CLINICAL TRIAL PROTOCOL

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

EudraCT Number:	N/A
IND Number:	**101738**
Investigational Medicinal Product:	Sodium Picosulfate, Magnesium Oxide and Anhydrous Citric Acid Oral Solution
Indication:	Bowel preparation for colonoscopy
Phase:	III
Name and Address of Sponsor:	Ferring International PharmaScience Center U.S., Inc. (FIPCUS) 100 Interpace Parkway Parsippany, NJ 07054 P: 973-796-1600
GCP Statement:	This trial will be performed in compliance with GCP, including the archiving of essential documents.

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SYNOPSIS

TITLE OF TRIAL

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

SIGNATORY INVESTIGATOR(S)

Not Applicable

TRIAL SITE(S)

Approximately 10-15 sites in the United States (US) and Canada.

PLANNED TRIAL PERIOD	CLINICAL PHASE
First patient first visit (FPFV): Q1 2017 Last patient last visit (LPLV): Q4 2017	III

BACKGROUND AND SCIENTIFIC JUSTIFICATION FOR CONDUCTING THE TRIAL

Sodium picosulfate with magnesium citrate is a low-volume cleansing agent that was developed to provide an efficient and well tolerated method of clearing the bowel prior to X-ray examination, endoscopy, or surgery. The safety, tolerability, and efficacy of PREPOPIK® were demonstrated in two well-controlled clinical trials, and PREPOPIK® was approved in 2012 in the US for cleansing of the colon as a preparation for colonoscopy in adults.

PREPOPIK® is currently formulated as a powder for reconstitution with cold water immediately before use. A ready to drink oral solution of Sodium Picosulfate, Magnesium Oxide and Anhydrous Citric Acid (NaP/MC) has been developed that eliminates the need for the reconstituting and mixing steps by the subject. The new oral solution has the same active ingredients in the same quantities as PREPOPIK®. The dosage administered to the subject remains the same as that of PREPOPIK®. Thus, the Sodium Picosulfate, Magnesium Oxide, Anhydrous Citric Acid (NaP/MC) Oral Solution should be as effective as PREPOPIK® in colon cleansing, with a similar safety and tolerability profile.

The current study will be conducted to assess the non-inferiority of a split-dose regimen of NaP/MC Oral Solution to a split-dose regimen of PREPOPIK® in adult subjects undergoing elective colonoscopy.

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

ENDPOINTS

Primary endpoint:

- Proportion of subjects classified as a responder defined by "excellent" or "good" using the Modified Aronchick scale (Aronchick et al, 1999, as cited by the American Society for Gastrointestinal Endoscopy [ASGE] et al, 2015)[1]

*Secondary endpoint*s:

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

METHODOLOGY

The study will be conducted at approximately 10-15 study sites in the US and Canada.

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

Only the subject and the site-designated unblinded coordinator and or 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, attesting to their agreement that they will not disclose the treatment group to anyone. Treatment will be blinded to the designated endoscopist and study site personnel assessing the efficacy of the two tested preparations.

Following randomization, subjects will perform colon cleansing using NaP/MC Oral Solution or PREPOPIK® as follows:

For each treatment arm, subjects 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.

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

> 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 take anything by mouth within two (2) hours before the time of the colonoscopy.

PREPOPIK® (supplied as two packets per subject) is reconstituted using the cup provided. The doses are prepared by combining the contents of one packet 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).

> 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.

Note: Liquids with **red, purple or blue coloring are not allowed** before the colonoscopy.

Permissible clear liquids include the following, as long as they are not red, purple or blue in color:

- Broth/bouillon: chicken, beef, vegetable
- Juices without pulp: apple juice, white grape juice, white cranberry juice.
- Water: plain or flavored
- Soda: Sprite, Seven Up, ginger ale
- Popsicles: orange, lime, lemon
- Jell-O: orange, lime, lemon
- Other permissible liquids: Gatorade, Crystal Light, Pedialyte, coffee, tea (do not add dairy/non-dairy cream or milk)

The following diet requirements and restrictions should be followed for subjects admitted into the study regardless of the treatment group:

On the day (i.e., 24 hours) before the colonoscopy, all subjects enrolled in the study are limited to a clear liquid diet only. Special meal instructions for diabetic subjects are provided in (Appendix B). The designated unblinded coordinator, who dispenses the study drug, will instruct the subject regarding the exact requirements during the randomization visit (See Section 6.2), including the need for correct hydration prior to starting bowel preparation.

For a subset of subjects, pharmacokinetic samples will be collected for sodium 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 (approximately 2 hours prior to the colonoscopy).

Subjects will return for three follow-up visits: 1-2 days (Visit 4, see Section 6.4), seven days (Visit 5, see Section 6.5), and four weeks (Visit 6, see Section 6.6) after the colonoscopy procedure.

NUMBER OF SUBJECTS

A sufficient number of subjects will be screened to ensure 900 randomized subjects (approximately 450 subjects per treatment arm). Approximately 60 subjects (30 subjects per treatment arm) will be assessed for additional PK sampling.

CRITERIA FOR INCLUSION / EXCLUSION

Inclusion Criteria

1. Male or non-pregnant female subjects aged 18 to 80 years, inclusive, being scheduled to undergo elective colonoscopy
2. Females of childbearing potential must agree to use an adequate contraception during the course of the trial. Accepted forms of contraception are: i.e., implants, injectables, hormonal intrauterine device, combined hormonal contraceptives, sexual abstinence, and vasectomized sexual partner. Premenopausal women who are of childbearing potential must have a negative serum pregnancy test result at screening and a negative urine pregnancy test result at randomization prior to colonoscopy. In the case of oral contraceptive use, women should have been taking the same pill consistently for a minimum of twelve (12) weeks before taking study medication. Sterilized or postmenopausal women may also participate. Women are considered to be postmenopausal and are not considered to be of childbearing potential if they have had twelve (12) months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation.
3. An average of at least 3 spontaneous bowel movements per week for one month prior to the colonoscopy
4. Willing, able, and competent to complete the entire procedure and to comply with study instructions
5. Written informed consent obtained at screening

Exclusion Criteria

1. Known or suspected gastrointestinal obstruction, perforation, ileus, or gastric retention
2. Acute intestinal or gastric ulceration
3. Severe acute inflammatory bowel disease (IBD), diverticulits, toxic colitis, or toxic megacolon
4. Undergoing colonoscopy for foreign body removal or decompression
5. Reduced level of consciousness or inability to swallow without aspiration
6. Any prior colorectal surgery (excluding appendectomy, hemorrhoid surgery, or prior endoscopic procedures)
7. Upper gastrointestinal surgery (gastrectomy, gastric banding, gastric by-pass)
8. Uncontrolled angina and/or myocardial infarction (MI) within last three months, congestive

heart failure (CHF), uncontrolled hypertension, or ascites

9. Severely reduced renal function (<30 mL/min/1.73 m^2)
10. Pregnant or lactating women
11. Taking another investigational medicinal product within 30 days prior to receiving study medication (or within 60 days for investigational drugs with an elimination half-life greater than 15 days)
12. Any clinically relevant abnormal findings in medical history, physical examination, vital signs, electrocardiogram (ECG), clinical chemistry, hematology, coagulation, or urinalysis at Screening Visit (V1, see Section 6.1) or Randomization Visit (V2, see Section 6.2), which in the opinion of the Investigator(s), might put the subject at risk because of his/her participation in the trial
13. Current alcohol and/or drug abuse as judged by the Investigator
14. Severe dehydration as judged by the Investigator
15. Rhabdomyolysis
16. Chronic nausea and vomiting
17. Hypermagnesemia
18. Considered by the Investigator to be unsuitable to participate in the trial for any other reason
19. Hypersensitivity to any of the ingredients
20. Undergoing treatment with Lithium

Exclusionary Medications

The following medications exclude subjects' participation in the study and/or must be suspended prior to the procedure:

- Laxatives (within 24 hours prior to procedure)
- Constipating drugs such as opiates, anticholinergics, calcium channel blockers, and clonidine (within 48 hours prior to procedure)
- Antidiarrheals such as loperamide (within 72 hours prior to procedure)
- Oral iron preparations (within 1 week prior to procedure)

MEDICINAL PRODUCTS

NaP/MC Oral Solution supplied as two 160 mL bottles per subject. No reconstitution before administration will be required:

- First dose administered the day before the colonoscopy between 5:00 and 9:00 PM
- Second dose administered the next day (day of colonoscopy) at least 5 hours but not more than 9 hours prior to the colonoscopy

PREPOPIK® supplied as two packets per subject. One dose is prepared by combining the contents of one packet with approximately five (5) ounces of water:

- First packet reconstituted and administered the day before the colonoscopy between 5:00 and 9:00 PM
- Second packet reconstituted and administered the next day (day of colonoscopy) at least 5 hours, but no more than 9 hours, prior to the colonoscopy

DURATION OF TREATMENT

Treatment and follow-up: 2-day treatment and four week follow-up.

TRIAL PROCEDURES / ASSESSMENTS

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)**	**1-2 Days**	**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[7]				
Schedule colonoscopy	x					
Laboratory (chemistry, coagulation, hematology)	x[2]		x	x	x	x
PK sampling			x[3,4]			
Urinalysis	x		x[5]	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[6]			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 (approximately 2 hours prior to the colonoscopy).
5. At the colonoscopy visit, the urinalysis panel will include urine osmolality.
6. Drug accountability will be performed by an unblinded coordinator or unblinded pharmacist (if applicable) and an unblinded monitor only.
7. Premenopausal women of childbearing potential must have a urine pregnancy test performed within 3 days prior to colonoscopy. For women of childbearing potential **randomization must occur within 3 days prior to colonoscopy**

STATISTICAL METHODS

Sample Size Calculation

The primary objective of this study is to demonstrate non-inferiority (NI) of NaP/MC Oral Solution to PREPOPIK® for overall colon cleansing prior to colonoscopy using the Modified Aronchick Scale (see Appendix C), as assessed by a blinded endoscopist.[1] 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% based on the Modified Aronchick Scale (FE2009-01 and FE2009-02). It is assumed that the true responder rates of subjects treated with PREPOPIK® or NaP/MC Oral Solution are the same. A non-inferiority (NI) margin of 8% was chosen, to ensure no more than a 10% relative decrease from the control. Four hundred fifty (450) randomized subjects per treatment group are required, in a 1:1 randomization, to maintain 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.

Efficacy:

The primary objective of the trial is to demonstrate the NI of NaP/MC Oral Solution to PREPOPIK® for colon cleansing in preparation for colonoscopy. 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 C]) 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 adjusted for 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. Subjects who do not have an excellent or good rating according to the Modified Aronchick Scale (see Appendix C) for any reason

will be considered treatment failures (i.e., not a responder). If the lower limit of the 95% confidence interval is greater than the NI 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. The primary efficacy analysis will be conducted for the modified intention-to-treat population, defined as all randomized (as planned) subjects who received at least one dose of treatment. If the NI criteria are satisfied in both the primary efficacy analysis and the secondary efficacy analysis of the right colon, then a test for superiority will be performed for the primary efficacy analysis by comparing the lower bound of the confidence interval with 0.0%. If the lower bound of the confidence interval is above 0.0%, then superiority will be declared.

The NI analysis will also be conducted for the per-protocol (PP) population as a sensitivity analysis. For the three secondary responder endpoints that are based on BBPS (cleansing of right, left and transverse segment), using the mITT population and the analysis methodology described for the primary endpoint a 95% two-sided confidence interval for responder rate difference of NaP/MC Oral Solution minus PREPOPIK® will be constructed. The NI of NaP/MC Oral Solution compared with split-dose PREPOPIK® in cleansing of the right colon will be assessed if and only if non-inferiority is demonstrated for the primary endpoint. The NI assessment for this endpoint will be similar to the NI assessment of primary endpoint and will be using the same NI margin of -8%.

The responses to Mayo Clinic Bowel Prep Tolerability Questionnaire questions (see Appendix D) will be summarized by treatment arm. All safety data will be summarized descriptively.

PK Assessment:

For PK assessment, blood samples will be collected on a subset of sixty (60) subjects three times on the day of colonoscopy. Sixty (60) subjects (approximately 30 per arm) are considered to be sufficient to characterize the PK population for sodium picosulfate and BHPM. In addition to this, all subjects enrolled in the study, including this PK subset, will have one (1) PK blood sample drawn for sodium picosulfate and BHPM immediately prior to their colonoscopy (approximately 2 hours prior to the colonoscopy).

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

List of Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ASGE	American Society for Gastrointestinal Endoscopy
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BBPS	Boston Bowel Preparation Score
BHPM	bis-(p-hydroxyphenyl)-pyridyl-2-methane
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CHF	Congestive Heart Failure
CRF	Case Report Form
CRO	Contract Research Organization
DMC	Data Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOT	End of Treatment
FDA	Food and Drug Administration
FIPCUS	Ferring International PharmaScience Center U.S.
FPFV	First Patient First Visit
FPLV	First Patient Last Visit
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transferase
GMP	Good Manufacturing Practice
IBD	Inflammatory Bowel Disease
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intention-To-Treat
LOCF	Last-Observation-Carried-Forward
MED	Minimum Effective Dose
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
mITT	Modified Intention-to-Treat
NaP/MC	Sodium Picosulfate, Magnesium Oxide and Anhydrous Citric Acid
NDA	New Drug Application
NI	Non-Inferiority

NIH	National Institutes of Health
NIMP	Non-Investigational Medicinal Product
NLM	National Library of Medicine
OC	Observed Cases
PEG	Polyethylene Glycol
PIND	Pre-Investigational New Drug
PK	Pharmacokinetic(s)
PP	Per Protocol
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDV	Source Data Validation
SF	Short Form
SOC	System Organ Class
SUSARS	Suspected Unexpected Serious Adverse Reactions
UK	United Kingdom
US	United States
WHODrug	World Health Organization Drug

1 INTRODUCTION

1.1 Background

A colonoscopy is a minimally invasive endoscopic examination of the colon that is effective as a cancer prevention tool, diagnostic method, and therapeutic intervention. In the United States (US), where colonoscopy has been the standard for colorectal cancer screening, there has been a 3% annual decrease in colorectal cancer incidence each year for the past three decades.[4] Regular screening, beginning at age 50 for average-risk individuals (age 45 for African Americans), is recommended to prevent colorectal cancer.[5] However, screen rates remain lower than the American Cancer Society's target rate, with only 63% of adults age 50 years or older having a colonoscopy in 2015.[6] Getting subjects to participate in screening programs is difficult, and the overall experience—including the cleansing procedure—influences subjects' willingness to undergo screening colonoscopy or repeat procedures.[7]

The diagnostic accuracy of colonoscopy requires thorough visualization of the colonic mucosa, which is achieved by thorough bowel cleansing prior to the procedure.[2] Bowel cleansing agents are used to empty and clean the bowel prior to colonoscopy, and inadequate bowel cleansing can lead to missed lesions, prolonged procedure durations, lower cecal intubation rates, need for repeat colonoscopy, or a scheduled colonoscopy at an earlier interval.[2,8]

The ideal bowel preparation procedure should clean the colon of all fecal material, without mucosal damage or electrolyte imbalance and with minimal discomfort to the subject.[9] Because colon cleansing must be performed by the subject, cleansing agents that are associated with good subject compliance are preferable. Regimens that cause subject discomfort or adverse reactions, require a large volume of fluid, and/or have an unpleasant taste can result in low compliance rates and unsatisfactory cleansing, leading to a poor-quality examination.[8,10,11] An agent that can be administered as a split dose is preferable due to superior bowel cleaning efficacy compared with single-dose administration and a better subject experience, as measured by greater willingness by the subject to undergo a future colonoscopy.[8] In addition, recent evidence confirms that a split-dose regimen results in higher adenoma detection rates.[12]

Sodium picosulfate, magnesium oxide and anhydrous citric acid powder for oral solution is a low-volume cleansing agent that was developed to provide an efficient, simple and pleasant tasting method of clearing the bowel prior to X-ray examination, endoscopy or surgery. The formulation includes a stimulant cathartic, sodium picosulfate, together with an osmotic laxative, magnesium citrate, which is formed in solution by the reaction of magnesium oxide and anhydrous citric acid. The combined effect stimulates peristalsis, and by retaining water in the bowel, provides a washout effect. It has been available as Picolax® in the United Kingdom (UK) since 1980, and in Canada as Pico-Salax® since 2004. In the US, Low-Volume Sodium Picosulfate, Magnesium Oxide and Anhydrous Citric Acid

Powder for Oral Solution (PREPOPIK®) was approved in 2012 and is currently indicated for cleaning of the colon as a preparation for colonoscopy in adults.

The current, approved formulation of PREPOPIK® is a powder, supplied as a two-packet treatment (20 mg sodium picosulfate in divided doses), which is reconstituted by the subject immediately before use. PREPOPIK® may be administered as either a split-dose regimen, with the second dose taken on the day of the colonoscopy, or as a day-before regimen, in which both doses are taken the evening before the colonoscopy.

In the US, the colon cleansing efficacy of PREPOPIK® was established in two randomized, Investigator-blinded, active-controlled, multicenter trials in subjects scheduled to have an elective colonoscopy. In all, 1195 adult subjects were evaluated in the primary efficacy analyses. Subjects ranged in age from 18 to 80 years (mean age 56 years); 61% were female and 39% male.

Subjects randomized to PREPOPIK® in the two studies were treated with one of two dosing regimens:

In the first study,[13] PREPOPIK® was given by "Split-Dose" (evening before and day of) dosing, where the first dose was taken the evening before the colonoscopy (between 5:00 and 9:00 PM), followed by 5 eight-ounce glasses of clear liquid, and the second dose was taken the morning of the colonoscopy (at least five hours prior to but no more than nine hours prior to colonoscopy), followed by 3 eight-ounce glasses of clear liquid.

In the second study,[6] PREPOPIK® was given by "Day-Before" (afternoon/evening before only) dosing, where both doses were taken separately on the day before the colonoscopy, with the first dose taken in the afternoon (between 4:00 and 6:00 PM), followed by 5 eight-ounce glasses of clear liquid, and the second dose taken in the late evening (approximately six hours later, between 10:00 PM and 12:00 AM), followed by 3 eight-ounce glasses of clear liquid.

The comparator in each study was a preparation containing two liters of polyethylene glycol plus electrolyte solution (PEG + E) and two 5-mg bisacodyl tablets, administered the day before the procedure. All subjects in both the PREPOPIK® and comparator groups were limited to a clear liquid diet on the day (i.e., 24 hours) before the procedure.

The primary efficacy endpoint was the proportion of subjects with successful colon cleansing ("good" or "excellent"), as assessed by a blinded colonoscopist using the Modified Aronchick scale.[1] With day-before dosing, PREPOPIK® was non-inferior to the comparator cleansing regimen.[6] PREPOPIK® administered in a split-dose regimen met the pre-specified criteria for superiority to the comparator for colon cleansing.[6]

Subject acceptance and tolerability were measured and were significantly superior ($p<0.0001$) with PREPOPIK® compared with the PEG + E and bisacodyl tablet regimen in both studies. A greater proportion of subjects rated the PREPOPIK® regimen as "very easy" or "easy" to consume and as having an "excellent" or "good" taste compared with PEG and bisacodyl tablets.[6,13] In addition, subject compliance was better with PREPOPIK®: a greater proportion of subjects who received PREPOPIK® reported having consumed the entire preparation as instructed compared with subjects who received PEG and biscodyl tablets. [6,13]

In these randomized, multicenter, controlled clinical trials, the adverse reactions nausea, headache, and vomiting were the most common ones following PREPOPIK® administration.

Ferring Pharmaceuticals has developed a pre-mixed oral solution of Sodium Picosulfate, Magnesium Oxide and Anhydrous Citric Acid (NaP/MC) that eliminates the need for reconstituting and mixing steps. The dosage administered to the subject remains the same as that of PREPOPIK®. Thus, NaP/MC Oral Solution should be as effective as and have a similar safety and tolerability profile to PREPOPIK® for colon cleansing in preparation for colonoscopy.

1.2 Scientific Justification for Conducting the Trial

The current study will be conducted to directly compare the NaP/MC Oral Solution with PREPOPIK® using a split dose regimen for colon cleansing in adult subjects undergoing colonoscopy.

1.3 Benefit / Risk Aspects

Compared with other existing alternatives for bowel cleansing, PREPOPIK® has a relatively smaller volume of liquid for the subjects to drink.[11] PREPOPIK® is also safe, effective and tolerable. NaP/MC Oral Solution has the same active ingredients, in the same quantities as PREPOPIK® when dosed by the patients and is expected to have a similar efficacy, safety, and tolerability profile.

Subjects' vital signs, ECG, laboratory values, and any AEs reported will be monitored throughout the two-day treatment period and during a four-week follow-up period.

2 TRIAL OBJECTIVES AND ENDPOINTS

2.1 Objectives

Primary Objective

- To demonstrate non-inferiority (NI) of split-dose 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 C).[1]

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 C)
- Proportion of subjects classified as a responder defined by a score ≥2 in the transverse segment of the colon using the BBPS (Appendix C)
- Proportion of subjects classified as a responder defined by a score ≥2 in the left segment of the colon using the BBPS (Appendix C)
- Frequency of each category of the Mayo Clinic Bowel Prep Tolerability Questionnaire (Appendix D)
- 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 BHPM

3 INVESTIGATIONAL PLAN

3.1 Overall Trial Design

3.1.1 Trial Design Diagram

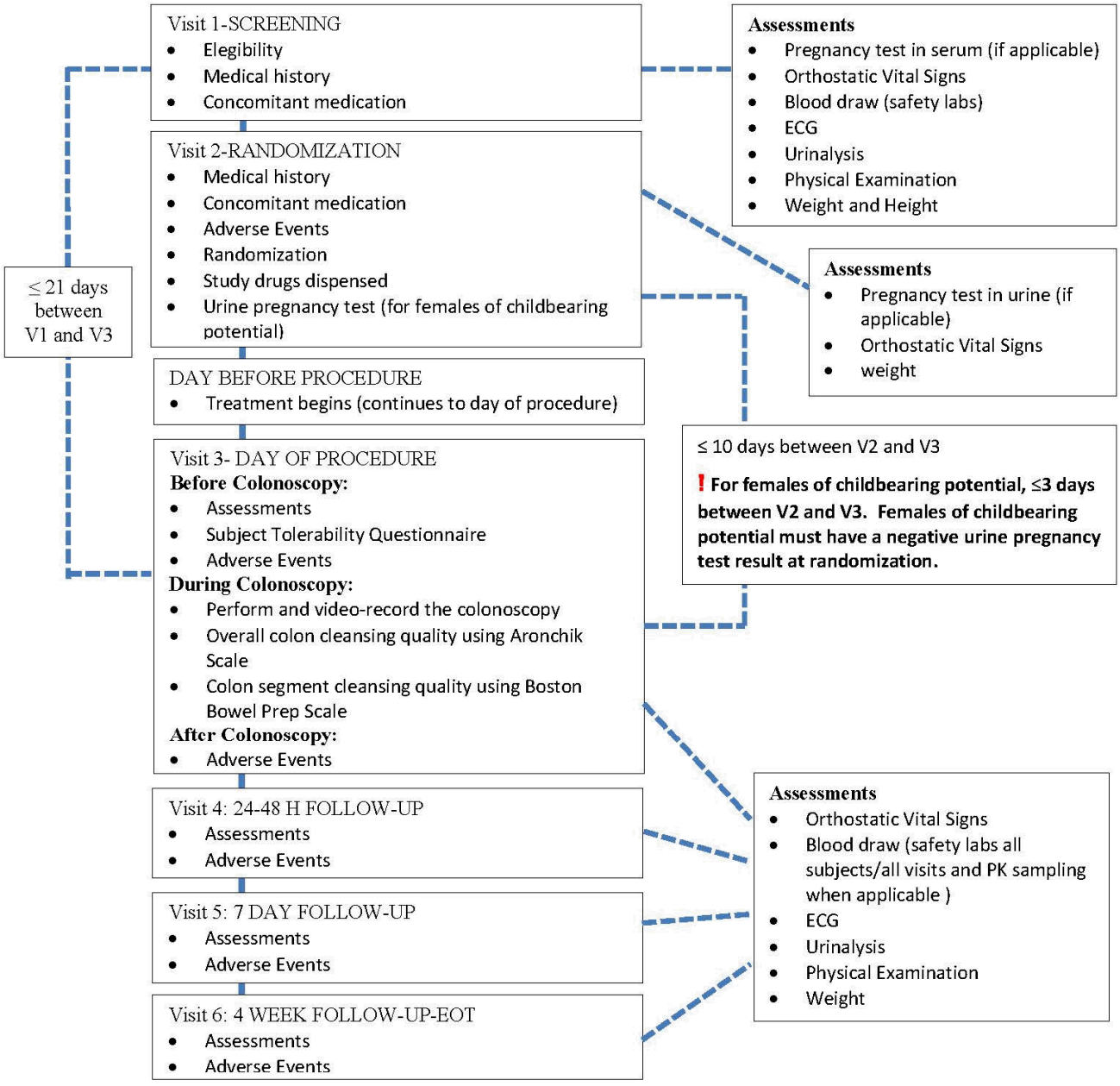

Figure 1 Trial Flow Chart

Subjects participating in the PK subset should remain in the clinical research unit for needed blood draws on the day/night before the colonoscopy (Visit 3).

3.1.2 Overall Design and Control Methods

This study is a randomized, assessor-blinded, NI, multi-center study that will be conducted in approximately 10-15 study centers in the US and Canada, following approval by appropriate oversight bodies and regulatory agencies.

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

- NaP/MC Oral Solution: Supplied as two 160-mL bottles per subject. The medication needs no further reconstitution before administration.
- PREPOPIK®: Supplied as two packets per subject. Subjects will be instructed to reconstitute the medication by combining the contents of one packet 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).

Only the subject and the site-designated, unblinded coordinator and pharmacist (if applicable) will know the treatment group in which the subjects 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 (Appendix A), attesting to their agreement that they will not disclose the treatment group to anyone. Treatment will be blinded to the designated endoscopist and study site personnel assessing the efficacy of the two tested preparations.

For each treatment arm, subjects will begin treatment (first dose) on the evening before the colonoscopy between 5:00 PM and 9:00 PM, and will complete the treatment (second dose) the following day at least 5 hours, but no more than 9 hours, prior to the colonoscopy.

Subjects randomized to the NaP/MC Oral Solution:

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 take anything by mouth within two (2) hours before the time of the colonoscopy.

Subjects randomized to PREPOPIK®:

Subjects will be instructed to reconstitute the medication by combining the contents of one packet 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).

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.

Note: Liquids with **red, purple, or blue coloring are not allowed** before the colonoscopy.

Permissible clear liquids include the following, as long as they are not red, purple or blue in color:

- Broth/bouillon: chicken, beef, vegetable
- Juices without pulp: apple juice, white grape juice and white cranberry juice
- Water: plain or flavored
- Soda: Sprite, Seven Up, ginger ale
- Popsicles: orange, lime, lemon
- Jell-O: orange, lime, lemon
- Other permissible liquids: Gatorade, Crystal Light, Pedialyte, coffee, tea (do not add dairy/non-dairy cream or milk)

On the day (i.e., 24 hours) before the procedure, all subjects enrolled in the study are limited to a clear liquid diet only. Special meal instructions for diabetic subjects are provided in Appendix B. The designated unblinded coordinator, who dispenses the study drug, will instruct the subject regarding the exact requirements during the randomization visit (V2, see Section 6.2), including the need for correct hydration prior to starting bowel preparation.

Subjects will return for three follow-up visits, 1-2 days (V4, see Section 6.4), seven days (V5, see Section 6.5) and four weeks (V6, see Section 6.6) after the colonoscopy procedure.

3.1.3 Trial Schedule

It is anticipated that the first patient first visit (FPFV) will be in the first quarter of 2017 and the last patient last visit (LPLV) will be in the fourth quarter of 2017.

3.2 Planned Number of Trial Sites and Subjects

The study will be conducted at approximately 10-15 sites in the US and Canada. A sufficient number of subjects will be screened to ensure enrollment of 900 randomized subjects (approximately 450 subjects per treatment group).

3.3 Interim Analysis

No interim analysis is planned for this study.

3.4 Data Monitoring Committee (DMC)

No Data Monitoring Committee (DMC) is planned for this trial.

3.5 Safety Review Committee (SRC)

A Safety Review Committee (SRC) will be established for this program. Cumulative safety outputs will be regularly produced for the SRC review. The timing for the generation of these outputs will be specified in the SRC documentation.

3.6 Discussion of Overall Trial Design and Choice of Control Groups

3.6.1 Trial Design

The study design is an assessor-blinded and randomized non-inferiority trial. Persons involved in the conduct and evaluation of the study will be blinded while the drug dispensing coordinator and subject are unblinded.

3.6.2 Selection of Endpoints

NI of split-dose NaP/MC Oral Solution to PREPOPIK® in overall colon cleansing in preparation for colonoscopy will be assessed by a blinded endoscopist using the Modified Aronchick scales (Appendix C) as the primary endpoint in this study. Results will be expressed as a proportion of subjects classified as responders, i.e., “excellent” and “good” according to the Modified Aronchick Scale (see Appendix C).

Efficacy of right, transverse, and left colon cleansing will be assessed by the blinded gastroenterologist using the Boston Bowel Preparation Scale (BBPS) (Appendix C).

Subject tolerability and satisfaction with the bowel cleansing preparation will be assessed by the validated[3] Mayo Clinic Bowel Preparation Questionnaire (Appendix D), administered to subjects on the day of the colonoscopy and prior to the procedure.

3.6.3 Blinding/Unblinding

3.6.3.1 Blinding

Study treatment(s) will be allocated according to computer-generated randomization codes prepared for all study sites and assigned via IVRS. The randomization assignment will be available only to the person dispensing the drug (unblinded coordinator or pharmacist (if applicable)), but not to any other personnel involved in the conduct and evaluation of the study until the study database is locked. Treatment is blinded to the endoscopist performing the colonoscopy and assessing the efficacy of the tested preparations and his/her assistant(s).

Prior to the start of the study, the investigator will assign a coordinator and a pharmacist (if applicable) to act as the site-designated unblinded coordinator. These individuals will be the only individuals unblinded to the subject's treatment group and will be responsible for the distribution and accountability of the study drug. The unblinded coordinator will instruct each subject how and when to properly administer the study drug and will explain any dietary restrictions. The unblinded coordinator will be available to answer the subject's questions regarding the study drug and its administration.

The integrity of blinding will be further preserved by requiring each subject, the unblinded coordinator, and the unblinded pharmacist (if applicable) to sign a nondisclosure affidavit form instructing subjects, the unblinded coordinator and the unblinded pharmacist (if applicable) not to disclose the assigned treatment group to the endoscopist performing the colonoscopy and his/her assistants.

3.6.3.2 Unblinding of Individual Subject Treatment

In case of an emergency, emergency decoding envelope will be available to the investigator and the sponsor's medical monitor. Breaking of the blind for individual subjects is only permitted in the case of a serious, unexpected or other important AE, when the knowledge of the investigational product in question is required for therapeutic decisions for the management of the subject.

If it is necessary to unblind an individual subject's treatment for the purposes of expedited reporting to the authorities and/or IRBs, only those individuals within Ferring Pharmaceuticals whose responsibility it is to report this information will know the identity of the IMP. Every effort will be made to maintain the blinding of site and sponsor personnel throughout the course of the study. Other personnel may be unblinded for suspected unexpected serious adverse reactions, including trial site staff as well as staff acting on behalf of Ferring.

As far as the emergency permits, the need to break the blind will be agreed by the investigator and the sponsor. It should be recorded in the CRF that the blind is broken, why, when, and by whom.

In case of accidental unblinding (e.g., the subject tells the assessor), the same documentation as for emergency unblinding must be obtained, i.e., the code envelope must be opened and why, when, and

by whom must be noted both on the code envelope and in the CRF, and the disclosure and reason must also be recorded in the subject's medical record.

Information on whether the blind has been broken for any subjects must be collected before the database is declared clean and is released to the statistician.

3.6.4 Selection of Doses in the Trial

NaP/MC Oral Solution is a new liquid formulation that is provided as an oral solution with the same active ingredients, in the same quantities as PREPOPIK® when dosed by the patient. The dosage administered to the subject remains the same as that of PREPOPIK®.

PREPOPIK® was chosen as the active comparator because when reconstituted it has the same active ingredients as the IMP and has been demonstrated to be safe and effective as a colon cleansing preparation.

3.6.5 Selection and Timing of Dose for Each Subject

For each treatment arm, the first dose is administered the evening before the colonoscopy between 5:00 and 9:00 PM. The second dose is administered the next day at least 5 hours but no more than 9 hours prior to the colonoscopy.

Each subject will be randomly assigned to one of the following treatments:

- Split-dose Low-Volume NaP/MC Oral Solution
- Split-dose Low-Volume PREPOPIK®

Complete dosing and timing instructions for the study drugs are found in Section 0.

3.6.6 Withdrawal Criteria

A subject has the right to withdraw from the trial at any time for any reason, without the need to justify their decision. However, the Investigator should record the reason for the subject's withdrawal, if possible. The Investigator also has the right to withdraw subjects. The reason should be discussed with the Sponsor prior to withdrawing the subject and that reason should be fully documented in the eCRF.

For any withdrawal, the Investigator will obtain all the required details and document the date and main reason for the withdrawal in the eCRF. Should the subject develop conditions during the course of the study which would have prevented his/her entry into the study according to the exclusion criteria, he/she must be withdrawn immediately.

If, at the time of withdrawal, a dose of the investigational product has already been administered, the subject must be advised that follow-up safety investigations are required, which will include all procedures outlined in the follow-up visit.

Reasons for withdrawal may include:

- A subject's desire to withdraw for any reason
- Loss to follow-up (every effort must be made to contact the subject; a certified letter must be sent or phone calls on three separate days must be made)
- An AE which, in the opinion of the investigator, necessitates withdrawal
- A subject's substantial non-compliance. Before withdrawing a subject from the trial due to substantial non-compliance, the investigator should contact the sponsor to discuss the withdrawal
- The investigator may withdraw a subject anytime, if it is considered to be in the subject's best interest

3.6.7 Subject Replacement

Subjects discontinued or withdrawn from the study will not be replaced.

3.6.8 Follow-up Procedures

Subjects will return for three follow-up visits, at 1-2 days (V4, see Section 6.4), seven days (V5, see Section 6.5), and four weeks (V6, see Section 6.6) after the colonoscopy procedure.

At each follow-up visit, vital signs, laboratory values, and ECGs will be assessed, and any adverse events reported by the subject will be recorded. Adverse events requiring therapy must be treated with the recognized standards of medical care to protect the health and well-being of the subject.

New illness or worsening of concomitant illness should be reported as AEs.

4 SELECTION OF TRIAL POPULATION

4.1 Trial Population

Adult subjects age 18-80, scheduled to undergo an elective colonoscopy and who meet all inclusion and exclusion criteria may be enrolled in this trial.

4.1.1 Inclusion Criteria

Subjects who meet all of the following criteria will be eligible for the study:

1. Male or non-pregnant female subjects aged 18 to 80 years, inclusive, being scheduled to undergo elective colonoscopy
2. Females of childbearing potential must agree to use an adequate contraception during the course of the trial. Accepted forms of contraception are: i.e., implants, injectables, hormonal intrauterine device, combined hormonal contraceptives, sexual abstinence, and vasectomized sexual partner. Premenopausal women who are of childbearing potential must have a negative serum pregnancy test result at screening and a negative urine pregnancy test result at randomization prior to colonoscopy. In the case of oral contraceptive use, women should have been taking the same pill consistently for a minimum of twelve (12) weeks before taking study medication. Sterilized or postmenopausal women may also participate. Women are considered to be postmenopausal and are not considered to be of childbearing potential if they have had twelve (12) months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation.
3. An average of at least 3 spontaneous bowel movements per week for one month prior to the colonoscopy
4. Willing, able, and competent to complete the entire procedure and to comply with study instructions
5. Written informed consent obtained at screening

4.1.2 Exclusion Criteria

The presence of any of the following excludes a subject from study enrollment:

1. Known or suspected gastrointestinal obstruction, perforation, ileus, or gastric retention
2. Acute intestinal or gastric ulceration
3. Severe acute inflammatory bowel disease (IBD), diverticulitis, toxic colitis, or toxic megacolon
4. Undergoing colonoscopy for foreign body removal or decompression
5. Reduced level of consciousness or inability to swallow without aspiration
6. Any prior colorectal surgery, excluding appendectomy, hemorrhoid surgery, or prior endoscopic procedures

7. Upper gastrointestinal surgery (gastrectomy, gastric banding, gastric by-pass)
8. Uncontrolled angina and/or myocardial infarction (MI) within last three months, congestive heart failure (CHF), uncontrolled hypertension, or ascites
9. Severely reduced renal function (<30 mL/min/1.73 m^2)
10. Pregnant or lactating women
11. Taking another investigational medicinal product within 30 days prior to receiving study medication (or within 60 days for investigational drugs with an elimination half-life greater than 15 days)
12. Any clinically relevant abnormal findings in medical history, physical examination, vital signs, ECG, clinical chemistry, hematology, coagulation, or urinalysis at Screening Visit (V1, see Section 6.1) or Randomization Visit (V2, see Section 6.2), which in the opinion of the Investigator(s) might put the subject at risk because of his/her participation in the trial
13. Current alcohol and/or drug abuse as judged by the Investigator
14. Severe dehydration as judged by the Investigator
15. Rhabdomyolysis
16. Chronic nausea and vomiting
17. Hypermagnesemia
18. Considered by the Investigator to be unsuitable to participate in the trial for any other reason
19. Hypersensitivity to any of the ingredients of the study medication
20. Undergoing treatment with Lithium

4.2 Method of Assigning Subjects to Treatment Groups

4.2.1 Recruitment

Adult subjects age 18-80 who are being scheduled to undergo an elective colonoscopy will be screened to determine if they meet all inclusion/exclusion criteria and are willing to participate in the study. A screening log of all subjects considered for participation in the study will be maintained at each study site.

Each subject must receive a detailed explanation of the study and must sign the Informed Consent Form after having sufficient time to consider his or her participation in the study.

Under no circumstances will subjects in the study be permitted to re-screen for a second time in this study.

4.2.2 Randomization

The randomization list will be generated by an independent, unblinded statistician prior to the first subject's first visit. Each subject will be randomized (1:1) to one of the two treatment arms, NaP/MC Oral Solution or PREPOPIK®, prior to the distribution of study drug. Randomization numbers will be

allocated sequentially to the subjects at each site, in the order in which the subjects are randomized at the site.

A subset of subjects will participate in a PK assessment and will have blood samples collected four times on the day that the colonoscopy is performed. Approximately 60 randomized subjects will be included in this PK sub-group. A subset of sites will be identified as PK sites and subjects for this sub-group will come from these sites. Randomization will be stratified by site and PK sub-group (whether or not a subject participates in the PK sub-group).

Under no circumstances will subjects enrolled in the study be permitted to re-enroll for a second time in this study.

4.3 Restrictions

4.3.1 Water Insufflation During Colonoscopy Insertion

In order to standardize the insufflation procedure during colonoscopy insertion, only air insufflation will be permitted in this study. Water insufflation is not permitted in this study as a first line practice. In the rare event that water insufflation is necessary to complete the procedure, the use of water insufflation will be recorded in the eCRF together with the volume of liquid used to complete the procedure.

4.3.2 Prior and Concomitant Therapies

Use of any concomitant medication should be recorded in the eCRF.

4.3.3 Prohibited Therapy

- The following medications exclude subjects' participation in the study and/or must be suspended prior to the Laxatives (within 24 hours prior to procedure)
- Constipating drugs such as opiates, anticholinergics, calcium channel blockers, and clonidine (within 48 hours prior to procedure)
- Antidiarrheals such as loperamide (within 72 hours prior to procedure)
- Oral iron preparations (within one week prior to procedure)

4.3.4 Other Restrictions

On the day before the colonoscopy, subjects are limited to a liquid diet only. The unblinded coordinator, who dispenses the study drugs, will instruct the subject(s) about the exact requirements during Randomization Visit (V2, see Section 6.2). Diet and liquid intake will be collected on the CRF.

5 TREATMENTS

5.1 Treatments Administered

Each subject will be randomly assigned to one of the following treatment groups:

- NaP/MC Oral Solution: Supplied as two 160-mL bottles per subject. The medication needs no further reconstitution before administration.
- PREPOPIK®: Supplied as two packets per subject. Subjects will be instructed to reconstitute the medication by combining the contents of one packet 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).

5.1.1 Investigational Medicinal Product (IMP)

Sodium Picosulfate, Magnesium Oxide and Anhydrous Citric Acid (NaP/MC) Oral Solution

Dose: Sodium Picosulfate, Magnesium Oxide and Anhydrous Citric Acid (NaP/MC) Oral Solution will be provided as two 160-mL bottles to be administered in divided doses.

The first dose is administered the evening before the colonoscopy between 5:00 PM and 9:00 PM. The second dose is administered at least five (5) hours, but no more than nine (9) hours, prior to the colonoscopy.

***Preparation*:** NaP/MC Oral Solution is supplied as two 160-mL bottles per subject and needs no further reconstitution before administration.

Compliance will be documented in the eCRF. Subjects will be considered compliant if the dosing occurs within 30 minutes of specified timings above.

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 take anything by mouth within two (2) hours before the time of the colonoscopy.

PREPOPIK®

***Dose*:** PREPOPIK®: Is supplied as two (2) packets per subject. One dose is prepared by combining the contents of one packet with approximately five (5) ounces of water.

Subjects will take the first dose the evening before the colonoscopy between 5:00 and 9:00 PM and will complete the treatment (second dose) the following day at least 5 hours prior but no later than 9 hours prior to the colonoscopy.

***Preparation*:** Mix the contents of one (1) packet with cold water (approximately five (5) ounces) in the cup provided. Stir for two to three minutes and drink the solution. In some cases the cup may feel warm, which is normal.

Compliance will be documented in the eCRF. Subjects will be considered compliant if the dosing occurs within 30 minutes of specified timings above.

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.

Note: Liquids with **red, purple, or blue coloring are not allowed** before the colonoscopy.

Permissible clear liquids include the following, as long as they are not red, purple or blue in color:

- Broth/bouillon: chicken, beef, or vegetable
- Juices without pulp: apple juice, white grape juice, white cranberry juice
- Water: plain or flavored
- Soda: Sprite, Seven Up, ginger ale
- Popsicles: orange, lime, lemon
- Jell-O: orange, lime, lemon
- Other permissible liquids: Gatorade, Crystal Light, Pedialyte, coffee, tea (do not add dairy/non-dairy cream or milk)

The following diet requirements and restrictions should be followed for subjects admitted into the study regardless of the treatment group:

On the day (i.e., 24 hours) before the procedure, subjects are limited to a clear liquid diet only. Special meal instructions for diabetic subjects are provided in Appendix B. The unblinded coordinator who dispenses the drug will explain any dietary restrictions or requirements during the randomization visit (V2, see Section 6.2), including the need for correct hydration prior to starting bowel preparation.

5.2 Characteristics and Source of Supply

All medicinal products are provided by Ferring Pharmaceuticals and will be handled according to the principles of Good Manufacturing Practice (GMP).

5.2.1 Investigational Medicinal Product

5.2.1.1 Sodium Picosulfate, Magnesium Oxide and Anhydrous Citric Acid (NaP/MC) Oral Solution

NaP/MC Oral Solution will be supplied in two (2) 160-mL bottles and contains the following active ingredients:

- Sodium Picosulfate 10.0 mg
- Magnesium Oxide, Light 3.5 g
- Citric Acid, Anhydrous 12.0 g

Magnesium oxide and anhydrous citric acid react in solution to form magnesium citrate.

NaP/MC Oral Solution is manufactured and supplied by Ferring Pharmaceuticals in boxes containing two 160 mL bottles each.

5.2.1.2 PREPOPIK®

PREPOPIK® is a white crystalline powder for oral solution and will be supplied in two (2) packets. Each packet of PREPOPIK® contains the following ingredients:

- Sodium Picosulfate 10.0 mg
- Magnesium Oxide, Light 3.5 g
- Citric Acid, Anhydrous 12.0 g

Magnesium oxide and anhydrous citric acid react in solution to form magnesium citrate.

PREPOPIK® is manufactured and supplied by Ferring Pharmaceuticals for the U.S. market in boxes containing two packets and a dosing cup.

5.3 Packaging and Labeling

Packaging and labeling of the IMPs will be performed under the responsibility of the Ferring IMP department. All packaging and labeling operations will be performed according to the requirements of GMP and national regulatory requirements.

The IMPs will be labeled with trial-specific labels, and the content on the labels will be in accordance with ANNEX 13, EudraLex volume 4, and national requirements in the countries where the study will

be conducted. The labels will contain a self-adhesive tear-off portion to be affixed to the dispensing log maintained at the trial site.

5.4 Conditions for Storage and Use

The Investigator will ensure that the medicinal products will be stored in appropriate conditions in a secure location with controlled access. The storage compartment shall be monitored regularly and the temperature shall be documented. Deviations in storage temperature must be reported to Ferring without delay and the IMPs must not be used until further instructions are received.

5.4.1 Investigational Medicinal Product

NaP/MC Oral Solution should be stored in the original package at temperatures not exceeding 25°C (77°F) and protected from light.

PREPOPIK® should be stored in the original package at temperatures not exceeding 25°C (77°F) and protected from light.

5.5 Blinding / Unblinding

5.5.1 Blinding

Treatment is blinded to the endoscopist performing the colonoscopy and assessing the efficacy of the tested preparations and his/her assistant(s). Prior to the start of the study, the investigator will assign a coordinator and a pharmacist (if applicable) to act as the unblinded coordinator and unblinded pharmacist (if applicable). The designated unblinded study coordinator or unblinded pharmacist (if applicable) will be responsible for distribution and accountability of the drug and will instruct the subject and his/her parent/guardian about the use of the bowel preparation, including dietary restrictions.

5.5.2 Unblinding of Individual Subject Treatment

Emergency unblinding will be available to the investigator and designated persons at Sponsor via a centralized randomization system. In addition, one set of emergency decoding envelopes will be available at Sponsor as a back-up for unblinding.

Breaking of the blind in individual subjects is only permitted in case of a suspected unexpected serious adverse reaction (SUSAR) or in case of an important AE where the knowledge of the investigational product in question is required for therapeutic decisions for the management of the subject.

As far as the emergency permits, the need to break the blind will be agreed by the investigator and the sponsor. It should be recorded in the source documentation that the blind is broken, why, when, and by whom. In case of accidental unblinding (e.g., the subject tells the assessor), the same documentation as

for emergency unblinding must be obtained and the event must also be recorded in the source documentation.

It may be necessary to unblind an individual subject's treatment for the purposes of expedited reporting to the authorities or to the site's Institutional Review Board (IRB), or both. In that situation, every effort will be made to maintain blinding of sponsor personnel involved in data analysis and interpretation. Other personnel may be unblinded for SUSARs, including trial site staff as well as staff acting on behalf of Ferring. Information on whether the blind has been broken for any subjects must be collected before the database is declared clean and is released to the statistician.

5.6 Treatment Compliance

5.6.1 Dispensing and Accountability

IMP will be dispensed only to subjects who meet the eligibility criteria and are randomized to a treatment group in the trial. The unblinded coordinator or unblinded pharmacist (if applicable) (or his/her designated personnel, e.g., trial nurse) will maintain a Drug Dispensing Log detailing the dates and quantities of IMP dispensed to, and used by, each subject, as well as the unique batch identifier used in the trial. The unblinded monitor will verify the drug accountability during the trial and will document any discrepancies.

5.7 Assessment of Compliance

Subjects will be considered compliant if dosing occurs within ±30 minutes of specified timings. The time of administration will be recorded in a subject diary. This diary will be provided to the subject by the unblinded coordinator or unblinded pharmacist who dispenses the drug. The subject diary and specified medication time periods will be documented in the eCRF by the unblinded coordinator during the procedure at Visit 3. The sponsor and the blinded endoscopist will not have access to this information during the trial.

5.8 Return and Destruction of Medicinal Products

All used medicinal products can be destroyed at the trial site (in accordance with local requirements) after drug accountability has been finalized, verified by the unblinded monitor, and signed off by the unblinded coordinator or unblinded pharmacist (if applicable).

All unused medicinal products must be returned for destruction, as instructed by the Ferring IMP department, after the drug accountability has been finalized, verified by the unblinded monitor, and signed off by the unblinded coordinator or unblinded pharmacist (if applicable). Products will be destroyed in accordance with local requirements.

6 TRIAL PROCEDURES

6.1 Screening Visit (Visit 1)

Prior to or at the Screening Visit, the subject must receive a detailed explanation of the study and must sign the Informed Consent Form after having sufficient time to consider his/her participation in the study. After the subject has signed the Informed Consent Form, the following will be performed:

- Obtain a thorough medical history and record demographic data
- Document any concomitant medications up to seven days prior
- Measure body weight and height
- Measure orthostatic vital signs (blood pressure and pulse)
- Perform a complete physical examination
- Obtain central laboratory sample: chemistry hematology and coagulation
- Urinalysis
- Serum pregnancy test for females of childbearing potential
- Conduct an ECG
- Schedule date of colonoscopy (≤21 Days from V1)
- Schedule Randomization Visit (V2, see Section 6.2): date of randomization (V2 ≤03 days from V3)

6.2 Randomization Visit (Visit 2)

Randomization Visit 2 (V2) takes place ≤10 days from the Procedure/Colonoscopy Visit. For **females of childbearing potential,** the Randomization Visit (V2) **must occur within three (3) days prior to the colonoscopy** procedure. Females of childbearing potential **must** have a **negative urine pregnancy test** result at randomization. For males and postmenopausal women, the Randomization Visit (V2) must occur ≤10 days prior to the colonoscopy procedure (see Section 6.3). The following will be performed:

If the study screening requirements are met:

- Confirm eligibility
- Measure orthostatic vital signs (blood pressure and pulse)
- Measure body weight

- Urine pregnancy test (onsite) for females of childbearing potential (For females of childbearing potential randomization **must occur within three (3) days** prior to the colonoscopy procedure. Females of childbearing potential **must** have **a negative urine pregnancy test** result at randomization within 3 days prior to the colonoscopy.)
- Assign Subject Randomization number
- Dispense study medication
- Instruct the subject how to self-administer the study medication and provide them with a Subject Diary Card and detailed information, complete with assigned times of drug administration
- Provide the Acceptability and tolerability questionnaire to be completed prior to the procedure Visit (V3)
- Adverse events (recorded by study personnel)
- Document any new concomitant medications

6.3 Procedure/Colonoscopy Visit (Visit 3)

If the subject is participating in the PK subset, additional laboratory samples will be obtained for sodium picosulfate and BHPM at the following timepoints:

- 15 minutes before the second dose of IMP
- 1 to 2 hours after the second dose of IMP
- 3 to 6 hours after the second dose of IMP

Immediately prior to the colonoscopy, a PK sample will be obtained for **all participating subjects** in the study (approximately 2 hours prior to the colonoscopy).

Before the colonoscopy, the following will be performed:

- Treatment completed
- Collect Subject Diary Card
- Collect the Acceptability and tolerability completed questionnaire*
- Obtain orthostatic vital signs (blood pressure and pulse)
- Measure body weight
- Obtain laboratory sample (chemistry, hematology)
- Adverse events (recorded by study personnel)
- Document any concomitant medications

- PK subset only: PK samples for sodium picosulfate and BHPM 15 minutes before the second dose, and 1 to 2 hours and 3 to 6 hours after the second dose of the IMP
- All subjects: PK sample immediately prior to colonoscopy (approximately 2 hours prior to the colonoscopy)
- Perform study drug accountability by the unblinded coordinator or unblinded pharmacist (if applicable)

*Subjects should be instructed to fill out the questionnaire during the visit in a private area prior to contact with the Investigator and to return the completed questionnaire to the study coordinator. If the coordinator is not available during the procedure, the subject will put the completed questionnaire in a sealed envelope and provide it to a member of the surgical team. The study coordinator should check each questionnaire for completion, and if the subject did not answer all/some of the questions, note the reasons on the first page of the questionnaire. No one (including study coordinator or a family member) should interpret questions or response choices for the subject.

During the colonoscopy procedure, the blinded endoscopist will:

- Video-record the colonoscopy
- Use the Modified Aronchick Scale (see Appendix C) to score the quality of the bowel preparation in the overall colon after use of the study drug
- Use the Boston Bowel Preparation Scale (see Appendix C) to score the quality of the preparation in the different segments of the colon after use of the study drug
- Record the outcome of the colonoscopy

After the colonoscopy procedure, the following will be performed/recorded:

- Adverse events (additional to those recorded prior to colonoscopy)
- Measure orthostatic vital signs (blood pressure and pulse)
- ECG
- Urinalysis (including urine osmolality, which will be collected at this visit only)
- Directed physical Examination

The subject will be scheduled to return in 1-2 days for a Follow-Up Visit (V4, see Section 6.4).

6.4 Follow-up Visit (Visit 4)

Follow-up visit (Visit 4) takes place 1 – 2 Days after the colonoscopy. The Investigator will perform the following:

- A directed physical examination
- Measure orthostatic vital signs (blood pressure and pulse)
- Measure body weight
- Interview the subject about any changes in concomitant medications, concomitant illness, or any new illnesses since the last visit. New illnesses or worsening in concomitant illnesses should be reported as AEs
- Obtain central laboratory sample: chemistry and hematology
- Urinalysis
- ECG

The subject will be scheduled to return in seven (7) days (±2 days) for a Follow-Up Visit (V5, see Section 6.5).

6.5 Follow-up Visit (Visit 5)

Follow-up visit (Visit 5) takes place seven (7) days (±2 days) after the colonoscopy. The Investigator will:

- Perform a directed physical examination
- Measure orthostatic vital signs (blood pressure and pulse)
- Measure body weight
- Interview the subject about any changes in concomitant medications, concomitant illness, or any new illnesses since the last visit. New illnesses or worsening in concomitant illnesses should be reported as AEs
- Obtain central laboratory sample: chemistry and hematology
- Urinalysis
- ECG

The subject will be scheduled to return in twenty-eight (28)-Days (± 2 Days) for a Follow-Up Visit (V6, see Section 6.6).

6.6 Follow-up Visit (Visit 6)

Follow-up visit (Visit 6) takes place twenty-eight (28) Days (± 2 Days) after the colonoscopy. The Investigator will:

- Perform a directed physical examination
- Measure orthostatic vital signs (blood pressure and pulse)
- Measure body weight
- Interview the subject about any changes in concomitant medications, concomitant illness, or any new illnesses since the last visit. New illnesses or worsening in concomitant illnesses should be reported as AEs
- Obtain central laboratory sample: chemistry and hematology
- Urinalysis
- ECG

6.7 Trial Assessments

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)**	**1-2 Days**	**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[7]				
Schedule colonoscopy	x					
Laboratory (chemistry, coagulation, hematology)	x[2]		x	x	x	x
PK sampling			x[3, 4]			
Urinalysis	x		x[5]	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[6]			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 (approximately 2 hours prior to the colonoscopy).
5. At the colonoscopy visit, the urinalysis panel will include urine osmolality.
6. Drug accountability will be performed by an unblinded coordinator or unblinded pharmacist (if applicable) and an unblinded monitor only.
7. Premenopausal women of childbearing potential must have a urine pregnancy test performed within 3 days prior to colonoscopy. For

women of childbearing potential **randomization must occur within 3 days prior to colonoscopy**

7 TRIAL ASSESSMENTS

The efficacy of the colon cleansing will be measured by a blinded endoscopist using the Modified Aronchick Scale and The Boston Bowel Preparation Scale. The endoscopist performing the colonoscopy and evaluation will be blinded to the treatment.

7.1 Assessments Related to Endpoints

7.1.1 The Modified Aronchick Scale

The efficacy of overall colon cleansing will be measured by a blinded endoscopist using the Modified Aronchick scale. The overall colon will be graded as "Excellent", "Good", "Fair", or "Inadequate" according to the definitions in Table 2.

Table 2 Modified Aronchick Scale

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

The subject is considered to be a responder if overall colon cleansing equals "excellent" or "good" on this four-point scale.

The blinded endoscopist will record in the eCRF whether or not the colonoscopy was completed. If the colonoscopy was not completed, he/she will need to state the reason why and whether a repeat is required.

7.1.2 The Boston Bowel Preparation Scale

The efficacy of right colon cleansing, transverse colon cleansing, and left colon cleansing will be measured by a blinded endoscopist using the Boston Bowel Preparation Scale after washing/suctioning. Colon cleansing will be graded 0, 1, 2, or 3, according to the definitions in The Boston Bowel Preparation Scale (see Appendix C).[2]

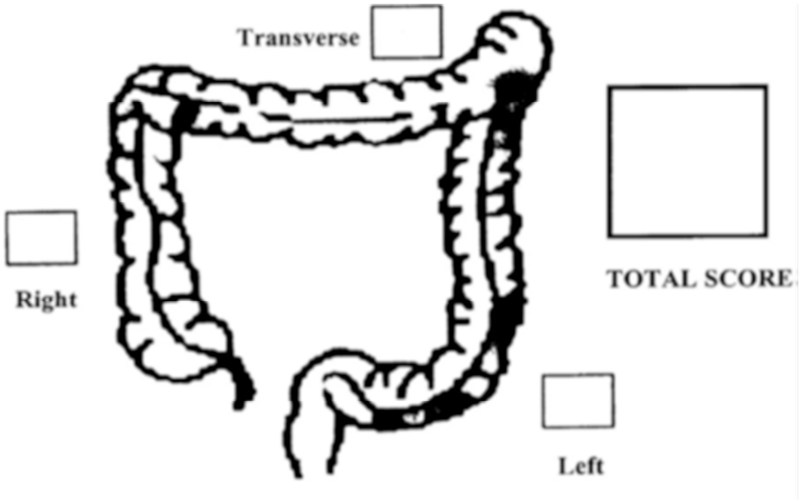

Figure 2 The Boston Bowel Preparation Scale

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.

Each region of the colon receives a "segment score" from 0 to 3, and these segment scores are summed for a total BBPS score ranging from 0 to 9. The maximum BBPS score for a perfectly clean colon without any residual liquid is 9, and the minimum BBPS score for an unprepared colon is 0. If an endoscopist aborts a procedure due to an inadequate preparation, then any non-visualized proximal segments are assigned a score of 0.

Both the Modified Aronchick scale and BBPS Scale are attached as Appendix C.

7.1.3 Mayo Clinic Bowel Preparation Tolerability Questionnaire

A secondary efficacy endpoint will be assessed by the validated[3] Mayo Clinic Bowel Preparation Tolerability Questionnaire. This questionnaire will be administered to the subject to the subject at Visit 3 on the day of the colonoscopy procedure. The Mayo Clinic Bowel Prep Tolerability Questionnaire is a simple, comprehensive questionnaire developed to evaluate the tolerability of various types of bowel preparations. The Mayo Clinic Bowel Preparation Tolerability Questionnaire is attached as Appendix D.[3]

7.2 Other Assessments

7.2.1 Physical Examinations

A complete physical examination will be conducted at the investigational site at Visit 1. At the other scheduled visits (and at early termination if applicable), a directed physical examination will be performed. Height will be measured at Visit 1 only, but weight will be measured in every visit.

After study drug administration, any new abnormal findings or worsening of an ongoing abnormal condition will be recorded as an AE.

7.2.2 Orthostatic Vital Signs

Orthostatic vital signs (blood pressure and pulse) will be measured at each scheduled visit (and at early termination, if applicable) as follows. Blood pressure and pulse will be measured after at least 5 minutes of rest in supine position and after 3 minutes in standing position. Standing measurements should be repeated after 10 minutes in patients with symptoms of volume depletion (e.g. mild dizziness) that have not presented changes in orthostatic vital signs after 3 minutes of standing.

7.2.3 Clinical Laboratory Variables

All laboratory measurements will be performed using appropriately validated methods by a central laboratory selected by the Sponsor. Sample handling and storage will be provided to all sites directly from the central laboratory.

Laboratory values will be reported to the Investigator and Sponsor (or the Sponsor's representative) and will automatically be uploaded to a database. The database will be maintained by a clinical research organization selected by the Sponsor.

Out of range values will be described in the laboratory manual to be provided by the central laboratory. Investigators will assess all out of range values as being either clinically significant or not clinically significant via the eCRF. Clinically significant abnormal laboratory measurements should be reported as AE.

Sites will be specially instructed to review all laboratory results in order to determine if the subject is eligible for study participation and to determine any adverse events post study drug administration.

Sites will be provided with sampling supplies and materials for shipment and a manual detailing all sample collection and shipment procedures.

Following Screening Visit (V1, see Section 6.1), subjects with clinically significant abnormal laboratory values will not be randomized into this study.

The following values will be collected and sent out to the central laboratory at all study visits except the randomization visit.

- Hematology panel:
  - Full CBC and differential
- Full chemistry panel:
  - Serum Chemistry: serum osmolality, bicarbonate, fasting glucose, blood urea nitrogen (BUN), creatinine, magnesium, potassium, sodium, chloride, calcium, protein total, albumin, bilirubin total, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma glutamyl transferase (GGT)
  - Calculated creatinine clearance and BUN/creatinine ratio
- Urinalysis panel (at the colonoscopy visit (V3), this includes urine osmolality)

The following values will be collected at the site during the Screening Visit only (see Section 6.1):

- Serum pregnancy test for premenopausal female subjects
- Coagulation Panel:
  - PT, APTT

The following value will be collected during Randomization Visit only (V2, see Section 6.2):

- Urine pregnancy test (onsite) for premenopausal female subjects

The Investigator will review the laboratory results and evaluate and document whether the results are normal or abnormal and whether abnormal results are non-clinically or clinically significant. The Laboratory Report will be signed and dated by the Investigator.

7.2.4 ECG

A standard 12-lead ECG will be performed as indicated in Table 1 Trial Assessment Table. After at least a 5-minute rest in a supine position, an ECG will be obtained at each visit (and at early termination, if applicable). Additional ECGs may be obtained if clinically indicated.

At each visit when an ECG is done, the investigator must review and initial the tracing. The tracing must then be stored with the subject's source documents.

The baseline ECG performed at the Screening Visit must be reviewed for major abnormalities before dosing.

If the ECG findings are clinically relevant and would prevent the subject from participating in the study (taking into account the subject's overall status), the subject should not receive the IMP.

All other abnormalities noted on the baseline ECG are reported in the Medical History eCRF. Clinically relevant abnormalities noted after the baseline ECG (Randomization Visit) should be recorded as AE

7.2.5 Fluid Intake and Dosing Diary

Subject should complete the fluid intake diary at the time of the bowel preparation. The goal is to record subjects compliance with regards to type and amount of fluid intake during dosing.

The diary will also record the time of the assigned preparation doses. The fluid intake diary will be completed for both bowel preparations. The first section of the diary should be completed after the first dose of the assigned bowel preparation. The second section of the diary should be completed after the second dose and prior to the colonoscopy procedure.

7.2.6 Other Colonoscopy Assessments

Colonoscopies will be video-recorded. Colonoscopy times (time from insertion to cecum and withdrawal time) and findings such as number and histology of polyps (i.e. adenomas, hyperplastic) identified during the colonoscopy will be collected and registered in the CRF.

Recommended colonoscopy follow up intervals based on the results of the current procedure will also be registered, including those scheduled before the recommended interval of 10 years due to inadequate preparation.

7.3 Drug Concentration Measurements

For approximately sixty (60) subjects in the two (2) PREPOPIK® groups that are participating in the PK subset, additional blood samples for measurement of sodium picosulfate and BHPM plasma concentrations will be collected. Samples will be obtained for sodium picosulfate and BHPM at Visit 3 at the following timepoints:

- 15 minutes before the second dose of IMP
- 1 to 2 hours after the second dose of IMP
- 3 to 6 hours after the second dose of IMP

In addition, **all subjects enrolled** in the study will have a PK sample for sodium picosulfate and BHPM collected immediately prior to their colonoscopy (approximately 2 hours prior to the colonoscopy).

Accurate dosing information of both doses and timing of PK samples relative to dosing will be recorded.

7.4 Handling of Biological Samples

Sampling tubes, material for shipment of urine and blood samples, and a laboratory manual detailing all sample collection and shipment procedures will be provided and distributed by the central safety laboratory and the PK laboratory at each individual trial site. Sampling tubes, material for shipment of PK blood samples, and a laboratory manual detailing all sample collection and shipment procedures will be provided and distributed by the central PK laboratory to all trial sites. Shipment of stored PK samples from the site to the PK laboratory should be on a prespecified basis. The study sites will ship one aliquot of the PK samples on dry ice to the PK laboratory. The remaining PK samples must be kept at the study centers as backup samples. These remaining samples will only be disposed of after approval by the sponsor (approximately 6 to 12 months after the publication of the clinical study report).

The actual date and time of the PK sample collection will be entered in the eCRF under ‘Blood collection for PK’ or ‘Unscheduled blood collection for PK’, as appropriate. Sampling problems will be noted in the ‘Reason sample not taken’ section of the eCRF.

Any remaining blood samples that are not analyzed for the trial will be stored at the PK laboratory until the clinical trial report has been finalized.

8 ADVERSE EVENTS

8.1 Adverse Event Definition

An adverse event is any untoward medical occurrence in a subject participating in a clinical trial. It includes:

- Any unfavourable and unintended sign, symptom, or disease, whether or not considered to be caused by the IMP
- Adverse events commonly observed and adverse events anticipated based on the pharmacological effect of the IMP
- Any laboratory abnormality, vital sign, or finding from physical examination assessed as clinically significant by the Investigator. [Note: pre-existing conditions diagnosed through assessments and examinations at the Screening Visit (V1, see Section 6.1) or during the screening period are not adverse events, but are recorded as medical history]
- Accidental injuries, reasons for any change in medication (drug and/or dose), reasons for any medical, nursing, or pharmacy consultation, or reasons for admission to hospital or surgical procedures
- Overdoses and medication errors with and without clinical consequences

An adverse drug reaction (ADR) is an AE evaluated by the investigator as having a reasonable possibility of being related to treatment with the IMP.

A serious ADR is a serious adverse event (SAE) evaluated by the investigator and/or by Ferring as having a reasonable possibility of being related to treatment with the IMP.

An unexpected AE is an AE not identified in nature, severity, or frequency in the section “Undesirable Effects” in the sponsor’s current Investigator’s Brochure and current approved label.

A treatment-emergent AE is any AE that begins during the treatment period, or is a worsening of a pre-existing medical condition. The treatment period is defined as the period during which a subject receives IMP.

8.2 Collection and Recording of Adverse Events

8.2.1 Collection of Adverse Events

The Investigator must monitor the condition of the subject throughout the trial from the time of obtaining informed consent until the last visit.

The sources of adverse events cover:

- The subject's response to questions about his/her health (a standard non-leading question such as "How have you been feeling since your last visit?" is asked at each visit)
- Symptoms spontaneously reported by the subject
- Investigations and examinations where the findings are assessed by the Investigator to be clinically significant changes or abnormalities
- Other information relating to the subject's health becoming known to the Investigator (e.g. hospitalization)

8.2.2 Recording of Adverse Events

The Investigator must record all adverse events in the Adverse Event Log provided in each subject's eCRF with information about:

- Adverse event
- Date and time of onset
- Severity
- Causal relationship to IMP
- Action taken to IMP
- Other action taken
- Date and time of outcome (or ongoing at trial end if no outcome)
- Outcome
- Seriousness

Each of the items in the Adverse Event Log is described in detail in the following sections.

Adverse Event

Adverse events should be recorded as diagnoses, if available. If not, separate signs and symptoms should be recorded. One diagnosis/symptom should be entered per record.

If a subject suffers from the same adverse event more than once and the subject recovers in between the events, the adverse events should be recorded separately. If an adverse event changes in intensity, a

worst-case approach should be used when recording the event, i.e., the highest intensity and the longest duration of the event.[a]

Note the following**:** A procedure is not an adverse event; the reason for conducting the procedure is. Hospitalization is not an adverse event (it is an outcome); the reason for hospitalization is. Death is not an adverse event (it is an outcome); the cause of death is (an exception is sudden death of unknown cause, which is, itself, an adverse event).

Date and Time of Onset

The date of onset is the date when the first sign(s) or symptom(s) were first noted. If the adverse event is an abnormal, clinically significant laboratory test or outcome of an examination, the onset date is the date the sample was taken or the examination was performed.

Intensity

The intensity of an adverse event must be classified using the following three-point scale:

Mild: Awareness of signs or symptoms, but no disruption of usual activity.

Moderate: Event sufficient to affect usual activity (disturbing).

Severe: Inability to work or perform usual activities (unacceptable).

Causal Relationship to IMP

The possibility of whether the IMP caused the adverse event must be classified as one of the following:

Reasonable possibility:

There is evidence or argument to suggest a causal relationship between the IMP and the adverse event. The adverse event may occur as part of the pharmacological action of the IMP or may be unpredictable in its occurrence.

Examples:

- Adverse events that are uncommon but are known to be strongly associated with IMP exposure

[a] Exception: if an adverse event with onset before the first IMP administration (i.e., a pre-treatment adverse event) worsens in intensity, this must be recorded as two separate events. The initial adverse event should be recorded with outcome “not recovered,” and the date and time of outcome is when the intensity changed. The second adverse event should be recorded with date and time of onset when the intensity changed.

- Adverse events that are not commonly associated with IMP exposure, but the event occurs in association with other factors strongly suggesting causation, such as a strong temporal association, or the event recurs on rechallenge.

No reasonable possibility:

There is no reasonable evidence or argument to suggest a causal relationship between the IMP and the adverse event.

Examples:

- Known consequences of the underlying disease or condition under investigation
- Adverse events common in the trial population, which are also anticipated to occur with some frequency during the course of the trial, regardless of IMP exposure

Action Taken to IMP

The action taken to the IMP in response to an adverse event must be classified as one of the following:

- No change (medication schedule maintained or no action taken)
- Withdrawn
- Interrupted

Other Action Taken

Adverse events requiring therapy must be treated with recognized standards of medical care to protect the health and well-being of the subject. Appropriate resuscitation equipment and medicines must be available to ensure the best possible treatment of an emergency situation.

If medication is administered to treat the adverse event, this medication should be entered in the Concomitant Medication Log.

Date and Time of Outcome

The date and time the subject recovered or died.

Outcome

The outcome of an adverse event must be classified as one of the following:

- Recovered (fully recovered or the condition has returned to the level observed at initiation of trial treatment)
- Recovered with sequelae (resulted in persistent or significant disability/incapacity)

- Recovering (the event is improving)
- Not recovered
- Fatal

8.3 Pregnancy and Pregnancy Outcome

If a pregnancy occurs, the IMP should be immediately stopped and Global Pharmacovigilance at Ferring Pharmaceuticals must be informed using the Pregnancy Report Form within 3 calendar days. Note that the pregnancy itself is not a serious adverse event (SAE).

The mother and the fetus must be followed-up at least until the birth of the infant and four to six weeks after the birth of the infant. In general, the follow-up will include course, duration, and the outcome of the pregnancy, as well as neonatal. If a pregnancy results in an abnormal outcome (birth defect/congenital anomaly) this must be reported as a serious adverse event to Global Pharmacovigilance at Ferring Pharmaceuticals as described in section 8.4.2.

In cases in which a fetus may have been exposed through transmission of the IMP via semen following paternal exposure, and the pregnancy results in an abnormal outcome (birth defect/congenital anomaly), this must be reported as a serious adverse event to Global Pharmacovigilance at Ferring Pharmaceuticals as described in section 8.4.2.

8.4 Serious Adverse Events

8.4.1 Serious Adverse Event Definition

Serious adverse events (SAEs) are defined in Table 3.

Table 3 Serious Adverse Events During the Trial

An event is defined a serious adverse event if it:	Guidance
results in **death**	Any event resulting in a fatal outcome must be fully documented and reported, including deaths occurring within four weeks after the treatment ends and irrespective of the causal relationship to the IMP. The death of a subject enrolled in a trial is per se not an event, but an outcome.
is **life-threatening**	The term *life-threatening* refers to an AE in which the subject was at immediate risk of death at the time of the event. It does not refer to an event, which may have caused death if it were more severe.
requires in-patient **hospitalization** or prolongation	The term hospitalization means that the subject was admitted to hospital or that existing hospitalization was extended as a result of an event. Hospitalization describes a period of

An event is defined a serious adverse event if it:	Guidance
of existing hospitalization	at least 24 hours. Overnight stay for observation, stay at emergency room, or treatment on an out-patient basis do not constitute a hospitalization. However, medical judgement must always be exercised, and when in doubt, the case should be considered serious (i.e., if case fulfills the criterion for a medically important event). Hospitalizations for administrative or social purposes do not constitute an SAE. Hospital admissions and/or surgical operations planned before trial inclusion are not considered adverse events, if the illness or disease existed before the subject was enrolled in the trial, provided that the condition did not deteriorate during the trial.
results in persistent or significant **disability/incapacity**	Disability/incapacity means a substantial disruption of a person's ability to conduct normal life functions. In doubt, the decision should be left to medical judgement by the Investigator.
is a **congenital anomaly/birth defect**	Congenital anomaly/birth defect observed in any offspring of the subject conceived during treatment with the IMP.
is an **important medical event**	Important medical events are events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of important medical events include AEs that suggest a significant hazard, contraindication or precaution, occurrence of malignancy, or development of drug dependency or drug abuse. Medical and scientific judgement should be exercised in deciding whether events qualify as medically important. Important medical events include any suspected transmission of an infectious agent via a medicinal product. Any organism virus or infectious particle (e.g., prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings, indicating an infection in a subject exposed to a medicinal product.

8.4.2 Collection, Recording and Reporting of Serious Adverse Events

SAE Reporting by the Investigator

All SAEs must be reported **immediately** to Ferring Pharmacovigilance as soon as it becomes known to the investigator and not later than within 24 hours of their knowledge of the occurrence of an SAE.

SAEs (initial and follow-up) that are recorded *electronically* in the eCRF system should be entered, saved and e-signed within 24 hours of awareness of the SAE or changes to an existing SAE. The data

will automatically be submitted to Ferring Pharmacovigilance immediately after investigator signature or 24 hours after entry, whichever occurs first.

Follow- up information provided should describe whether the event has resolved or continues, if and how it was treated, whether the treatment code was broken or not and whether the subject continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs.

SAEs (initial and follow-up) that are recorded *on the paper SAE form* should be faxed within 24 hours of awareness of the SAE or changes to an existing SAE to Ferring Pharmacovigilance using the contact details below. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site. Follow-up information should be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE.

The investigator is responsible for submitting the completed SAE Report Form with the fullest possible details **within 3 calendar days** of his/her knowledge of the SAE.

The SAE Report Form is available in the investigator's file. The SAE report form should be completed in accordance with the instructions provided on the form and sent to Ferring Pharmacovigilance using the contact details below.

Global Pharmacovigilance, Ferring Pharmaceuticals A/S

E-mail: safety.mailbox@ferring.com

Fax: (1) 973-796-1791

Demographics, adverse events, medical history, and concomitant medication will be included in initial reports and in follow-up reports if any changes have been made since the initial report. If additional information is needed, site personnel may refer to EDC system.

Additional information relevant to the SAE, such as hospital records, results from investigations, e.g., laboratory parameters, invasive procedures, scans and x-rays, and autopsy results can be faxed or scanned and e-mailed to Ferring Pharmacovigilance using the contact details in the section above. In any case, this information must be supplied by the investigator upon request from Ferring. On any copies provided, such details such as subject's name, address, and hospital ID number should be concealed and instead subject number should be provided.

The investigator will supply Ferring and the IRB with any additional requested information such as results of post-mortem examinations and hospital records.

Expedited Reporting by Ferring

Ferring will report all adverse events that are **serious, unexpected and with a reasonable possible causality to the IMP** as judged by Ferring to the relevant parties within the stipulated timelines.

SAEs will be considered reportable regardless of whether or not the IMP was used in accordance with the provisions in the protocol, Investigator's Brochure and labeling.

8.5 Follow-up of Adverse Events and Serious Adverse Events

8.5.1 Follow-up of Adverse Events with Onset During the Trial

During the trial, the investigator must follow-up on each adverse event until it is resolved or until the medical condition of the subject is stable.

After the subject's last visit, the investigator must follow-up on any adverse event classified as serious or considered to have a reasonable possible causality to the IMP until it is resolved or until the medical condition of the subject is stable. All such relevant follow-up information must be reported to Ferring. If the event is a chronic condition, the investigator and Ferring may agree that further follow-up is not required.

8.5.2 Collection of Serious Adverse Events with Onset After Last Visit in the Trial

If an investigator becomes aware of an SAE after the subject's last visit, and he/she assesses the SAE to have a reasonable possible causality to the IMP, the case will have to be reported to Ferring, regardless how long after the end of the trial this takes place.

9 STATISTICAL METHODS

All analyses will be detailed in a separate Statistical Analysis Plan (SAP).

9.1 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 C), as assessed by a blinded endoscopist.[1] 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. 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, blood samples will be collected on a subset of sixty (60) subjects three times on the day of colonoscopy. Sixty (60) subjects (approximately 30 per arm) are considered to be sufficient to characterize the PK population for sodium picosulfate and BHPM. In addition to this, all subjects enrolled in the study, including this PK subset, will have one (1) PK blood sample drawn for sodium picosulfate and BHPM immediately prior to their colonoscopy (approximately 2 hours prior to the colonoscopy).

9.2 Subject Disposition

All subjects screened and randomized will be accounted for. All post-randomization discontinuations will be summarized by time of, and reason for, discontinuation. The number of subjects screened and not randomized will be presented.

9.3 Protocol Deviations

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Ferring or its agents, if any, monitoring the trial to request approval of a protocol deviation, as protocol deviations will not be granted.

Major or minor protocol deviations will be defined and documented prior to database lock. Details will be provided in the Statistical Analysis Plan and/or in the Clean File document.

9.4 Analysis Sets

9.4.1 Intention-to-Treat (ITT) Analysis Set

The ITT analysis set comprises all randomized subjects. The ITT analysis set will be analyzed according to randomized treatment.

9.4.2 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 treatment. The mITT analysis set will be analyzed according to randomized treatment.

9.4.3 Per Protocol (PP) Analysis Set

The PP analysis set comprises all mITT subjects except those excluded as a result of major protocol deviations. Subjects not taking the study medication in the prescribed time intervals will be excluded from the PP analysis set. These subjects will be identified prior to breaking the study blind. The PP analysis set will be analyzed according to the actual randomized treatment received.

9.4.4 Safety Analysis Set

The safety analysis set comprises all subjects who received any amount of study medication. The safety analysis set will be analyzed according to the actual treatment received.

9.5 Trial Population

9.5.1 Demographics and Other Baseline Characteristics

Descriptive statistics of demographics, other baseline characteristics, and medical history will be presented for the mITT and Safety analysis sets separately. In addition, since this is a multi-site trial, a summary of demographic and baseline characteristics will be presented by trial site.

9.5.2 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.

9.5.3 Prior and Concomitant Medication

Prior and concomitant medications will be coded using World Health Organization Drug (WHODrug) Dictionary version 01SEP2013 or later. Medications will be listed by treatment and subject as well as summarized by treatment group, Anatomical Therapeutic Chemical (ATC) classification 1st level

(alphabetically), and ATC classification 2nd level (in decreasing order of frequency) for the subjects in the mITT and safety analysis sets, separately. Medications will be tabulated separately for:

1) Prior medication; i.e., medication taken exclusively prior to first IMP administration, *i.e.,* with stop date before date of first IMP administration
2) Concomitant medication, i.e., medication taken after IMP administration (regardless of whether the drug began before first IMP administration), i.e., medication that was not stopped before date of first IMP administration and not started after the end-of-trial visit

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

9.6 Endpoint Assessments

9.6.1 General Considerations

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 in this study, the NI of the cleansing within the right colon will only be assessed if NI is demonstrated within the mITT analysis set for the primary endpoint. Superiority for the primary endpoint will be assessed if and only if NI is demonstrated for both the primary efficacy endpoint and the secondary efficacy endpoint for the right colon.

9.6.2 Primary Endpoint(s)

The difference between the responder rates in overall colon cleansing using NaP/MC Oral Solution or PREPOPIK® will be assessed. 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 C).[1] 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 C)) 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 adjusted for 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. Subjects who do not have an excellent or good rating according to the Modified Aronchick Scale (see Appendix C) for any reason will be considered treatment failures (i.e., not a responder). 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 9.6.3.1), and if the lower bound of the confidence interval is above 0% then, superiority will be declared.

The NI analysis will also be conducted for the per-protocol (PP) population as a sensitivity analysis. An additional sensitivity analysis may be performed, where a multiple imputation method will be applied to impute for subjects with missing colonoscopy assessment for reasons other than drug tolerability and for patients where water insufflation was used. Details of such analysis will be described in the analysis plan.

9.6.3 Secondary Endpoint(s)

9.6.3.1 BBPS (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, this 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.

9.6.3.2 BBPS (Transverse Colon)

The responder rate for the transverse colon using BBPS will be analyzed 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 (Transverse Colon) score of the transverse colon is ≥2.

9.6.3.3 BBPS (Left Colon)

The responder rate for the left colon using BBPS will be analyzed 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 (Left Colon) score of the left colon is ≥2.

9.6.3.4 Tolerability and Satisfaction

Mayo Clinic Bowel Prep Tolerability Questionnaire (see Appendix D) questions 2, 3, 4, 6 (for each category), and 9 will be analyzed 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 variables.

9.6.3.5 Drug Concentration Measurements/Pharmacokinetics

Drug concentrations of sodium picosulfate, magnesium and BHPM will be summarized by descriptive statistics. Apparent clearance and volume of distribution will be estimated, if possible.

9.7 Extent of Exposure and Treatment Compliance

The total treatment exposure, the amount of study drug reported as consumed, and the reported timing of treatment administration will be summarized and listed by study treatment group for the Safety Analysis Set. The number and proportion of subjects deviating from the treatment regimen will be tabulated by treatment group. The amount of study drug consumed and the timing of treatment administration for each subject according to the instructions will be presented in a data listing.

9.8 Safety

9.8.1 General Considerations

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

9.8.2 Adverse Events

Treatment-emergent adverse events (TEAEs) will be summarized overall and tabulated by System Organ Class (SOC) and Preferred Term (PT) using Medical Dictionary for Regulatory Activities (MedDRA) version 16.1 or later. A 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.

Summary tables will be prepared for:

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

A data listing will also be provided for all adverse events.

9.8.3 Safety Laboratory Variables

All safety laboratory values outside normal range will be listed separately by subject number, including demographic information and flagging values.

Continuous laboratory safety data will be summarized by treatment group and scheduled time point using descriptive statistics: sample size, mean, median, standard deviation, minimum, and maximum values. Changes from baseline will be summarized in the same way.

Categorical laboratory safety data will be summarized separately by treatment group and scheduled time point using the number and percentage of subjects in each category.

The incidence of clinically significant changes in laboratory values will be summarized separately by treatment group and scheduled time point.

9.8.4 Other Safety Variables

9.8.4.1 Vital Signs

Each vital sign will be summarized by treatment group and scheduled time point using descriptive statistics: sample size, mean, median, standard deviation, minimum, and maximum values. In addition changes from pre-treatment will be summarized in the same way.

The incidence of clinically significant changes in vital signs will be summarized separately by treatment group and scheduled time point.

The incidence of markedly abnormal changes in vital sign values will be summarized by treatment group.

9.8.4.2 ECGs

The incidence of clinically significant changes in ECGs will be summarized separately by treatment group and scheduled time point.

ECGs at each evaluation will be listed for the safety dataset. Subjects with abnormal values will be noted on the data listings.

9.8.4.3 Physical Findings

Physical examination at each evaluation will be listed for the safety dataset. Subjects with abnormal values will be noted on the data listings.

9.9 Interim Analyses

No interim analysis is planned for this study.

10 DATA HANDLING

10.1 Source Data and Source Documents

Source Data – ICH Definition

Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Source Documents - ICH Definition

Source documents are defined as original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial).

Trial-Specific Source Data Requirements – Ferring

The investigator shall retain all trial documentation including all the source records and relevant correspondence for a period of at least 15 years after regulatory approval [or longer if required by local laws] after the completion or discontinuation of the trial, if no further instructions are given by Ferring. For each subject enrolled, the investigator will indicate in the source record(s) that the subject participates in this study, and will record all study specific information including: any AE, any concomitant therapy, primary response variable/s, progress notes and status at treatment end, and the end of the subject's participation.

10.2 Electronic Data Capturing System (EDC)

In the trial an EDC system provided by an independent third party will be used for data capture. The system is fully validated and access at all levels to the system is granted/revoked following Sponsor and vendor procedures, in accordance with regulatory requirements and system requirements.

The EDC system and the database are hosted at an independent third party. After the trial database is declared clean and is released to the statistician, a final copy of the database will be stored at the Sponsor within the SAS Drug Development system. The Investigator will also receive a copy of the trial site's final and locked data a (including audit trail, electronic signature, and queries) as write-protected PDF-files produced by the independent third party. The PDF-files will be stored on a CD and will be provided to the investigator before access to the eCRF is revoked.

The Investigator will approve/authorise the EDC entries for each subject with an electronic signature which equals a handwritten signature.

Trial data has to be entered into the system within a maximum of three to five working days after the subject has attended the visit. Errors occurring in the e-CRF will be corrected electronically. Such corrections/modifications will be automatically tracked by an audit trail detailing the date and time of the correction and the name of the person making the correction. Study data from Visit 3 must be entered prior to Visit 4.

10.3 Patient Reported Outcome (PRO)

Subject tolerability and satisfaction with the preparation will be assessed by the validated Mayo Clinic Bowel Prep Tolerability Questionnaire[3] administered on the day of the colonoscopy and prior to the procedure; attached as Appendix D.

10.4 Data Management

A data management plan will be created under the responsibility of the Biometrics Department of Ferring International PharmaScience Center U.S. The data management plan will be issued before data collection begins and will describe all functions, processes, and specifications for data collection, cleaning, and validation.

A data flow diagram will describe data capture methods, who is authorized to enter data, decision about ownership of data, source data storage, which data will be transferred (including timing of transfers), the origin and destination of the data, and who will have access to the data at all times.

10.5 Provision of Additional Information

On request, the Investigator will provide Ferring with additional data relating to the trial, or copies of relevant source records, duly anonymized and protected in accordance with applicable requirements.

11 MONITORING PROCEDURES

11.1 Periodic Monitoring

The monitor will contact and visit the Investigator periodically to ensure adherence to the protocol, PK sample laboratory manuals, International Conference of Harmonisation-Good Clinical Practice (ICH-GCP), standard operating procedures and applicable regulatory requirements, maintenance of trial-related source records, completeness, accuracy, and verifiability of eCRF entries compared with source data, and verification of drug accountability, and compliance to safety reporting instructions.

The Investigator will permit the monitor direct access to all source data, including electronic medical records, and/or documents in order to facilitate data verification. The Investigator will co-operate with the monitor to ensure that any discrepancies that may be identified are resolved. The Investigator is expected to be able to meet the monitor during these visits.

For this trial, the first on-site monitoring visit will take place at each site within 4 weeks following the first subject randomized. Subsequent on-site monitoring visits will occur every 6-8 weeks.

11.2 Audit and Inspection

The Investigator will make all the trial-related source data and trial records available at any time to quality assurance auditor(s) mandated by Ferring or to domestic/foreign regulatory inspectors or representatives from IRBs who may audit/inspect the trial.

The main purposes of an audit or inspection are to assess compliance with the trial protocol and the principles of ICH-GCP, including the Declaration of Helsinki and all other relevant regulations.

The subjects must be informed by the Investigator and in the Informed Consent Documents that authorized Ferring representatives, and representatives from regulatory authorities and IRBs, may wish to inspect their medical records. During audits/inspections, the auditors/inspectors may copy relevant parts of the medical records. No personal identification apart from the screening/randomization number will appear on these copies.

The Investigator should notify Ferring without any delay of any inspection by a regulatory authority or IRB.

11.3 Confidentiality of Subject Data

The Investigator will ensure that the confidentiality of the subjects' data will be preserved. Subjects in the EDC system will not be identified by their names, but by an identification system, which consists of an assigned number in the trial. Documents that are not for submission to Ferring, e.g., the confidential subject identification code and the signed Informed Consent Documents, will be

maintained by the Investigator in strict confidence. Handling of subject data will be in accordance with all local privacy regulations.

12 CHANGES IN THE CONDUCT OF THE TRIAL

12.1 Protocol Amendments

Any change to this protocol will be documented in a protocol amendment, issued by Ferring, and agreed upon by the Investigator and Ferring prior to its implementation. Amendments may be submitted for consideration to the approving IRB(s) and regulatory authorities, in accordance with local regulations. Changes to the protocol to eliminate immediate hazard(s) to trial subjects may be implemented prior to IRB approval/favorable opinion.

12.2 Deviations from the Protocol

If deviations from the protocol occur, the Investigator must inform the monitor, and the implications of the deviation must be reviewed and discussed. Any deviation must be documented, either as an answer to a query in the eCRF, in a protocol deviation report, or a combination of both. A log of protocol deviation reports will be maintained by Ferring. Protocol deviation reports and supporting documentation must be kept in the Investigator's File and the Trial Master File.

12.3 Premature Trial Termination

Both the Investigator (with regard to his/her participation) and Ferring reserve the right to terminate the trial at any time. Should this become necessary, the procedures will be agreed upon after consultation between the two parties. In terminating the trial, Ferring and the Investigator will ensure that adequate consideration is given to the protection of the best interests of the subjects. Regulatory authorities and IRBs will be informed.

In addition, Ferring reserves the right to terminate the participation of individual trial sites. Conditions that may warrant termination include, but are not limited to, insufficient adherence to protocol requirements and failure to enter subjects at an acceptable rate.

13 REPORTING AND PUBLICATION

13.1 Clinical Trial Report

The data and information collected during this trial will be reported in a clinical trial report prepared by Ferring.

13.2 Confidentiality and Ownership of Trial Data

Any confidential information relating to the IMP or the trial, including any data and results from the trial, will be the exclusive property of Ferring. The Investigator and any other persons involved in the trial will protect the confidentiality of this proprietary information belonging to Ferring.

13.3 Publications and Public Disclosure

13.4 Publication Policy

At the end of the trial, one or more manuscripts for joint publication may be prepared in collaboration between the Investigator(s) offered authorship and Ferring. In a multi-site trial based on the collaboration of many sites, any publication of results must acknowledge all sites. Results from multi-site trials must be reported in their entirety in a responsible and coherent manner and results from subsets should not be published in advance of or without clear reference to the primary publication of the entire trial.

Authorship is granted based on the ICMJE criteria (see current official version: http/www.ICMJE.org). The total number of authors is based on the guideline from the relevant journal or congress. In the event of any disagreement in the content of a publication, both the Investigator's and Ferring's opinion will be fairly and sufficiently represented in the publication.

Any external CRO or laboratory involved in the conduct of this trial has no publication rights regarding this trial.

If the Investigator wishes to independently publish/present any results from the trial, the draft manuscript/presentation must be submitted in writing to Ferring for comments prior to submission. Comments will be given within four weeks from receipt of the draft manuscript. This statement does not give Ferring any editorial rights over the content of a publication, other than to restrict the disclosure of Ferring's intellectual property. If the matter considered for publication is deemed patentable by Ferring, scientific publication will not be allowed until after a filed patent application is published. Under such conditions the publication will be modified or delayed at the Investigator's discretion, to allow sufficient time for Ferring to seek patent protection of the invention.

13.5 Public Disclosure Policy

ICMJE member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public clinical trials registry. Thus, it is the responsibility of Ferring to register the trial in an appropriate public registry, i.e., www.ClinicalTrials.gov, a website maintained by the National Library of Medicine (NLM) at the US National Institutes of Health (NIH). A summary of the trial results is made publicly available in accordance with applicable regulatory requirements.

14 ETHICAL AND REGULATORY ASPECTS

14.1 Institutional Review Board (IRB)

An IRB will review the protocol and any amendments and recruitment advertisements. The IRB will review the Subject Information Sheet and the Informed Consent Form, their updates (if any), and any other written materials given to the subjects. A list of all IRBs to which the protocol has been submitted and the names of the committee chairs will be included in the Clinical Trial Report.

14.2 Regulatory Authority(ies) Authorization / Approval / Notification

The regulatory permission to perform the trial will be obtained in accordance with applicable regulatory requirements. All ethical and regulatory approvals must be available before a subject is exposed to any trial-related procedure, including screening tests for eligibility.

14.3 End-of-Trial and End-of-Trial Notification

The trial will be considered ended when the last subject completes the last follow-up visit (V6).

14.4 Ethical Conduct of the Trial

This trial will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki (World Medical Association Declaration of Helsinki, 55th WMA General Assembly, Tokyo 2004), in compliance with the approved protocol, ICH-GCP and applicable regulatory requirements.

14.5 Subject Information and Consent

The Investigator (or the person delegated by the Investigator) will obtain a freely given written consent from each subject after an appropriate explanation of aims, methods, sources of funding, any possible conflicts of interest, anticipated benefits, potential risks of the study and the discomfort it may entail, post-study provisions, and any other aspects of the trial which are relevant to the subject's decision to participate. The trial subject must be given ample time to consider participation in the trial, before the consent is obtained. The Informed Consent Documents must be signed and dated by the subject and the Investigator who has provided information to the subject regarding the trial before the subject is exposed to any trial-related procedure, including screening tests for eligibility. Subjects must be given the option of being informed about the general outcome and the results of the trial.

The Investigator (or the person delegated by the Investigator) will explain that the subject is completely free to refuse to enter the trial or to withdraw from it at any time, without any consequences for his/her further care and without the need to justify his/her decision.

The subject will receive a copy of the Subject Information and his/her signed Informed Consent Form.

If new information becomes available that may be relevant to a trial subject's willingness to continue participation in the trial, a new Subject Information and Informed Consent Form will be forwarded to the IRB(s) (and regulatory authorities, if required). The trial subjects will be informed about this new information and re-consent will be obtained.

Each subject will be informed that the monitor(s), quality assurance auditor(s) mandated by Ferring, IRB representatives, or regulatory authority inspector(s), in accordance with applicable regulatory requirements, may review his/her source records and data. Data protection will be handled in compliance with national/local regulations.

For subjects not qualified to give their legal consent, the written informed consent must be obtained from a legally acceptable representative in accordance with national/local regulations. If such subjects can understand the risks and benefits of the trial, they should also be informed and provide their written assent.

14.6 Compliance Reference Documents

The Declaration of Helsinki, the consolidated ICH-GCP, and other applicable law(s) and guidelines in the country where the trial takes place shall constitute the main reference guidelines for ethical and regulatory conduct.

15 LIABILITIES AND INSURANCE

15.1 ICH-GCP Responsibilities

The responsibilities of Ferring, the monitor, and the Investigator are defined in the ICH-GCP consolidated guideline and applicable regulatory requirements in the country where the trial takes place. The Investigator is responsible for adhering to the ICH-GCP responsibilities of Investigators, for dispensing the IMP in accordance with the approved protocol or an approved amendment, and for its secure storage and safe handling throughout the trial.

15.2 Liabilities and Insurance

Ferring is, as Sponsor, responsible for ensuring appropriate general/product liability insurance and, as required in accordance with applicable laws and regulations, country-specific liability insurance coverage for claims made by a trial subject for injury arising from the subject's participation in the trial.

16 ARCHIVING

16.1 Investigator File

The Investigator is responsible for maintaining all the records, which enable the conduct of the trial at the site to be fully understood, in compliance with ICH-GCP. The trial documentation, including all the relevant correspondence, should be kept by the Investigator for at least 15 years after regulatory approval, if no further instructions are given by Ferring.

The Investigator is responsible for the completion and maintenance of the confidential subject identification code, which provides the sole link between identifiable subject source records and de-identified data in the clinical database for Ferring. The Investigator must arrange for the retention of this Subject Identification Log and signed Informed Consent Documents for at least 15 years after regulatory approval.

No trial site document may be destroyed without prior written agreement between the Investigator and Ferring. Should the Investigator elect to assign the trial documents to another party, or move them to another location, Ferring must be notified. If the Investigator retires and the documents can no longer be archived by the site, Ferring can arrange having the Investigator File archived at an external archive.

16.2 Trial Master File

Ferring will archive the Trial Master File in accordance with ICH-GCP and applicable regulatory requirements.

17 REFERENCES

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13. Rex DK, Katz PO, Bertiger G, et al. Split-dose administration of a dual-action, low-volume bowel cleanser for colonoscopy: the SEE CLEAR I study. *Gastrointest Endosc.* 2013;78(1):132–141.

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APPENDICES

Appendix A Subject's Confidential Non-Disclosure Affidavit

CONFIDENTIAL NON-DISCLOSURE AFFIDAVIT

I, _____, agree to keep confidential my study medication assignment provided to me by: _____, Study Coordinator.

On this date: _____, I agree not to discuss or to disclose the type of study medication, or the timing of the dosage assigned to me with the study doctor performing my colonoscopy and anyone other than the above Study Coordinator in order to protect the integrity of the data being collected for this clinical research study. I understand that the study doctor performing my colonoscopy will not know my study medication assignment and will not be allowed to ask me questions about my study medication assignment. If I have questions concerning my study medication assignment, I agree to use the following contact information.

Study Contact: _____

Study Contact Number: _____

SIGNATURES

I have read this affidavit and understand the above information. The content and meaning of this information has been explained to me.

_____	_____	_____
Date/Time	Print Subject Name	Subject Signature
_____	_____	_____
Date/Time	Name of Person conducting Discussion	Signature of Person conducting Discussion

Copy of signed/dated confidential non-disclosure affidavit given to subject on (date) _____ by _____ (initials)

Appendix B Dietary Guidelines for Diabetics

Additional Guidelines for Diabetes Management

Even though you will be on a diet of clear fluids for the whole day before your colonoscopy examination, it is still possible for you to get sufficient carbohydrates in this diet. Besides drinking lots of fluids, you must remember that these fluids need to contain sufficient amounts of carbohydrate. If you don't drink enough fluids, your blood sugars may go low, or surprisingly, they may begin to go higher.

Guidelines

- Follow your doctor's directions for taking your insulin or pills.
- Your blood sugars should be monitored regularly. Please discuss this with your doctor, nurse or dietician.
- You must meet your needs for more fluids. Drink a lot of water, clear soup, clear broth, sugar-free drinks, sugar-free popsicles, and sugar-free Jell-O. Your goal is to drink at least one tall glass of fluid every hour, and have plenty of fluids as your meals for the day. There is no restriction to these.
- In addition to fluids, you must also meet your needs for carbohydrate every hour. See the list below for the drink ideas and portion sizes for your hourly need during the day.

To get enough carbohydrate during the day, take one choice from this list every waking hour:

One quarter cup grape juice	One third cup apple juice
One third cup cranberry juice	One third cup pineapple juice
One half cup orange juice	One half cup grapefruit juice
One half cup regular pop or soda	One quarter cup regular Jell-O
One third cup regular Kool-Aid	One half popsicle
One quarter cup sherbet	Two hard candies

Call the doctor

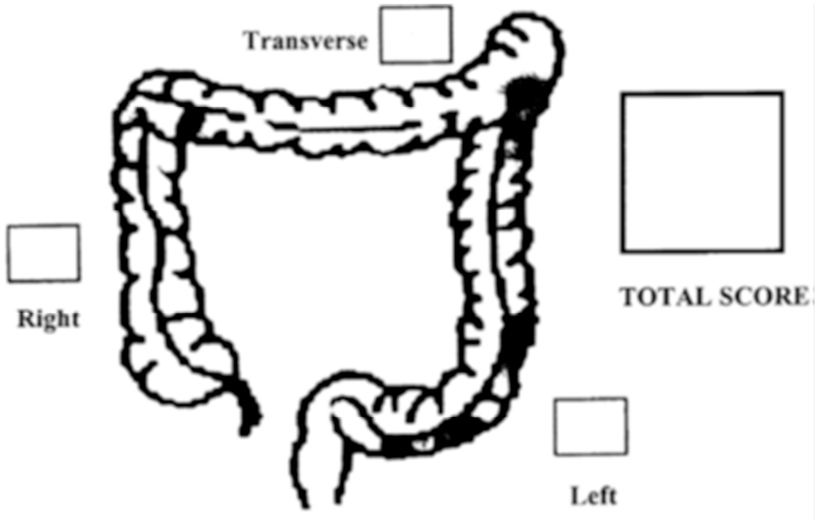
- If you have persistent nausea or vomiting.
- If you have questions or worries.

Appendix C 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 D Mayo Clinic Bowel Prep Tolerability Questionnaire

MAYO CLINIC BOWEL PREP

TOLERABILITY QUESTIONNAIRE

PROTOCOL 000253 – FERRING PHARMACEUTICALS

SITE No.: __ __ __ __ __ __ PI NAME: _____

SUBJECT No.: __ __ __ __ __ __ S __ __ __

Please follow these instructions:
• *Complete this questionnaire **PRIOR** to colonoscopy procedure* • *Mark the most appropriate response according to your current experience with the bowel preparation (for example✓)* • *Return this questionnaire to the Study Coordinator. If the SC is not available, place the questionnaire in a sealed envelope and provide it to a member of the surgical team*

Date: _____

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 a 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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SITE No.: _____ PI NAME: _____ SUBJECT No.: _____

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 completing this questionnaire.

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