value ^b	0.2176	0.0042	<0.0001	0.8764

	Part B			
	OPT003 (N=30)	OPT007 (N=30)	OPT006 (N=30)	MOVIPREP® (N=30)
Mean (SD) [g]	3050.5 (705.41)	3215.1 (634.25)	2675.3 (612.15)	2487.1 (634.69)
Median (range) [g]	3065.70 (1357.9 - 4102.0)	3290.20 (1501.7 - 4433.3)	2657.95 (1153.8 - 3846.8)	2636.40 (968.9 - 3430.8)
[90% CI]	[2831.62;3269.28]	[3018.32;3411.84]	[2485.41;2865.21]	[2290.25;2684.03]
p-value ^b	0.0268	0.0004	0.4907	0.9691

CI = confidence interval; N = number of subjects with data; SD = standard deviation.

source: Table 2.7.2.36 of the Applicant's submission, Module 2.7.2.: Clinical summary – summary of clinical pharmacology studies

The bowel cleansing was measured in Part B of the study. The results in Table A-13 show that cleansing success (Grade A and B) was 100% in OPT003 and OPT007 groups compared to 90% in OPT006 and MOVIPREP groups.

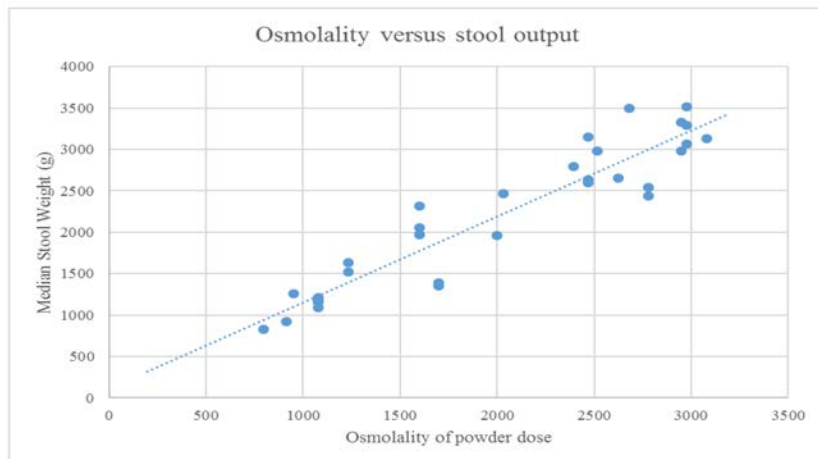
Table A-13: Cleansing rate (OPT Study)

Treatment	n (%) with Success	Comparison Against MOVIPREP®	
		90% CI	p-value ^a
OPT003	30 (100)	[0.88;1.00]	0.2373
OPT007	30 (100)	[0.88;1.00]	0.2373
OPT006	27 (90)	[0.02;0.27]	1.0000
MOVIPREP®	27 (90)	-	-

source: Table 2.7.3.2.2 of the Applicant's submission, Module 2.7.3: Clinical summary – summary of clinical pharmacology studies

Overall, the results of the two studies [Phase I NER1006-01/2011(OUT) and NER1006-01/2012(OPT)] show an association between osmolality and stool output (Figure A-2 and Table A-14).

Figure A-2: Relationship of osmolality* to stool output from start of first dose and following 24 hours for total NER1006 formulations used in the OUT and the OPT studies and the dose 1 and dose 2 formulations used in the OUT Study



The osmolality and median stool output data points used to construct the Figure are from the phase I (OUT) and phase II (OPT) studies conducted by the Applicant to explore the ideal weight combination of the individual active ingredients for the final product. The amount of total dose, osmolality and median stool output with several of these formulations tested in OUT and OPT studies are shown.

* Osmolality of powder dose = Volume of deionized water to be added to powder formulation to reach an osmolality close to 350 mOsm/kg, the osmolality of fecal water ('V350')

source: Figure 2.7.2-1 of the Applicant's submission, Module 2.7.2.: Clinical summary – summary of clinical pharmacology studies

Table A-14: Osmolality and median stool output data points used in Figure 1

Formulation	Amount of Total Dose	Osmolality, V350 (mL)	Median Stool Output (g)	Formulation	Amount of Total Dose	Osmolality, V350 (mL)	Median Stool Output (g)
E2/M3	Dose 1 + Dose 2	2515	2981	E2-Part A	Dose 1 only	915	925.8
E3/M3	Dose 1 + Dose 2	2680	3493	M3-Part A	Dose 2 only	1600	2055.5
E-IP/M3	Dose 1 + Dose 2	2395	2797	E3-Part A	Dose 1 only	1080	1178.5
MOVIPREP®	Dose 1 + Dose 2	2470	3146	M3-Part A	Dose 2 only	1600	2314.7
E3/M1	Dose 1 + Dose 2	3080	3129	E-IP-Part A	Dose 1 only	795	826.7
E3/M4	Dose 1 + Dose 2	2780	2546	M3-Part A	Dose 2 only	1600	1970.1
E3/M5	Dose 1 + Dose 2	2780	2440	MOVIPREP® E-Part A	Dose 1 only	1235	1629.2
E3/M-IP	Dose 1 + Dose 2	2030	2467	MOVIPREP® M-Part A	Dose 2 only	1235	1516.8
OPT001	Dose 1 + Dose 2	2950	2979	E3-Part A	Dose 1 only	1080	1170
OPT002	Dose 1 + Dose 2	2950	3326	M1-Part B	Dose 2 only	2000	1958.9
OPT003	Dose 1 + Dose 2	2975	3513	E3-Part A	Dose 1 only	1080	1156.5
OPT004 (MOVIPREP®)	Dose 1 + Dose 2	2470	2597	M4-Part B	Dose 2 only	1700	1389.5
OPT003	Dose 1 + Dose 2	2975	3065	E3-Part A	Dose 1 only	1080	1091.1
OPT007	Dose 1 + Dose 2	2975	3290	M5-Part B	Dose 2 only	1700	1349
OPT006	Dose 1 + Dose 2	2625	2658	E3-Part A	Dose 1 only	1080	1210.7
OPT004 (MOVIPREP®)	Dose 1 + Dose 2	2470	2636	M-IP-Part B	Dose 2 only	950	1256.2

source: Table 2.7.2.-2 of the Applicant's submission, Module 2.7.2.: Clinical summary – summary of clinical pharmacology studies

Additional analysis: Osmolality of components of NER1006

At the request of the Division, the Applicant measured the contribution of osmolality of each active ingredient of the NER1006 used in phase 3 trials. The osmolality contribution of each of the non-absorbed active components of NER1006, as measured by V350, is shown in Table A-15. This supports that each of the active ingredient/components makes a contribution to the claimed effects.

Table A-15: Osmolality of components of NER1006, individually and in combinations

Osmolality (mL)	Active component	
700	PEG	140 g PEG 3350
1400	Ascorbate	48.11 g sodium ascorbate + 7.54 g ascorbic acid
400	Sulfate	9.0 g sodium sulfate
1750	Ascorbate + Sulfate	48.11 g sodium ascorbate + 7.54 g ascorbic acid + 9.0 g sodium sulfate
1100	PEG + Sulfate	140 g PEG 3350 + 9.0 g sodium sulfate
1850	PEG + Ascorbate	140 g PEG 3350 + 48.11 g sodium ascorbate + 7.54 g ascorbic acid

source: Table 2.7.2-3 of the Applicant's submission, Module 2.7.2.: Clinical summary – summary of clinical pharmacology studies

Supportive literature:

The published studies identified by the Applicant to support the contribution of PEG and sodium sulfate components of NER1006 are summarized below:

PEG:

Hammer et al (1989)²³ reported a dose-response relationship between the amount of PEG and amount of diarrhea; 192 g of PEG induced stool output of 1118 mL (Figure A-3). The Applicant's Study N98002 (part of the MOVIPREP program) also showed that 210 gm of PEG generated 1465 gm stool.

DiPalma and Marshall (1990)²⁴ reported that 420 g PEG in 4 L were required to get a clean bowel.

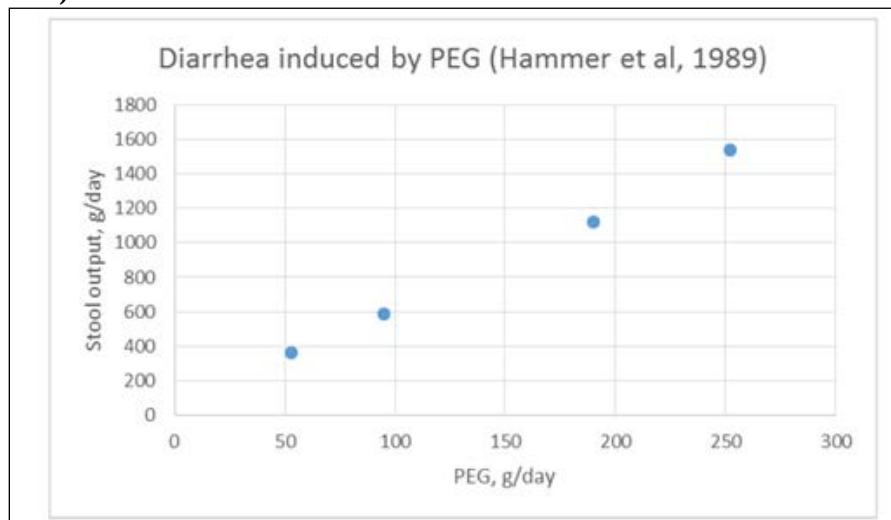
Patel et al, 2009²⁵ showed that 420 g PEG in a 4 L bowel preparation plus an additional 625 ml water gave a stool output of 3021 g.

23 Hammer et al. Studies of osmotic diarrhea induced in normal subjects by ingestion of polyethylene glycol and lactulose. J Clin. Invest. Volume 84, October 1989, 1056- 1062

24 DiPalma and Marshall et al. Comparison of a new sulfate-free polyethylene glycol electrolyte lavage solution versus a standard solution for colonoscopy cleansing. Gastrointest Endosc 1990; 36:285-289.

25 Patel et al. Intestinal and renal effects of low-volume phosphate and sulfate cathartic solutions designed for cleansing the colon: pathophysiological studies in five normal subjects. Am J Gastroenterol 2009; 104:953 – 965

Figure A-3: Dose response relationship between PEG administered and amount of diarrhea (Hammer et al 1989)



source: Figure 2.7.2-2 of the Applicant's submission, Module 2.7.2.: Clinical summary – summary of clinical pharmacology studies

Overall, the studies suggest that an effective dose of PEG is close to 420 g. Therefore, 140 gm of PEG alone, would not be able to generate sufficient stool output to give a clean bowel.

Sodium Sulfate

DiPalma 2009²⁶ reported that a 960 mL sulfate solution (35 g sodium sulfate, 6.3 g potassium sulfate and 3.2 g magnesium sulfate) with an additional 1920 mL of water were required to get a clean bowel. Patel et al, 2009²⁵ reported that a 200 mL sulfate solution (35 g sodium sulfate, 6.26 g potassium sulfate and 3.2 g magnesium sulfate) plus 3760 mL additional water generated 2854 gm stool. The studies show that the 9 g sodium sulfate alone on its own would not be able to clean the bowel.

Reviewer comments:

The studies show that each osmotically-active component, 140 g PEG, 9 g sodium sulfate and 56 (b) (4) ascorbate components, contributes to the efficacy of NER1006, and that lowering the concentrations of any of the osmotically-acting components in NER1006 would reduce its effectiveness proportionately. Based on the totality of the data presented, this reviewer concludes that the Combination Rule has been addressed.

26 DiPalma et al. A randomized clinical study evaluating the safety and efficacy of a new, reduced-volume, oral sulfate colon-cleansing preparation for colonoscopy. Am J Gastroenterol 2009; 104:2275–2284.

Appendix-D: Subject listing for Select Adverse Events of Interest (related to dehydration) across all 3 Studies

AE	NOCT		MORA			DAYB	
	NER1006 2-Day	Trisulfate	NER1006 2-Day	NER1006 1-Day	Moviprep	NER1006 Day Before	SP+MS*
	Patient ID	Patient ID	Patient ID	Patient ID	Patient ID	Patient ID	Patient ID
Dehydration	(b) (6)	(b) (6)				(b) (6)	None
Hypotension			None	None	None	None	None
GFR decreased			(b) (6)	None	None	None	(b) (6)
ALT increased		None	None	(b) (6)	None	None	(b) (6)
AST increased		None	None		None	None	None
Bilirubin increased	None	None	None	None	None	None	None
GGT increased	None	None	(b) (6)	None	None		(b) (6)
Syncope	None	(b) (6)	None	None	(b) (6)	None	None
Presyncope	(b) (6)		None	None	None	None	None
Fatigue			None	None	(b) (6)	None	None
Asthenia			None	None	None	None	None
Extreme tiredness	None	None	None	None	None	None	None

*SP+MS : Sodium Picosulfate and Magnesium Salt

source: Adapted from the Applicant's efficacy information amendment module 1.11.3, Table 1.11.3-1

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/s/

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