STATISTICAL ANALYSIS PLAN

A Randomized, Assessor-Blinded, Multi-Center Study Investigating the Efficacy, Safety, and Tolerability of Sodium Picosulfate, Magnesium Oxide and Anhydrous Citric Acid Oral Solution versus Sodium Picosulfate, Magnesium Oxide and Anhydrous Citric Acid Powder for Oral Solution (PREPOPIK®) for Colon Cleansing in Preparation for Colonoscopy

000253

Investigational Product:	Sodium Picosulfate, Magnesium Oxide and Anhydrous Citric Acid Oral Solution
Indication:	Bowel preparation for colonoscopy
Phase:	**III**
Author:	[redacted]
Date of issue:	December 1, 2017
Version:	Amendment 1

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Change log

Version No.	Effective Date	Reason for the Change / Revision	Supersedes
1	Oct 7, 2016	SAP based on Protocol dated 20 September 2016	None
2	Nov 29, 2017	• To lower the trigger for imputation based sensitivity analysis for the primary endpoint. • The Markedly notable analysis tables for laboratory, vital signs and ECG endpoints has been removed. • More justification for the margin selection has been added in Appendix 5. • The fluid intake summary was changed to just include information collected in the patient dairy card.	1 (for the amendment this would be the 1 version)

Signed[I] agreement on Statistical Analysis Plan

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1 Introduction

This document describes the planned statistical analyses for Study 000253 based on protocol Amendment 1, Version 2, dated 25 January 2017.

1.1 Definitions/ Abbreviations

1.1.1 Definition of Terms

Terms	Definitions
ITT	Randomized patients
mITT	Randomized patients that have been treated with IMP
Randomised	Subject randomised to trial treatment
Safety set	Patients that have been treated with IMP
Screened	Subject who enters the screening phase

1.1.2 Abbreviations

Abbreviations	Meaning of abbreviations in document
ADR	Adverse Drug Reaction
AE	Adverse Events
AST	Aspartate Aminotransferase
BBPS	Boston Bowel Preparation Score
BHPM	bis-(p-hydroxyphenyl)-pyridyl-2-methane
BMI	Body Mass Index
bpm	Beats per minute
BUN	Blood Urea Nitrogen
CRF	Case Report Form
ECG	Electrocardiogram
FAS	Full-Analysis Set
GGT	Gamma Glutamyl Transferase
IMP	Investigational Medicinal Product
ITT	Intention-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
mmHG	millimeter of mercury
mITT	Modified Intention-to-Treat
NaP/MC	Sodium Picosulfate, Magnesium Oxide and Anhydrous Citric Acid
NI	Non-Inferiority
PK	Pharmacokinetic(s)
PP	Per-Protocol
PT	Preferred Term
SAE	Serious Adverse Event
SD	Standard Deviation
SOC	System Organ Class
WHO	World Health Organization

2 Trial Objectives and Endpoints

2.1 Objectives

Primary Objective

- To demonstrate non-inferiority (NI) of split-dose Sodium Picosulfate, Magnesium Oxide and Anhydrous Citric Acid (NaP/MC) Oral Solution in overall colon cleansing in preparation for colonoscopy compared with split-dose PREPOPIK®

Secondary Objectives

- To demonstrate NI of NaP/MC Oral Solution compared with PREPOPIK® in cleansing of the right colon
- To evaluate the cleansing of the transverse and left colon
- To evaluate subjects' tolerability and satisfaction with the bowel preparation
- To evaluate overall safety through the collection of treatment-emergent AEs and clinically significant changes in vital signs, ECGs and laboratory values
- To evaluate pharmacokinetic (PK) characteristics of PREPOPIK® and NaP/MC Oral Solution

2.2 Endpoints

Primary Endpoint

- Proportion of subjects classified as a responder defined by "excellent" or "good" using the Modified Aronchick scale (Appendix 3).

Secondary Endpoints

- Proportion of subjects classified as a responder defined by a score ≥2 in the right segment of the colon using the BBPS (Appendix 3)
- Proportion of subjects classified as a responder defined by a score ≥2 in the transverse segment of the colon using the BBPS (Appendix 3)
- Proportion of subjects classified as a responder defined by a score ≥2 in the left segment of the colon using the BBPS (Appendix 3)
- Frequency of each category of the Mayo Clinic Bowel Prep Tolerability Questionnaire (Appendix 4)
- Incidence and intensity of treatment-emergent AEs and clinically significant changes in vital signs, ECGs, and laboratory values
- Plasma concentration of sodium picosulfate, magnesium and bis-(p-hydroxyphenyl)-pyridyl-2-methane (BHPM)

3 Trial design

This is a randomized, assessor-blinded, multi-center study investigating the efficacy, safety, and tolerability of split-dose Sodium Picosulfate, Magnesium Oxide and Anhydrous Citric Acid Oral Solution versus split-dose Low-Volume Sodium Picosulfate, Magnesium Oxide and Anhydrous Citric Acid Powder for Oral Solution (PREPOPIK®) for Colon Cleansing in Preparation for Colonoscopy.

3.1 General Design Considerations

Following appropriate informed consent procedures, subjects who fulfil eligibility criteria and require a colonoscopy will be randomized to one of the two treatment arms.

Only the subject and the site-designated unblinded coordinator and a pharmacist (if applicable) will know the treatment group in which the subject will be participating. The designated unblinded coordinator will instruct the subject on the use of the bowel preparation, and both will sign a nondisclosure affidavit form, preventing the subject and the unblinded coordinator from disclosing the bowel preparation treatment the subject used. Treatment will be blinded to the endoscopist assessing the efficacy of the two tested preparations.

Following randomization, subjects will perform colon cleansing using split-dose NaP/MC Oral Solution or split-dose PREPOPIK®.

NaP/MC Oral Solution (supplied as two 160-mL bottles per subject) needs no further reconstitution before administration.

Subjects randomized to the NaP/MC Oral Solution will begin treatment (first dose) the evening before colonoscopy between 5:00 and 9:00 PM, and will complete treatment (second dose) the following day, at least 5 hours, but no more than 9 hours, prior to the colonoscopy. After drinking the first dose, subjects should drink five (5) or more eight-ounce glasses of clear liquid within five (5) hours. After drinking the second dose, subjects should drink four (4) or more eight-ounce glasses of clear liquid within five (5) hours. Subjects should not ingest anything within two (2) hours before the time of the colonoscopy.

PREPOPIK® (supplied as two sachets per subject) is reconstituted using the cup provided. The doses are prepared by combining the contents of one sachet with approximately five (5) ounces of cold water and stirring for two to three minutes (in some cases the cup may feel warm, which is normal).

Subjects randomized to PREPOPIK® will begin treatment (first dose) the evening before the colonoscopy between 5:00 and 9:00 PM, and will complete treatment (second dose) the following day, at least five (5) hours, but no more than nine (9) hours, prior to the colonoscopy. After drinking the first dose, subjects should drink approximately five (5) eight-ounce glasses of clear liquid within five (5) hours. After drinking the second dose, subjects should drink three (3) eight-

ounce glasses of clear liquid within five (5) hours. Subjects should stop taking anything by mouth two (2) hours before the time of the colonoscopy.

For a subset of subjects, pharmacokinetic samples will be collected for picosulfate and BHPM concentration. Blood samples will be drawn within 15 minutes before the second dose, and 1 to 2 hours and 3 to 6 hours after the second dose of Prepopik or NaP/MC Oral Solution. Accurate dosing information of both doses and timing of PK samples relative to dosing will be recorded. All study subjects will have a PK sample drawn immediately prior to their colonoscopy.

Subjects will return for three follow-up visits: 24-48 hours (Visit 4), seven days (Visit 5), and four weeks (Visit 6) after the colonoscopy procedure.

3.1.1 Trial design diagram

Figure 1 Trial Flow Chart

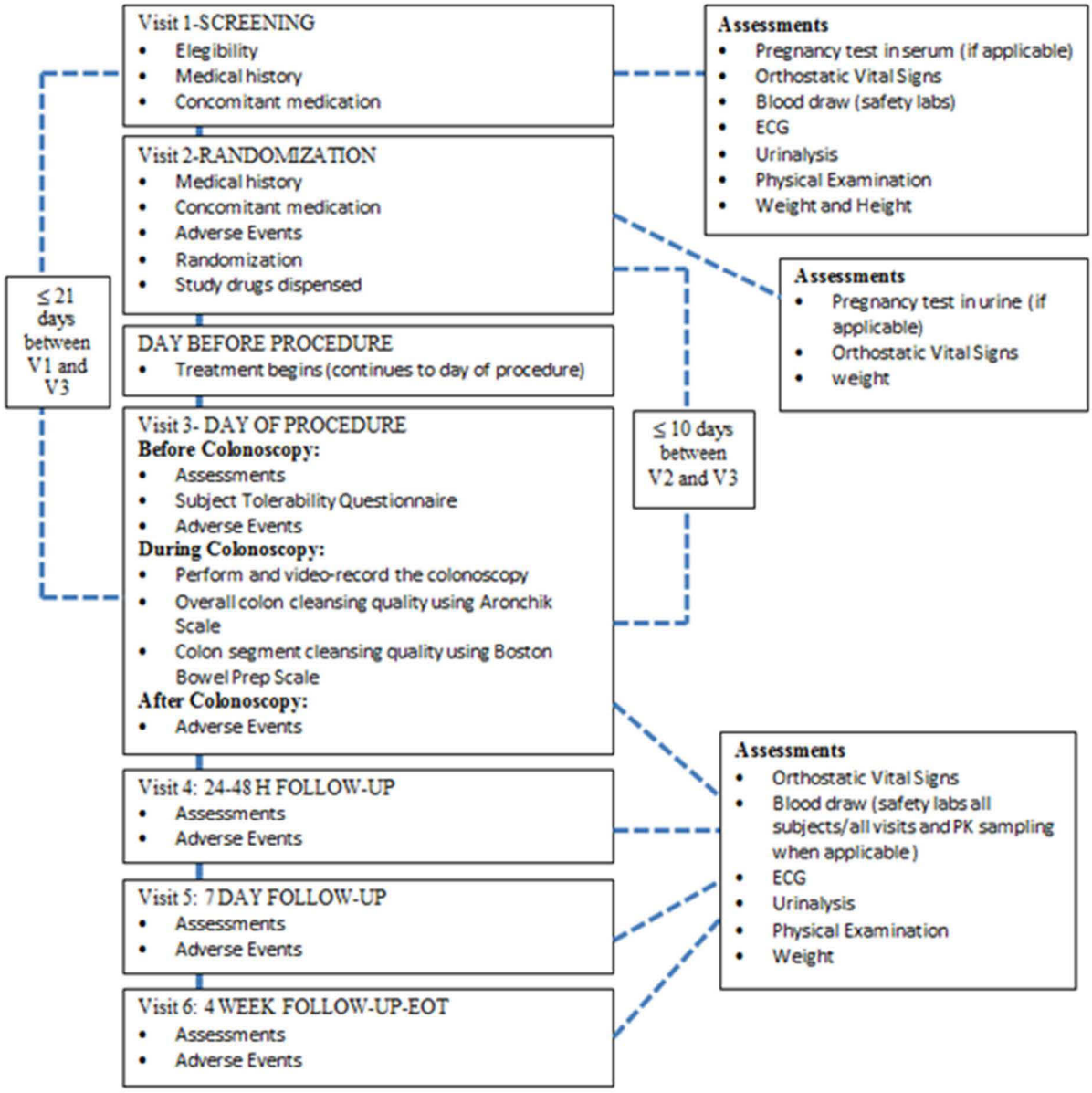
Visit 1-SCREENING
Eligibility
Medical history
Concomitant medication
Assessments
Pregnancy test in serum (if applicable)
Orthostatic Vital Signs
Blood draw (safety labs)
ECG
Urinalysis
Physical Examination
Weight and Height
Visit 2-RANDOMIZATION
Medical history
Concomitant medication
Adverse Events
Randomization
Study drugs dispensed
Assessments
Pregnancy test in urine (if applicable)
Orthostatic Vital Signs
weight
≤ 21 days between V1 and V3
DAY BEFORE PROCEDURE
Treatment begins (continues to day of procedure)
≤ 10 days between V2 and V3
Visit 3- DAY OF PROCEDURE
Before Colonoscopy:
Assessments
Subject Tolerability Questionnaire
Adverse Events
During Colonoscopy:
Perform and video-record the colonoscopy
Overall colon cleansing quality using Aronchik Scale
Colon segment cleansing quality using Boston Bowel Prep Scale
After Colonoscopy:
Adverse Events
Assessments
Orthostatic Vital Signs
Blood draw (safety labs all subjects/all visits and PK sampling when applicable)
ECG
Urinalysis
Physical Examination
Weight
Visit 4: 24-48 H FOLLOW-UP
Assessments
Adverse Events
Visit 5: 7 DAY FOLLOW-UP
Assessments
Adverse Events
Visit 6: 4 WEEK FOLLOW-UP-EOT
Assessments
Adverse Events

Table 1 Trial Assessment Table

Visit	**1 Screening**	**2 Randomization**	**3 Procedure**	**4 Follow-up**	**5 Follow-up**	**6 Follow-up (EOT)**
Timing versus Procedure	**(≤21) Days**	**(≤10) Days**	**Colonoscopy (T = 0)**	**24 – 48 Hours**	**7 Days (± 2 Days)**	**4 Weeks (± 2 Days)**
Informed consent	x					
Inclusion/exclusion criteria	x	x				
Demographic & Medical History	x					
Body weight, Height[1]	x	x	x	x	x	x
Urine/Serum Pregnancy Test	x	x				
Schedule colonoscopy	x					
Laboratory (chemistry, coagulation, hematology)	x[2]		x	x	x	x
PK sampling			x[3, 4]			
Urinalysis	x		x	x	x	x
ECG	x		x	x	x	x
Physical examination	x		x	x	x	x
Orthostatic vital signs (BP, pulse)	x	x	x	x	x	x
Concomitant medications	x	x	x	x	x	x
Adverse events	x	x	x	x	x	x
Dispense fluid intake diary and study medication		x				
Subject Tolerability Questionnaire			x			
Perform and video-record colonoscopy			x			
Score overall colon preparation – Modified Aronchick scale			x			
Score colon segments preparation – Boston Bowel Preparation Scale			x			
Drug accountability			x			

1. Height will only be collected at screening.
2. Coagulation samples will only be collected at screening.
3. In a subset of subjects, PK samples for sodium picosulfate and BHPM will be taken 15 minutes before the second dose, and 1 to 2 hours and 3 to 6 hours after the second dose of the Sodium Picosulfate, Magnesium Oxide and Anhydrous Citric Acid.
4. All subjects will have a PK sample drawn immediately prior to colonoscopy.

3.2 Determination of Sample Size

The primary objective of this study is to demonstrate NI of NaP/MC Oral Solution to PREPOPIK® for overall colon cleansing prior to colonoscopy using the Modified Aronchick Scale (see Appendix 3), as assessed by a blinded endoscopist. A subject is considered to be a "responder" if overall colon cleansing is either "excellent" or "good" on the Modified Aronchick Scale.

The assumed true responder rate for PREPOPIK® is 84% when using the Modified Aronchick Scale (FE2009-01 and FE2009-02). It is assumed that the true responder rate of subjects treated with PREPOPIK® or NaP/MC Oral Solution are the same. A NI margin of 8% was chosen, to ensure no more than a 10% relative decrease from the control. For details on the margin justification please see Appendix 5 . Four hundred and fifty randomized subjects per treatment group are required, in a 1:1 randomization, to maintain at least 90% power to demonstrate the NI of NaP/MC Oral Solution to PREPOPIK® for overall colon cleansing prior to colonoscopy at the one-sided 0.025 significance level.

For PK assessment, on a subset of subjects, blood sample will be collected four times on the day of colonoscopy. Approximately sixty (60) randomized subjects will be included in this PK sub-group. Sixty (60) subjects (approximately 30 per arm) are considered to be sufficient to characterize the population PK for picosulfate and BHPM. In addition to this, all subjects enrolled in the study will have a PK blood sample drawn for BHPM and picosulfate immediately prior to their colonoscopy. The PK assessment on all subjects will be used to explore the potential correlation between AEs and concentration levels of picosulfate, BHPM and magnesium.

4 Subject Disposition

All subjects screened will be accounted for. All post-randomization discontinuation and reasons for discontinuation will be summarized by treatment group. The number of patients in each patient population will also be summarized by treatment group. Associated listing will also be produced.

The number of subjects screened but not randomized/allocated to treatment will be presented with the reason(s) for screen failure in a data listing.

5 Protocol Deviations

Major protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. A subset of these major protocol deviations will lead to exclusion of the data from the PP analysis set.

Some of the criteria for major protocol deviation are listed below:

- significant deviation in the time of IMP dosing,
- taking the wrong IMP , or
- not following treatment regimen as specified in the protocol.

Regular blinded review of protocol deviations will be conducted prior to data base lock. The rating of protocol deviations as ‘minor’ or ‘major’ and exclusion from PP analyses will be also be discussed at these regular meeting and will be completed prior to the declaration of ‘clean file’ and lock of database.

Major protocol deviations will be summarized by treatment group for the mITT population.

6 Analysis sets

6.1 Intention-To-Treat Analysis Set

The intention-to-treat (ITT) analysis set comprises of all randomized subjects. The ITT analysis set will be analysed according to randomized treatment (as planned).

6.2 Modified Intention-to-Treat (mITT) Analysis Set

The primary efficacy analysis will be conducted for the mITT analysis set and is defined as all ITT subjects who received at least one dose of study treatment (i.e., IMP). The mITT analysis set will be analysed according to randomized treatment.

6.3 Per Protocol Analysis Set

The Per-protocol (PP) analysis set comprises all mITT subjects except those excluded as a result of major protocol deviations that affect efficacy. These subjects will be identified prior to breaking the study blind.

6.4 Safety Analysis Set

The safety analysis set comprises all subjects who took any amount of study medication (i.e., IMP). The safety analysis set will be analyzed according to the actual treatment received.

7 Trial population

7.1 Demographics and Other Baseline Characteristics

Categorical data will be summarised using numbers and percentages. The percentages are based on the total number of subjects with a corresponding assessment. Continuous data will be presented, for example, using the number of subjects (N), mean and standard deviation, median, minimum and maximum. These analyses will be presented for the mITT and safety population. In addition, since this is a multi-site trial, a summary of demographic characteristics will be presented by trial site. All baseline characteristics will be listed.

7.1.1 Demographics

Descriptive statistics of baseline demographics variables (e.g., age, race and ethnic origin, height, weight and BMI) will be summarized by treatment group.

7.2 Medical History

Medical history recorded at screening visit will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 16.1 or later. Medical history will be listed by treatment and subject, and summarized by treatment group, system organ class (SOC), and preferred term (PT) for the subjects in the mITT and safety analysis sets, separately.

7.3 Prior and Concomitant Medication

Prior and concomitant medication will be summarised using the WHO dictionary by ATC classification 1st level (alphabetically), ATC classification 2nd level (in decreasing order of frequency) and treatment group for the safety analysis set. These medications will be tabulated separately for:

1) Prior medication; i.e. medication taken exclusively prior to treatment (i.e. with stop date before date of first IMP administration);
2) Concomitant medication, i.e. medication taken during the treatment period (i.e. medication that was not stopped before date of first IMP-administration [and not started after the last visit date (i.e., visit 6)]).

If the timing of the dose of a medication cannot be established in relation to the administration of IMP, it will be considered as concomitant medication.

7.4 Physical Examination

Subjects with abnormalities at any screening, baseline, or post-baseline visit will be listed with all physical examination evaluations for the safety population.

8 Exposure and Treatment Compliance

8.1.1 Extent of Exposure

The number of patients that completed IMP treatment, the number of patients that took each dose of IMP and the number of patients that did not take any amount of IMP will be summarized and listed by treatment group for the safety analysis set.

8.1.2 Treatment Compliance

The number and proportion of subjects deviating from the treatment regimen will be summarized by treatment group for the safety population. The summary will include the following:

- the number of patient that did not consume the entire dose,
- deviations from protocol mandated administration time,
- the number of patients that did not fast two hours before colonoscopy,
- the number of patient that did not adhere to clear liquid diet 24 hours prior to colonoscopy and
- the number of subject that did not consume the recommended number eight-ounce glasses of clear liquid after each dose of IMP.

Furthermore, associated listing will be produced.

9 Efficacy

9.1 General Considerations

All statistical tests will be performed using a two-sided test at a 5% significance level.

The primary and secondary efficacy analyses will be conducted for the mITT analysis set. Continuous variables will be described with the number of non-missing values, mean, standard deviation, median, and minimum/maximum values. Categorical variables will be described with the number and percentage of subjects within each level.

In order to preserve the type I error for testing for the primary endpoint of the overall colon cleansing and the secondary endpoint of right colon cleansing, the NI for evaluating the cleansing within the right colon will only be assessed if NI is demonstrated for the primary endpoint using the mITT population. Superiority for the primary endpoint will be assessed if and only if NI is demonstrated for both the primary efficacy endpoint and the secondary right colon efficacy endpoint.

9.2 Primary Endpoint(s)

The primary endpoint is the Proportion of subjects classified as a responder defined by “excellent” or “good” using the Modified Aronchick scale.

9.2.1 Primary Variable(s) Analysis

For primary analysis what is of interest is the assessment of the difference in responder rates in overall colon cleansing between NaP/MC Oral Solution and PREPOPIK®. A subject is considered to be a “responder” if overall colon cleansing is classified as either “excellent” or “good” by the blinded endoscopist using the Modified Aronchick Scale (see Appendix 3). The NI margin for the difference between treatments (NaP/MC Oral Solution minus PREPOPIK®) will be -8% (absolute). The NI hypothesis to be tested for the primary endpoint will be:

$H_0: \pi_{\text{NaP/MC Oral Solution}} - \pi_{\text{PREPOPIK}^{®}} \leq -8\%$

against the alternative

$H_1: \pi_{\text{NaP/MC Oral Solution}} - \pi_{\text{PREPOPIK}^{®}} > -8\%,$

where $\pi_{\text{NaP/MC Oral Solution}}$ and $\pi_{\text{PREPOPIK}^{®}}$ denote the true percentage of subjects classified as responders (i.e., excellent and good according to the Modified Aronchick Scale (see Appendix 3)) among subjects treated with NaP/MC Oral Solution or PREPOPIK®, respectively, for colon cleansing in preparation for colonoscopy.

The null hypothesis (H_0) will be tested against the alternative by constructing a 2-sided 95% confidence interval for the difference in responder rates. The primary analysis will be stratified by the stratification factor, site, by using the Mantel-Haenszel method to combine results across sites. In brief, this corresponds to deriving a weighted average across sites where the weight depends on the number of observations in each treatment group in each stratum (see Appendix 2 for more details). Subjects who do not have an excellent or good rating according to the Modified Aronchick Scale (see Appendix 3) for any reason will be considered treatment failures (i.e., not a responder). Hence, treated patients that did not complete the colonoscopy assessment will be classified as non-responders. If the lower limit of the 95% confidence interval is greater than the margin (-8%), the null hypothesis will be rejected and it will be claimed that NaP/MC Oral Solution is non-inferior to PREPOPIK® with respect to colon cleansing in preparation for colonoscopy.

If NI is demonstrated for both the primary efficacy endpoint and the secondary efficacy endpoint for the right colon (see Section 9.3.1), and if the lower bound for the primary analysis results in a confidence interval that is above 0% then, superiority will be declared for the primary endpoint. Hence, this superiority test will be conducted at one sided significance level of 2.5%.

9.2.2 Sensitivity Analyses

As a sensitivity analysis, the NI analysis in section 9.2.1 will be repeated using the per-protocol population.

For the primary analysis, if a patient does not have efficacy assessment (colonoscopy), it is considered to be a treatment failure. There are two main reasons for applying such method of imputations. First, the number of patients missing efficacy assessment is expected to be very low. In the two pivotal Ferring studies (FE2009-01 and FE2009-02), the number of patients that were treated but did not have colonoscopy assessment were less than 1%. Furthermore, if the reason for not having efficacy assessment is related to tolerability then these can also be considered as treatment failures and treating such missing values as failures is appropriate. However, in this study, if the number of treated patients that do not have efficacy assessment for reasons other than tolerability is >=0.5%, there will be a sensitivity analysis, where, a multiple imputation method will be applied to impute for such missing colonoscopy assessment. Details of the multiple imputation method to be applied is found in Appendix 2

The patients that do not have colonoscopy results for other than tolerability issues will be identified using the question “was colonoscopy performed at this visit?” on the colonoscopy & assessment eCRF page. Using the “specify” responses to this question, prior to data base lock, the clinical team will review and categorize the reasons for not preforming or completing colonoscopy. One of the classification categories will be “tolerability”. If there are >=0.5% patients that did not have colonoscopy performed or completed for reasons other than “tolerability” a sensitivity analysis will be performed by applying multiple imputation method to impute for such missing assessments.

9.3 Secondary Endpoint(s)

9.3.1 Assessing the Cleansing of the Right Colon

The Boston Bowel Preparation Score (BBPS) will be used to assess the cleaning of the right colon. The difference between the responder rates in the right colon cleansing using NaP/MC Oral Solution or PREPOPIK® will be assessed. A subject is considered to be a "responder" if the BBPS (Right Colon) score is ≥2. Using the mITT population and the analysis methodology described for the primary endpoint a 95% two-sided confidence interval for the responder rate difference of NaP/MC Oral Solution minus PREPOPIK® will be constructed. If the NI objective is met for the primary endpoint, these CIs will be used to assess the NI of NaP/MC Oral Solution to PREPOPIK® in the cleansing of right colon as assessed by BBPS. The NI margin for the testing the difference between treatments (NaP/MC Oral Solution minus PREPOPIK®) for cleansing of the right colon is again set to be -8% (absolute). Hence, if the lower bound of this confidence interval exceeds -8.0% then NaP/MC Oral Solution will be declared non-inferior to PREPOPIK® with respect to the cleansing of the right colon.

9.3.2 Assessing the Cleansing of the Transverse Colon

The responder rate for the transverse colon using BBPS will be analysed in the same manner as the primary endpoint for the mITT analysis set, according to the subjects' randomized treatment group, and 95% confidence interval for the responder rate of NaP/MC Oral Solution minus PREPOPIK® will be presented. A subject is considered to be a "responder" if the BBPS score of the transverse colon is ≥2.

9.3.3 Assessing the Cleansing of the Left Colon

The responder rate for the left colon using BBPS will be analysed in the same manner as the primary endpoint for the mITT analysis set according to the subjects' randomized treatment group, and 95% confidence interval for the responder rate of NaP/MC Oral Solution minus PREPOPIK® will be presented. A subject is considered to be a "responder" if the BBPS score of the left colon is ≥2.

9.3.4 Tolerability and Satisfaction

For Mayo Clinic Bowel Prep Tolerability Questionnaire (see Appendix 4), each question will be analysed separately and summary statistics will be provided for all individual questions by randomized treatment group for the mITT population. The Wilcoxon Rank Sum 2-sided test will be used for the treatment comparison of ordered categorical responses. In contrast, for binary responses Fisher's exact test will be utilized.

9.3.5 Drug Concentration Measurements/Pharmacokinetics

Drug concentrations of picosulfate, BHPM and magnesium (which is part of the chemistry lab assessment) will be summarized by descriptive statistics. A population PK model will be developed

based on pooled data from the present study and previous study in adult subjects (000017). Apparent clearance and volume of distribution will be estimated, if possible. The population PK model and other PK endpoints will be summarized in a separate PK modelling report.

9.4 Other Endpoints

Whether or not colonoscopy was completed, whether or not cecum was reached, the overall colonoscopy evaluation, time taken to reach the cecum, time to withdrawal and number of polyps and histology will be summarized by treatment group. Furthermore, associated listing will be produced. The listing will include information on the histologic details of the polyps and the morphology.

9.4.1 Subgroup analysis

The primary endpoint will be summarized by age (<65 or ≥ 65), gender and site. The analysis outlined for the primary endpoint will be applied to age and gender subgroup analysis. For the by site summary, the proportion of responders will be presented by treatment group. Furthermore, the proportion difference between the treatment groups and associated 95% CI will be generated.

10 Safety

10.1 General Considerations

Safety parameters will be evaluated for the safety analysis data set according to actual treatment received. No formal statistical hypothesis testing will be conducted for the safety parameters.

10.2 Adverse Events

Adverse events (AEs) are classified according to the Dictionary for Regulatory Activities (MedDRA) version 16.1 or later.

A Treatment-emergent adverse event (TEAE) is any adverse event that occurs after the start of IMP and within 30 days from the last exposure to IMP, or a pre-treatment adverse event/medical condition that worsens in intensity after the start of IMP and within 30 days from the last exposure to IMP. The total number of subjects reporting a TEAE, the percentage of subjects (%) with a TEAE, and the number of treatment-emergent adverse Events (E) reported will be presented.

Missing values will be treated as missing, except for causality, intensity, seriousness, and outcome of AE. A 'worst case' approach will be used:

- if causality is missing, the AE will be regarded as related to the IMP
- if the intensity of an AE is missing, the AE will be regarded as severe
- if seriousness is missing, the AE will be regarded as serious
- if outcome is missing and no date of outcome is present, the outcome is regarded as 'Not yet recovered'

Missing event start and event stop dates will be imputed in the most conservative way, i.e. the event should start as early as possible based on the (partially) missing start date while remaining treatment emergent (if relevant), and last as long as possible, i.e. until last visit or one day prior to the next event with the same preferred term, if any. In the latter case both consecutive AEs (with the same PT) will remain to be regarded as two separate events (despite being adjacent).
Written narratives will be issued for all serious AEs (including deaths) and AEs leading to withdrawal.

10.2.1 Overview of Treatment-Emergent Adverse Events

An AE overview summary table will be prepared including the number of subjects reporting an AE, the percentage of subjects (%) with an AE, and the number of events (E) reported, for the following categories:

- Treatment-emergent adverse events
- Deaths
- Serious adverse events
- Adverse events leading to withdrawal

- Severe and life threatening adverse events
- Adverse drug reactions

10.2.2 Incidence of Adverse Events

Treatment-emergent adverse events will be summarised in a Table by SOC and PT using the latest version of MedDRA. The Table will display the total number of subjects reporting an AE, the percentage of subjects (%) with an AE, and the number of events (E) reported. AEs will be presented by system organ class (SOC) sorted alphabetically and preferred term (PT) sorted in decreasing frequency of occurrence.

Summary tables will be prepared for:

- All TEAEs
- TEAEs with an incidence of ≥5%
- Non-serious TEAEs with an incidence of ≥5%
- TEAEs by causality (related/unrelated)
- Adverse events leading to death
- TEAEs by intensity
- Serious adverse events
- Adverse events leading to withdrawal

Supporting data listings will be provided for:

- All adverse events sorted by centre and subject no.
- All adverse events sorted by MedDRA Preferred Term
- Serious adverse events
- Adverse events leading to death
- Adverse events leading to withdrawal.

A listing of pre-treatment and post-treatment AEs will be generated. A pre-treatment AE is any AE that ends prior to exposure to IMP. In contrast, a post-treatment IMP is an AE that starts 30 days after IMP exposure. The pre-treatment AE listing will include all patients that signed informed consent. In contrast, the post-treatment AE listing will be limited to the safety population.

10.3 Safety Laboratory Variables

Baseline for all laboratory analyses will be the values obtained at the last assessment prior to the first dose of the investigational medicinal product (IMP). Treatment-emergent laboratory data will include tests completed after the first dose of IMP. End of trial assessment will include the last post-baseline observation during the trial.

Laboratory variables will be grouped under “Haematology”, “Clinical Chemistry” or “Urinalysis”

10.3.1 Summary Statistics

Observed values and change from baseline values for each visit and for the end of trial (last visit) will be summarized for each laboratory variable by treatment group. The summary will include the number of subjects with data, mean (standard deviation), median, minimum, and maximum values.

10.3.2 Laboratory Variable Changes Relative to Normal Range

Changes relative to normal ranges are presented with shift tables with total number of subjects, and number and percent of subjects who experienced a shift by treatment group. The following categories for shift tables are defined:

- Low: Values which are below the lower reference range limit;
- Normal: Values which are within the lower and upper reference range;
- High: Values which are above the upper reference range limit.
- Absent: No value for measured variable (for urinalysis only)
- Present: Any value obtained for measured variable (for urinalysis only)

For all haematology and clinical chemistry variables, shift tables will be prepared to compare baseline values to the worst in-treatment value. More specifically, for haematology and clinical chemistry, tables presenting the changes from *Low* or *Normal* to *High* and from *High* or *Normal* to *Low* will be provided. For urinalysis variables, shift tables will summarise the number (%) of subjects who had “absent” values at baseline and “present” values during the treatment period.

10.3.3 Data Listings

Data listings will be prepared by treatment group and site for all subjects with any abnormal or markedly abnormal laboratory value at any time-point (including screening, baseline). The pre-specified markedly abnormal criteria are presented in Appendix 1 Appendix 1 .

10.3.4 Urinalysis

Categorical urinalysis laboratory data will be summarized separately by treatment group and scheduled time point using the number and percentage of subjects in each category. Furthermore, incidence of changes in urinalysis will be summarised by treatment group. A summary table with number of subjects with change from *Absent* at baseline to *Present* during trial will be summarised.

10.4 Vital Signs and ECG

10.4.1 Vital Signs

Baseline for all vital signs (sitting, supine or orthostatic) analyses will be the values obtained at the last assessment prior to the first dose of IMP. Treatment-emergent vital signs data will include tests completed after the first dose of IMP. Last assessment in the study will include the last post-baseline observation during the trial.

Observed and change from baseline values for standing, supine and orthostatic vital signs will be summarized by visit and for the last assessment in the study. For orthostatic vital signs only observed values will be summarized. The orthostatic blood pressure and pulse to be summarized are the change in these measures from supine position to standing position. In this study, BP and pulse, will be first measured after at least 5 minutes rest in supine position and after 3 minutes in standing position.

Orthostatic vital signs cut off that are suggestive of fluid volume depletion are as follows [14]:

- a decrease in systolic blood pressure greater or equal to 20 mmHG within 3 minutes of standing,
- a decrease in diastolic blood pressure greater or equal to 10 mmHG within 3 minutes of standing, or
- increase in heart rate (pulse rate) greater or equal to 30 beats per minute (bpm) in the presence of drop blood pressure.

At each visit the number of patients, with such changes in orthostatic vital signs will be summarized by treatment arm.

10.4.1.1 Summary Statistics

For each vital signs variable at each visit the assessments will be summarized by treatment arm. The summary includes descriptive statistics such us the number of subjects with data, mean (standard deviation), median, minimum, and maximum values, for observed values and change from baseline at each time-point for each vital signs variable. Change from baseline values will not be summarized for orthostatic vital signs.

.

10.4.1.2 Data Listings

Data listings will be prepared by site for all subjects with any abnormal or markedly abnormal vital signs value at any time-point (including screening, baseline). The pre-specified markedly abnormal criteria are presented in Appendix 1 .

Data listing of orthostatic vital signs will also be prepared by site for all subjects with any orthostatic vital sings values that are indicative of fluid volume depletion at any time-point.

10.4.2 ECGs

Overall ECG assessment will be categorized as ‘normal’, ‘abnormal, not clinically significant’, or ‘abnormal, clinically significant’ (as judged by the Investigator). These categorized values will be summarized by treatment for each assessment time for the safety population.

QTc will be calculated both using Bazett’s and Fridericia’s correction formulae (see below for definitions).

1) Bazett's correction (square root):

$$QTcB = QT/(RR)^{0.5}$$

2) Fridericia's correction (cube root):

$$QTcF = QT/(RR)^{1/3}$$

where RR is in sec (=1 for HR=60 bpm), whereas QT is in msec.

10.4.2.1 Summary Statistics

For the ECG parameters PR, QRS and QTc, descriptive statistics, i.e., the number of subjects with data, mean (standard deviation), median, minimum, and maximum values, will be presented for observed values and change from baseline at each time-point and for the last assessment in the study

10.4.2.2 Data Listings

Data listings will be prepared by treatment group and centre for all subjects with any abnormal ECG or markedly abnormal value at any time-point, including screening, baseline, during treatment, and post-treatment. The pre-specified markedly abnormal criteria are presented in Appendix 1 .

10.5 Other Safety Variables

The total fluid intake collected on patient diary will be summarized by treatment group. The summary will by each type liquid intake specified in the patient dairy. Associated listing will also be produced. The listing will include information on the time and type of liquid consumed from the start of the first dose of IMP to the time of colonoscopy. A separate listing will be produced for the volume of liquid used at time of procedure (including fluid IV).

11 Interim analyses

No interim analysis is planned for this study.

12 Deviations from protocol analysis

For the primary endpoint, subgroup analysis was added (Section 9.2.2 and 9.4.1). In the tolerability analyses section (see Section 9.3.4), the analysis for binary tolerability question was clarified. Furthermore, the analysis of additional efficacy and safety endpoints were specified in Sections 9.4 and 10.5, respectively.

In this amendment the markedly abnormal vital signs summary table that was specified in the protocol has been removed.

13 References

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14 Tables, Listings and Figures

The document with tables, figures and listings (TLF) shells presented in a separate document.

Appendix 1 Markedly Abnormal Laboratory Safety Values, Vital Signs and ECGs

Table 2: Markedly abnormal Criteria for Laboratory Tests

Variable	Units	Markedly abnormal Criteria	
		Low	**High**
Haematology			
Haemoglobin	g/L	≤ 115	Not applicable
Haematocrit	Ratio	≤ 0.37	≥ 0.56
Total WBC	10^9/L	≤ 2.8	≥ 16.0
Eosinophils	%	Not applicable	≥ 10
Neutrophils	%	≤ 15	≥ 90
Lymphocytes	%	≤ 10	≥ 80
Monocytes	%	Not applicable	≥ 20
Basophils	%	Not applicable	≥ 5
Bands	%	Not applicable	≥ 20
Platelets	10^9/L	≤ 75	≥ 700
Total RBC	10^{12}/L	≤ 3.5	Not applicable
Clinical Chemistry			
AST	IU/L	Not applicable	> 3xULN
ALT	IU/L	Not applicable	> 3xULN
Alkaline phosphatase	IU/L	Not applicable	> 3xULN and 25% increase from baseline
GGT	IU/L	Not applicable	> 3xULN
LDH	IU/L	Not applicable	> 3xULN
Total bilirubin	µmol/L	Not applicable	≥ 1.5xULN
Urea nitrogen	mmol/L	Not applicable	≥ 10.7
Creatinine	µmol/L	Not applicable	≥ 177
Total protein	g/L	≤ 45	≥ 90
Albumin	g/L	≤ 25	≥ 65
Sodium	mmol/L	≤ 130	≥ 155
Potassium	mmol/L	≤ 3.0	≥ 5.8
Chloride	mmol/L	≤ 90	≥ 115
Phosphorus	mmol/L	≤ 0.5	≥ 1.9
Calcium	mmol/L	≤1.8	≥ 3.9
Uric acid	mmol/L	Not applicable	≥ 0.62
Glucose	mmol/L	≤ 2.8	≥ 10
Total cholesterol	mmol/L	Not applicable	≥ 8.0
Urinalysis: Quantitative			
pH	None	≤ 4	Not applicable
Specific gravity	None	≤ 1.005	Not applicable
Urinalysis: Dipstick Chemistries			
Glucose	0 - 4+	Not applicable	Increase of 2 or more units from baseline

Variable	Units	Markedly abnormal Criteria	
		Low	**High**
Casts		Not applicable	Increase of 2 or more units from baseline
Protein	0 - 4+	Not applicable	Increase of 2 or more units from baseline
Ketones	0 - 4+	Not applicable	Increase of 2 or more units from baseline
Blood (Hgb)	0 - 4+	Not applicable	Increase of 2 or more units from baseline
Urinalysis: Microscopic Variables			
RBC	no./hpf	Not applicable	≥ 10
WBC	no./hpf	Not applicable	≥ 20
Casts	no./hpf	Not applicable	Neg at baseline to positive on-treatment
Bacteria	no./hpf	Not applicable	Neg at baseline to positive on-treatment
Cells	no./hpf	Not applicable	Neg at baseline to positive on-treatment
Crystals	no./hpf	Not applicable	Neg at baseline to positive on-treatment

Table 3: Markedly abnormal Criteria for Vital Signs*

Variable	Criterion Value	Change from Baseline
Systolic blood pressure	≥ 180 mmHg ≤ 90 mmHg	Increase of ≥ 20 mmHg Decrease of ≥ 20 mmHg
Diastolic blood pressure	≥ 105 mmHg ≤ 50 mmHg	Increase of ≥ 15 mmHg Decrease of ≥ 15 mmHg
Pulse rate	≥ 120 bpm ≤ 50 bpm	Increase of ≥ 15 bpm Decrease of ≥ 15 bpm
Body weight	None	Increase of ≥ 7% Decrease of ≥ 7%
Body temperature	≥ 38.3° C	Increase to ≥ 39.4°C

* To be identified as markedly abnormal, a treatment value must meet the criterion value and also the specified change from baseline.

Table 4: Abnormal Criteria for Quantitative ECG Data

Variable	Baseline	Abnormal Treatment-Emergent Value
ECG heart rate	Normal	≤ 50 bpm and decrease from baseline of ≥ 15 bpm ≥ 120 bpm and increase from baseline of ≥ 15 bpm
Duration of PR interval	Normal	≥ 220 msec
Duration of QRS interval	Normal	≥ 120 msec
Duration of QTc interval	Normal	≥ 450 msec
Duration of QTc interval	Normal	≥ 480 msec
Duration of QTc interval	Normal	≥ 500 msec
Duration of QTc interval*	Not applicable	Increase from baseline of ≥ 30 msec
Duration of QTc interval	Not applicable	Increase from baseline of ≥ 60 msec

* QTc will be calculated both using Bazett's and Fridericia's correction formulae.

Appendix 2 Statistical and programming details

Cochran-Mantel-Haenszel method for computing proportion differences adjusting for stratification factor ([11])

- p_{ij} is the portion of success for treatment *i (i-=1, 2)* and site *j (j=1,...,s)*
- $d_j = p_{1j} - p_{2j}$ is the jth site treatment difference
- $w_j = \frac{\left(\frac{n_{1j}n_{2j}}{n_{1j}+n_{2j}}\right)}{\sum_{j=1}^{S}\left(\frac{n_{1j}n_{2j}}{n_{1j}+n_{2j}}\right)}$

The Cocharan-Mantel-Haenszel confidence interval is as follows:

$$\sum_{j=1}^{s} w_j d_j \quad +/- z_{\alpha/2}\sqrt{\sum_{j=1}^{S} w_j^2\left(\frac{p_{1j}(1-p_{1j})}{n_{1j}} + \frac{p_{2j}(1-p_{2j})}{n_{2j}}\right)}$$

SAS code for generating multiple imputed data using *proc mi* procedure ([13])

If the primary endpoint (overall colon cleansing based on Modified Aronchick Scale) is missing for a mITT patient and the assessment is not available due to other than tolerability of the IMP the following SAS code can be used to generate 20 imputed data sets.

```
proc mi seed=xxx out=xxxx nimpute=20;
class outcome trt site;
monotone logistic(outcome = trt site);
var trt site outcome;
run;
```

Where *trt* represents treatment group and *site* represents the patient site.

Once the 20 imputed data sets are generated, for each imputed data the above formula can be used to derive the stratified difference and associated variance i.e.,

Estimated difference: $\hat{Q} = \sum_{j=1}^{s} w_j d_j$

Associated Variance: $\hat{U} = \sum_{j=1}^{S} w_j^2\left(\frac{p_{1j}(1-p_{1j})}{n_{1j}} + \frac{p_{2j}(1-p_{2j})}{n_{2j}}\right)$

Let $\widehat{Q_j}$ and $\widehat{U_j}$ be the point estimate and associated variance for the *j*th imputed data set (*j=1,..., k*). Then the point estimate pooling over the imputed data sets would be as follows:

$$\bar{Q} = \frac{1}{k}\sum_{j=1}^{k}\widehat{Q_j}$$

The within-imputation variance is given by

$$\bar{U} = \frac{1}{k}\sum_{j=1}^{k}\widehat{U_j}$$

And the between-imputation variance is given by

$$B = \frac{1}{k-1}\sum_{j=1}^{k}(\hat{Q}_j - \bar{Q})$$

Finally, the total variance associated with $\bar{Q}$ is as follows:

$$T = \bar{U} + \left(1 + \frac{1}{k}\right)B$$

Then

$$(Q - \bar{Q})T^{-1/2} \sim \textit{T-distribution with v degrees of freedom}$$

$$v = (k-1)[1 + \bar{U}/((1+k^{-1})B)]^2$$

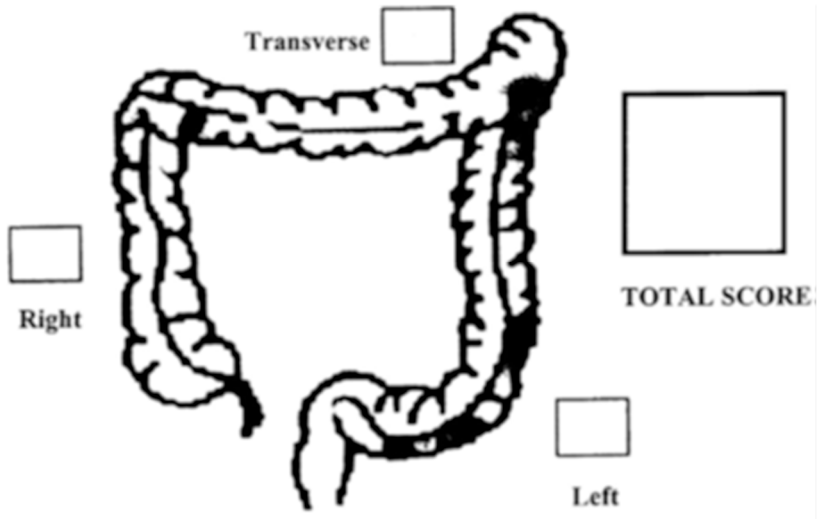
Where Q is the population parameter.

Appendix 3 Modified Aronchick Scale and Boston Bowel Preparation Scale

Modified Aronchick Scale (Aronchick et al, 1999, as cited by ASGE, 2015 [1])

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

Boston Bowel Preparation Scale ([2])



0 Unprepared colon segment with mucosa not seen due to solid stool that cannot 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.

Appendix 4 Mayo Clinic Bowel Prep Tolerability Questionnaire

Mayo Clinic Bowel Prep Tolerability Questionnaire

- *Please, fill this questionnaire the morning of your colonoscopy procedure*
- *Please mark (for example ✓) the most appropriate response according to your current experience with the bowel preparation.*
- *Please, return this questionnaire at the front desk in the Gastroenterology department when you check-in for your procedure.*

Patient name: _____

Age: _____ **Gender:** ☐ **Male** ☐ **Female**

Bowel prep: _____ **Regimen:** ☐ PM only (single dose) ☐ PM/AM (split dose)

1. How many bowel movements did you have in the week prior to starting colon preparation?
   - ☐ 3 or less/week
   - ☐ 4 to 8/week
   - ☐ 9 or more/week

2. How much of the bowel preparation solution was left in the bottle after drinking it to your best effort?
   - ☐ Less than 25%
   - ☐ 25% - 50% left
   - ☐ 50% -75% left
   - ☐ 75% or more left

3. How tolerable did you find the bowel preparation?
   - ☐ Easy
   - ☐ Acceptable
   - ☐ Somewhat difficult
   - ☐ Very difficult
   - ☐ Unacceptable

4. Based on your current experience, would you be willing to drink the same preparation again if you need another colonoscopy in the future?
   - ☐ Not willing at all
   - ☐ Somewhat willing
   - ☐ Mostly willing

5. In case you have experienced some difficulties in tolerating the bowel preparation, do you think that was due to your current health issues? (Check more than 1 option if applicable)
   - ☐ Yes
   - ☐ No
   - ☐ It does not apply to me (I did not have any difficulties tolerating bowel preparation)
   - ☐ It does not apply to me (I do not have any health issues)

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6. How much the following symptoms bothered you during bowel preparation?

Symptoms	None	Mild	Moderate	Severe
Bad taste in your mouth	1	2	3	4
Gastric fullness	1	2	3	4
Lack of sleep from excessive bathroom trips	1	2	3	4
Nausea/vomiting	1	2	3	4
Bloating/abdominal distention/gas	1	2	3	4
Abdominal pain/cramps	1	2	3	4
Headache	1	2	3	4

Others (please specify the symptom (s) and indicate how bothersome it was):

_____

_____

_____

7. Is this your first colonoscopy procedure?

- ☐ No (please, answer the following questions)
- ☐ Yes (end of the questionnaire)

8. Which type of bowel preparation did you take in your previous colonoscopy?

- ☐ GoLytely (1 gallon tasteless/salty solution)
- ☐ Moviprep (1/2 gallon flavored solution)
- ☐ MiraLax (Over the counter colon preparation)
- ☐ Other (please specify): _____
- ☐ Don't remember

9. In comparison with your previous experience, how would you rate your tolerability of the current bowel preparation?

- ☐ Worse than before
- ☐ About the same as before
- ☐ Better than before

Thank you very much for filling out this questionnaire.

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Appendix 5 Non-inferiority margin justification

Table 5 Historical references used to establish Clinical significance (M2)

Study	Study design	comparator	Overall response rate	Assessment method	Proposed non-inferiority margin	Study result
BLI850-301 (Suclear)[6]	Randomized single blind	Halflytely	158/176 (89.8%)	Four point scale with excellent and good as responders	15%	(-0.7, 13.2)
BLI850-302[6] (Suclear)	Randomized single blind	MoviPrep	173/186(93.5%)	Four point scale with excellent and good as responders	15%	(-5.0, 5.0)
FE2009-01 (Picoprep) [3]	Randomized assessor blinded	Halflytely	256/304 (84.2%)	Aronchick scale	9%	(2.9%, 15.7%)
FE2009-02 (Picoprep) [4]	Randomized assessor blinded		244/294 (83.0%)	Aronchick scale	9%	(-3.0%, 10.0%)
Osmoprep (two doses of Osmoprep) [9]	Randomized Investigator blinded		48g: 225/236 (95.3%) 60g: 226/233 (97.0%)	Four point scale with excellent and good as responders	10%	48g:(-2.8%, 4.7%) 60g: (-1.0%, 6.5%)
BL1800-301 Suprep (one day) [7]	Randomized single blind	MoviPrep	178/190		15%	(-5.8%, 3.6%)
BL1800-302 Suprep (split dose)[7]	Randomized single blind	MoviPrep	175/190		15%	(-2.2%, 5.4%)
5mg v.s. 10mg Halflytley [8]	Randomized investigator blinded	Halflytely 10 mg	114/147 (77.6%)		15%	(-11.9%, 6.8%)
Systemic/ review and meta-analysis: Sodium picosulfate/magnesium citrate vs. polyethylene glycol for colonoscopy preparation. [10]	Meta-analysis	polyethylene glycol for colonoscopy (PEG)			9% (10% relative decrease from PEG.)	Lower bound of the -4.57%

NER1006 vs. trisulfate [2]	Randomized blinded colonoscopist and central reader	trisulfate	85.1% vs. 85% (HCG criteria) 82.6% vs. 81.1% (BBPS criteria)	HCG and BBPS	10% (based on maximally clinically acceptable difference for studies of this type	-8.15% for HCG

The margin for this study was derived in consultation with the FDA guidance document "*Non-inferiority Clinical Trials to Establish Effectiveness"* [5] and extensive literature review on colonoscopy cleaning treatments.

No placebo controlled Prepopik study could be found in the literature. Furthermore, a randomized placebo controlled trial could not be found for colonoscopy cleaning treatments under consideration. However, without use of any treatment, the response rate (from a perspective of Aronchick scale) is expected to be about 0% and no higher than 15%. If on the conservative side the placebo response rate of 15% is assumed, then for the Prepopik study 2009 [3] the difference from placebo would be 84%-15%=69%. Furthermore, if 15% is assumed to be the true value, the 95% confidence interval for the difference between the estimated 84% and the constant 15%, true control response rate, is (65%, 73%). One common approach for non-inferiority margin is to take one-half of the lower limit of the 95% confidence interval of the difference of the active treatment to the control. In this case this would be 33%. Because of this high treatment effect, which is consistent across other major marketed treatments, and low placebo response rate, the margin cannot be justified in this manner. Hence, the margin rational in this study is based on clinical consideration (i.e., M2).

In this trial the assumed active control efficacy rate is 84%. Based on clinical consideration, the non-inferiority margin is selected so that at least 90% of the active control effect rate is retained. This results in a non-inferiority margin of 8%. Furthermore, in a recently published meta-analysis [10], comparing Polyethylene glycol (PEG) based treatment with sodium picosulfate/magnesium, citrate treatment, the margin for non-inferiority was based on 90% retention rate (of the PEG efficacy). In light of these, it is believed a retention rate of 10% for this study is acceptable.