CLINICAL TRIAL PROTOCOL

A Randomized, Assessor-Blind, Multicenter, Dose-Ranging Study Comparing the Safety and Efficacy of Prepopik® versus Polyethylene Glycol Preparation (Local Standard of Care) in Children Aged 9 Years to 16 Years

000103

IND Number:	101,738
Investigational Medicinal Product:	PREPOPIK® (sodium picosulfate, magnesium oxide, and anhydrous citric acid)
Indication:	Bowel preparation for pediatric colonoscopy
Phase:	Phase I/II-Post Approval Pediatric Study
Name and Address of Sponsor:	Ferring International Pharmascience Center U.S., Inc. (FIPCUS) 100 Interpace Parkway Parsippany, NJ 07054 P: 973-796-1600 F: 973-796-1699
GCP Statement:	This trial will be performed in compliance with GCP

SYNOPSIS

TITLE OF TRIAL

A Randomized, Assessor-Blind, Multicenter, Dose-Ranging Study Comparing the Safety and Efficacy of Prepopik® versus Polyethylene Glycol Preparation (Local Standard of Care) in Children Aged 9 Years to 16 Years

TRIAL SITE(S)

Approximately 6-8 sites in the United States (US)

PLANNED TRIAL PERIOD	CLINICAL PHASE
October 2013 to May 2015	Phase I/II-Post Approval Pediatric Study

OBJECTIVES

Primary objective

- To describe the efficacy of Prepopik in children aged 9 years to 16 years for overall colon cleansing in preparation for colonoscopy based on the Aronchick scale by including oral polyethylene glycol (PEG) based preparation/local standard of care as a reference group

Secondary objectives

- To describe the safety of Prepopik in children aged 9 years to 16 years through the collection of adverse events (AEs), clinical laboratory tests, and physical examination
- To describe the completion of prep as directed to colon cleansing by Prepopik in preparation for colonoscopy in children aged 9 years to 16 years
- To describe the tolerability and satisfaction of colon cleansing by Prepopik in preparation for colonoscopy in children aged 9 years to 16 years, as assessed by a standardized subject questionnaire administered at the study site before colonoscopy
- To evaluate pharmacokinetic (PK) characteristics of Prepopik in children aged 9 years to 16 years

ENDPOINTS

Primary endpoint

- Proportion of subjects classified as success defined by "excellent" or "good" in the Aronchick scale

Secondary endpoints

- Incidence of adverse events and abnormal findings in clinical laboratory test and physical examination
- Proportion of subjects who took the assigned dose for the IMP
- Frequency of each category of the Tolerability and Satisfaction Questionnaire
- PK exposure will be assessed utilizing a sparse sampling of subjects (Sparse sampling means no need for special PK time)

METHODOLOGY

Pediatric subjects, aged 9-16 years, requiring colonoscopy, who fulfill all screening criteria, and sign an informed consent and assent (as required), will be randomized to one of the treatment arms by the age group. Subjects aged 9 years to 12 years will be randomized into 3 arms: Prepopik ½ sachet x2, Prepopik 1 sachet x2, or standard of care. Subjects aged 13 years to 16 years will be randomized into 2 arms: Prepopik 1 sachet x2 or local standard of care. The designated unblinded coordinator will instruct the subject and his/her parent/guardian on the use of the bowel preparation, and along with the subject and his/her parent/guardian, will sign a nondisclosure affidavit form (APPENDIX 1), which will prevent the subject and the unblinded study coordinator from disclosing the bowel preparation treatment the subject used. Treatment will be blinded to the endoscopist and his/her assistant(s) assessing the efficacy of the tested preparations.

Colon cleansing will be performed using Prepopik for oral administration or oral PEG base preparation/local standard of care for oral solution.

There are two Prepopik dosing regimens, each requires two separate dosing times:

- "Split Dose" method is the preferred method
- "Day Before" method is the alternative method if "Split Dose" is not appropriate (see Section 5 for dosing and fluid instructions)

Subjects randomized to the "Split Dose" Prepopik group will begin treatment (1st dose) 1 day before colonoscopy between 5:00 and 9:00 PM, and will complete the treatment (2nd dose) ≥6 hours after on the next day, and at least 5 hours prior but no later than 9 hours prior to colonoscopy. Prepopik is reconstituted by mixing the powdered contents of the sachet in a cup with approximately 5 ounces of cold water. Following each administration of Prepopik, subjects will consume approximately five 8 ounce glasses of clear liquids after the first administration and at least three 8 ounce glasses of clear liquids after the second administration (all of the clear liquids should not be water).

Subjects randomized to the oral PEG based preparation/local standard of care, will follow appropriate label and/or institutional instructions.

On the day before the procedure (24 hours prior), all subjects will be limited to a liquid diet only. Special meal instructions for diabetic subjects are provided in APPENDIX 2. The coordinator who dispenses the drug will instruct the subject and his/her parent/guardian about the exact requirements during the Randomization Visit (Visit 2). Subjects will return to the site 5 (±2) days following their colonoscopy for a laboratory sample (chemistry and hematology). Subjects/parents or guardians will have a telephone assessment on Day 28 after the colonoscopy procedure.

Efficacy of the 2 tested preparations will be evaluated by a blinded endoscopist using the Aronchick scale for overall colon cleansing. A standardized subject questionnaire administered on the day of colonoscopy and prior to sedation and the procedure will assess tolerability and satisfaction of the product.

Pharmacokinetic assessments will be performed on a subset of subjects (10 subjects ages 9 years to 12 years; 5 subjects ages 13 years to 16 years). Assessments will consist of baseline and in the ~ times of C_{max} after the various analytes (time based on PK assessment of healthy volunteers).

NUMBER OF SUBJECTS

A sufficient number of subjects will be screened to ensure up to approximately 75 (for 9-12 years old, 15 subjects for the Prepopik ½ sachet x2, the Prepopik 1 sachet x2, and standard of care group; for 13-16 years old, 15 subjects for the Prepopik 1 sachet x2 and standard of care). For PK sampling, approximately 5 subjects per treatment group (a total of 15, 5 aged 13-16 years and 10 aged 9-12 years) will be assessed.

MAIN CRITERIA FOR INCLUSION / EXCLUSION

Inclusion Criteria

1. Male or female, aged 9 years to 16 years, inclusive, being scheduled to undergo elective colonoscopy
2. Females of childbearing potential must undergo a pregnancy test at screening and again at randomization
3. Subjects must have had ≥3 spontaneous bowel movements (SBM) per week for 1 month prior to the colonoscopy
4. Subjects should be willing, able, and competent to complete the entire procedure and to comply with study instructions
5. Written informed consent and assent obtained at screening

Exclusion Criteria

1. Acute surgical abdominal conditions (e.g., acute obstruction or perforation)
2. Hospitalized for inflammatory bowel disease
3. Any prior colorectal surgery, excluding appendectomy, hemorrhoid surgery, or prior endoscopic surgical procedures (subjects with diagnostic colonoscopy are not excluded)
4. Colon disease (history of colonic cancer, toxic megacolon, toxic colitis, idiopathic pseudo-obstruction, hypomotility syndrome, colon resection)
5. Ascites
6. Gastrointestinal disorder (active ulcer, outlet obstruction, retention, gastroparesis, ileus)
7. Upper gastrointestinal surgery (gastric resection, gastric banding, gastric bypass)
8. Significant cardiovascular disease as determined by the investigator
9. If subject has a history of renal insufficiency, serum creatinine and potassium must be within normal limits
10. Participation in an investigational study within 30 days prior to receiving study medication (or within 60 days for investigational drugs with an elimination half-life >15 days)
11. Any clinically significant laboratory value at screening, including pre-existing electrolyte abnormality, based on clinical history that the Investigator feels may affect the study evaluation
12. Hypersensitivity to active ingredients

Exclusionary Medications

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

1. Lithium
2. Laxatives (suspend for 24 hours prior to procedure. Laxatives as part of the SOC colonoscopy prep are not prohibited.)
3. Constipating drugs (suspend for 2 days prior to procedure)
4. Antidiarrheals (suspend for 72 hours prior to procedure)
5. Oral iron preparations (suspend for 1 week prior to procedure)

MEDICINAL PRODUCTS

- Prepopik® (sodium picosulfate 10 mg; magnesium oxide 3.5 g and anhydrous citric acid 12 g) for oral solution
- Oral PEG based preparation/local standard of care

DURATION OF TREATMENT

Prepopik: "Split Dose" treatment starts 1 day before colonoscopy (first sachet or first ½ sachet reconstituted), and completes* on the day of colonoscopy (second sachet or second ½ sachet reconstituted). *"Day Before" treatment option completes evening before colonoscopy.

Subjects randomized to the oral PEG based preparation (no enema or suppository)/local standard of care, will follow appropriate label and/or institutional instructions.

STATISTICAL METHODS

Sample size:

A total of at least 45 subjects will be exposed to Prepopik. In the two Phase 3 studies for adults, 83% and 84.2% of subjects were classified as success after bowel preparation with Prepopik. With 45 subjects, if 80% of subjects are classified as success in this study, the exact 95% confidence interval of the success rate will be calculated as 65% - 90%.

Statistical methods:

The primary efficacy endpoint will be the proportion of subjects classified as success defined by excellent or good in the Aronchick scale. The primary efficacy analysis will be based on the ITT dataset. The proportion will be presented by treatment group within each age group, for all Prepopik 1 sachet groups combined, for all Prepopik groups combined, and all standard of care groups combined with the 95% confidence interval.

The treatment group difference will be assessed by constructing the 95% confidence interval of the difference in proportions between each Prepopik group and standard of care within each age group, all Prepopik 1 sachet groups combined and all standard of care groups combined, and all Prepopik groups combined and all standard of care groups combined.

The analyses will be conducted for the PP populations as well.

The following secondary endpoints will be summarized in the same manner as the primary endpoint: proportion of subjects who completed colon cleansing, proportion of subject who record treatment as tolerable or better and proportion who rate treatment as satisfactory as provided on the Tolerability and Satisfaction Questionnaire, and proportion of subjects who completed colonoscopy procedure.

All the safety data will be summarized descriptively.

DOCUMENT APPROVAL

The Principal Investigator and Ferring International Pharmascience Center U.S., Inc. agree to conduct the study as outlined in this protocol with reference to national/local regulations and in accordance with current Good Clinical Practice (GCP) guidelines. Any modification to the protocol must be agreed upon by both the Principal Investigator and Ferring and documented in writing. By written agreement to this protocol, the Investigator agrees to allow direct access to all documentation, including source data, to authorized individuals representing Ferring (including monitoring staff and auditors), to Institutional Review Boards/Independent Ethics Committees (IRBs/IECs) and/or to domestic and foreign regulatory authorities.

FERRING REPRESENTATIVE

_____ _____

Name: Raymond E. Joseph, MD *Date (dd/mm/yyyy)*
Title: Associate Vice President, Gastroenterology

Principal Investigator

Print Name: _____

Site Name: _____

Address: _____

_____

_____ _____

Principal Investigator Signature *Date (dd/mm/yyyy)*

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADR	adverse drug reaction
AE	adverse event
C_{max}	maximum concentration
CRF	case report form
DMC	Data Monitoring Committee
ECG	electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IMP	investigational medicinal product
IRB	Institutional Review Board
ITT	intent-to-treat
IVRS	interactive voice response system
MedRA	medical dictionary for regulatory activities
NDA	new drug application
PEG	polyethylene glycol
PK	pharmacokinetic
PP	per protocol
PREA	Pediatric Research Equity Act
SAE	serious adverse event
SBM	spontaneous bowel movement defined as a bowel movement that occurs in the absence of a laxative use or manual disimpaction
SOC	standard of care
US	United States
V	visit

1 INTRODUCTION

1.1 Background

Colonoscopy is a well-established and routinely used procedure for diagnostic exploration and therapeutic procedures of the colon mucosa in all age groups. The overall success of the procedure is directly related to the ability of the pre-investigational bowel preparation to purge the colon of all fecal material, thereby allowing unobstructed visualization of the bowel wall. Inadequate colon cleansing can lead to inaccurate results, as well as increasing the time it may take to conduct the procedure and increasing the risk of complications.[1] A poor quality bowel preparation may require that the examination be repeated, resulting in additional health care costs, as well as inconvenience to the patient.[2]

Ideally, bowel cleansing should clear the colon of all solid material and cause no damage to the colonic mucosa. It should also be easy to administer, well tolerated by the patient with few adverse events (AEs), and cause minimal clinically relevant shifts in the patient's fluid and electrolyte balance. Colon cleansing is not a pleasant procedure for the patient; therefore, compliance with any colon cleansing agent is critical. Accordingly, pretreatment with a colon cleansing agent should be suitable for the patient to self-administer at home with minimal inconvenience and relatively short duration. All of the above bowel cleansing parameters are especially true for the pediatric subject.

Prepopik® (sodium picosulfate, magnesium oxide and citric acid) powder for oral solution, which cleanses the colon by means of a combination of 2 established purgative mechanisms, fulfills all of these criteria. Prepopik was approved in the United States (US) on 16 July 2012 for cleansing of the colon as a preparation for colonoscopy in adults ≥18 years of age.

The combination of sodium picosulfate with magnesium oxide and citric acid is currently approved for adult and pediatric use for colon cleansing in 34 countries around the world. The product, under the trade names Picolax, PicoSalax, Pico-Salax, Picoprep, or Prepopik (hereafter referred to as Prepopik), is currently marketed in Austria, Canada, Czech Republic, Denmark, France, Germany, Hungary, Ireland, Jordan, Malta, Netherlands, Norway, Portugal, Romania, Slovakia, United Kingdom, and the US.

The active drug substances in each pouch of Prepopik are sodium picosulfate (10 mg), a stimulant cathartic, plus magnesium oxide (3.5 g) and citric acid (12.0 g) which, upon mixing with water, form magnesium citrate, an osmotic laxative. Magnesium citrate, as an osmotic laxative, acts in both the small and large intestine to increase the bulk of the intestinal contents by causing the retention of water within the intestinal lumen. A possible additional action on cholecystokinin, which may increase intestinal fluid and electrolyte accumulation, has been reported.[3] Magnesium citrate has a rapid effect, producing a semi-liquid stool in approximately 3 hours. Sodium picosulfate, a stimulant cathartic, acts directly on the nerve endings in the colon to induce peristalsis. The purgative effect is exerted only after hydrolysis of picosulfate, by colonic bacteria, to the active metabolite bis-(p-hydroxy-phenyl)-pyridyl-2-methane.[4] Sodium picosulfate has a slower action than magnesium citrate, taking between 6 and 10 hours to exert its effect.[5,6] Thus, the combination of these 2 therapeutically active components

produces an efficient dual-action cleansing effect, enabling enhanced visibility for colonoscopy without mucosal harm.

Another important advantage of Prepopik is the ease with which patients can administer the preparation and how well it is tolerated. The preparation consists of a low-volume drink with a pleasant orange taste, followed by the consumption of clear fluids of the patient's choice, with no forced-time schedule. It has not escaped our attention that this combination should make the product desirable for all patients, pediatric patients and, in particular, the especially non-compliant adolescents. Prepopik will likely result in improved patient compliance, thus promoting more complete and timely screening procedures. Only further pediatric-driven research can establish this fact.

1.2 Scientific Justification for Conducting the Trial

The ideal pediatric bowel preparation should be effective, safe, and easily accepted by children. Currently, no bowel preparation serves the needs of all children. An important limitation of colonoscopy in children is inadequate bowel preparation. These variables certainly have a potential for improvement.

Prepopik has been shown to be an effective and well-tolerated method for bowel preparation compared with polyethylene glycol (PEG) with electrolyte solution in children.[7]

Polyethylene glycol is a long-chain polymer of ethylene oxide. Many products have an average molecular weight of 3350 g/mole and these are given the name PEG-3350. There is a perception that PEG is safe because it is minimally absorbed from the stomach and intestines. However, little is known regarding whether absorption in children differs from adults, especially in children who are constipated, have underlying intestinal disease, or are very young.

In this study, the efficacy and safety of Prepopik will be compared with oral PEG based preparation (local standard of care) in children 9 to 16 years of age in order to fulfill a post-marketing requirement for the US Food and Drug Administration (FDA) and to add to the body of knowledge in colon cleansing in this population. There is a long history of sodium picosulfate and magnesium citrate usage in colon cleansing in both adults and children.

Prepopik was first used in pediatrics in the United Kingdom in approximately 1980 and is currently used in several Western health arenas. Over 30 years' experience indicates that 12-18-year-old subjects respond well to the adult dosing. The current dosages used in pediatrics in the European Union for ages 9-18 years is 1 sachet (x2). In Canada, current pediatric dosage is ½ sachet (x2) for ages 9-12 years and 1 sachet (x2) for ages 13-18 years. This dosage has been studied in a well-controlled trial from the Toronto Hospital for Sick Children. It aimed to compare bowel preparation for colonoscopy in children with PicoSalax or PEG with electrolyte solution. Thirty five of PicoSalax patients (81%) were satisfied or very satisfied with the clean out compared with 19 (48%) in the PEG group (p=.001).[7] Therefore, in our study, the younger group will compare adult dose (1 sachet x2 as in the European Union) and ½ the adult dose (1/2 sachet x2, Canadian dose). Pharmacokinetics will be evaluated to assess potential age-related differences in systemic exposure to major constituents (picosulfate and magnesium).

1.3 Benefit / Risk Aspects

Since the original application was approved in 1980 in the United Kingdom, the colon-cleansing effects of Prepopik have been clearly demonstrated in clinical practice in both adults and children.[7,8,9,10,11,12,13,14,15,16,17,18,19] Furthermore, the cumulative worldwide exposure through 31 December 2010 is estimated to be 22,751,499 treatments, with a post-marketing adverse reaction reporting rate of <1 in 10,000 treatments. Thus, Prepopik has a global record of effectiveness and a safety profile established in clinical practice in adults and children.[1,7,8,9,12,13,16,20,21,22,23,24,25,26,27]

The effectiveness of any colon cleansing regimen must be achieved without sacrificing patient safety. While oral sodium phosphate products are highly effective and well tolerated, the risk of acute phosphate nephropathy has resulted in a Black Box warning for high-risk groups, including people >55 years of age, those who suffer from kidney disease, acute colitis, or delayed bowel emptying, and those who take certain medications that affect kidney function, to use the products with caution. Although PEG products are effective and reduce the amount of fluid shifts observed with other osmotic and stimulant laxatives, the large volume of salty fluid is poorly tolerated, frequently resulting in adverse effects that impact compliance as well as the overall effectiveness of the regimen.

In the phase 3 studies in adults, Prepopik demonstrated an acceptable safety profile for use in colon cleansing prior to colonoscopy. Among treatment-emergent AEs considered by the investigator to be possibly or probably related to study drug, only nausea (2.8%), headache (2.2%), and vomiting (1.2%) were experienced by >1.0% of subjects who received Prepopik. No deaths occurred and the incidence of subjects who experienced serious AEs (SAEs) or prematurely discontinued from study due to AEs was <1.0%. Similar results were observed for subjects who received the active comparator, HalfLytely, in the adult registration trials.

Additionally, clinical laboratory evaluation confirmed the safety of Prepopik in phase 3 studies. Bowel preparations can cause considerable dehydration, particularly in patient sub-populations such as the elderly or children, or those with cardiac disease or renal failure, and the resulting hemodynamic changes can prove hazardous to frail patients. Clinically insignificant changes in laboratory values consistent with expected shifts in fluid status as a result of the colon cleansing procedure tended to be greater following dosing with Prepopik compared with HalfLytely in the phase 3 studies, but shifts in these parameters resolved, and results were generally comparable between the treatment groups within 24-48 hours after the procedure. Adequate hydration should be maintained in all subjects during dosing with Prepopik to prevent electrolyte deficiencies such as hyponatremia or hypokalemia. The emphasis on additional fluid consumption in the dosage and administration of Prepopik aids in alleviating this risk.

The magnesium component of the Prepopik product led to transient increased magnesium levels in adult subjects following dosing in the phase 3 studies; however, the levels returned to baseline within 24-48 hours after the procedure without sequelae.

Assessments of vital signs and centralized evaluation of electrocardiogram (3000 ECGs) data from the phase 3 studies showed no signal for Prepopik on any cardiac electro-physiological functions.

Based on the worldwide safety data reported during the period covered by the periodic safety update reports (01 June 1990 – 31 December 2010), the overall benefit-risk profile of Prepopik remains favorable. Review of literature has revealed no important new safety findings. The safety profile of Prepopik is broadly consistent with the known risks as reported in the most current Summary of Product Characteristics for Prepopik. Predictably, cumulative safety data indicate that, overall, gastrointestinal disorders were the most commonly reported type of reaction, including vomiting, diarrhea, nausea, and abdominal pain. No novel or unexpected AEs were recorded in the adult registration trials.

A summary of the benefits and risks of Prepopik is provided in Table 1-1. Prepopik offers a significant improvement over other currently marketed products in the US, with an ideal balance of efficacy, safety and tolerability for cleansing of the colon as a preparation for colonoscopy.

Table 1-1 Summary of Benefits and Risks of Prepopik

Benefits	Risks
Easy to consume • Good taste • Low volume of preparation • Ability to consume clear liquids of choice • Ability to consume additional liquids at own pace • Expected high compliance Proven dual-action components • Non-inferior to a proven product • Well established safety profile • Phosphate-free preparation Two different dosing regimens • Flexible scheduling of procedure Split-dose dosing regimen • Superior overall efficacy • Superior cleansing of ascending colon Similar efficacy and safety profile in demographic subgroups	Transient increases in magnesium due to the magnesium component of the preparation Expected shifts in fluid status due to colon cleansing Potential for hypovolemia if sufficient additional clear liquids are not consumed

2 TRIAL OBJECTIVES AND ENDPOINTS

2.1 Objectives

Primary objective

- To describe the efficacy of the Prepopik in children aged 9 years to 16 years for overall colon cleansing in preparation for colonoscopy based on the Aronchick scale by including oral polyethylene glycol (PEG) based preparation/local standard of care as a reference group

Secondary objectives

- To describe the safety of Prepopik in children aged 9 years to 16 years through the collection of AEs, clinical laboratory tests, and physical examination
- To describe the completion of prep as directed to colon cleansing by Prepopik in preparation from colonoscopy in children aged 9 years to 16 years
- To describe the tolerability and satisfaction of colon cleansing by Prepopik in preparation for colonoscopy in children aged 9 years to 16 years as assessed by a standardized subject questionnaire administered at the study site before colonoscopy
- To evaluate pharmacokinetic (PK) characteristics of Prepopik in children aged 9 years to 16 years

2.2 Endpoints

Primary Endpoint

- Proportion of subjects classified as success defined by “excellent” or “good” in the Aronchick scale

Secondary Endpoints

- Incidence of adverse events and abnormal findings in clinical laboratory test and physical examination
- Proportion of subjects who took the assigned dose for the IMP
- Frequency of each category of the Tolerability and Satisfaction Questionnaire
- PK exposure will be assessed utilizing a sparse sampling of subjects (Sparse sampling means no need for special PK time)

3 INVESTIGATIONAL PLAN

3.1 Overall Trial Design

This study is a randomized, assessor-blind, multicenter, dose-ranging study. Subjects undergoing an elective complete colonoscopy will randomly receive one of the following products:

- "Split Dose" Prepopik: 2 divided doses given the night before (first dose) and approximately 5 hours prior (second dose) to procedure. A dose is defined for one subset of subjects aged 9 years to 12 years as ½ sachet, for another subset of subjects aged 9 years to 12 years per randomization as 1 sachet and for subjects aged 13 to 16 years as 1 sachet. For "Day Before" Prepopik and fluids see Section 5.

- Oral PEG based preparation/local standard of care per appropriate label and/or institutional instructions.

Table 3-1 Overview of Study Treatment Groups by Age

Treatment Group	Age Group		Total
	9-12 years	13-16 years	
Prepopik: ½ sachet	15	0	15
Prepopik: 1 sachet	15	15	30
Standard of care	15	15	30
Total subjects	45	30	75

Pediatric subjects requiring colonoscopy, who fulfill all screening criteria, and sign an informed consent and assent (as required), will be randomized. One of the treatment arm products will be provided to the subject in a randomized fashion. The designated unblinded coordinator will instruct the subject and his/her parent/guardian on the use of the bowel preparation, and along with the subject and his/her parent/guardian, will sign a nondisclosure affidavit form (APPENDIX 1), which will prevent the subject and the unblinded coordinator from disclosing the bowel preparation treatment the subject used. Treatment will be blinded to the endoscopist and his/her assistant(s) assessing the efficacy of the 2 tested preparations when local or institutional methods are used. Their dosage timing and diet will be captured in the data. This approach had been used successfully in the Prepopik adult trials.

Colon cleansing will be performed using Prepopik for oral administration or oral PEG based preparation/local standard of care for oral solution.

Subjects randomized to the "Split Dose" Prepopik group will begin treatment (1st dose) 1 day before colonoscopy between 5:00 and 9:00 PM, and will complete the treatment (2nd dose) ≥6 hours after on the next day, and at least 5 hours prior but no later than 9 hours prior to colonoscopy. Additionally, if the subject is in the hospital, instructions will be written to follow as close as possible the aforementioned dosage schedule. Prepopik is reconstituted by mixing the powdered contents of the sachet in a cup with approximately 5 ounces of cold water. Following each administration of Prepopik, subjects will consume approximately five 8 ounce glasses of clear fluids after the first administration and at least three 8 ounce glasses of clear fluids after the second administration. For "Day Before" Prepopik and fluids see section 5.

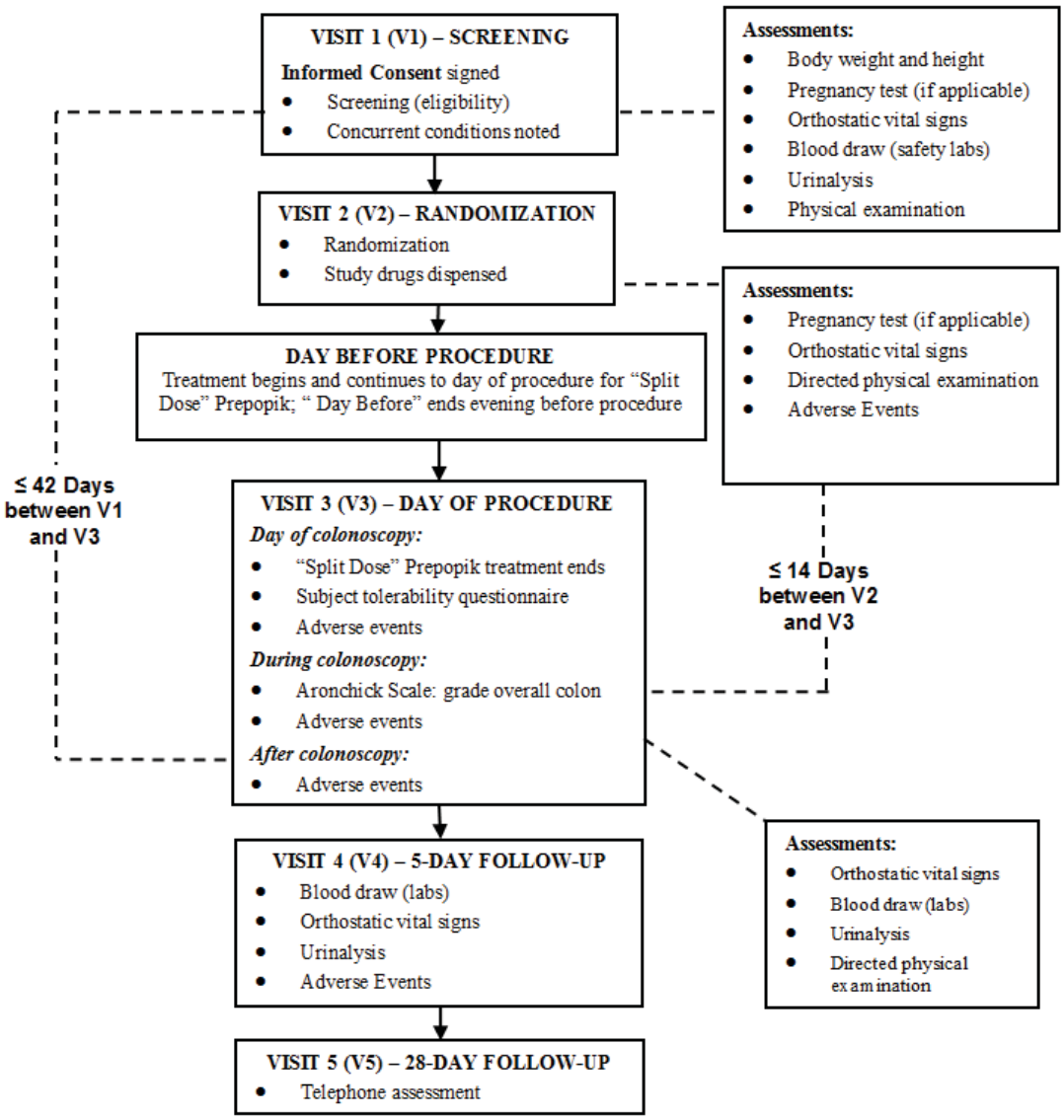
Subjects randomized to the oral PEG based preparation/local standard of care will follow appropriate label and/or institutional instructions.

On the day before the procedure (24 hours prior), all subjects will be limited to a liquid diet only. Special meal instructions for diabetic subjects are provided in APPENDIX 2. The coordinator who dispenses the drug will instruct the subject and his/her parent/guardian about the exact requirements during the Randomization Visit (Visit 2).

Subjects will return to the site 5 (±2) days following their colonoscopy for a laboratory sample (chemistry, hematology and coagulation). Subjects/parents or guardians will have a telephone assessment on Day 28 after the colonoscopy procedure.

Efficacy of the tested preparations will be evaluated by an assessor-blinded endoscopist using the Aronchick scale for overall colon cleansing. A standardized subject questionnaire administered on the day of colonoscopy and prior to sedation and the procedure will assess tolerability and satisfaction of the product (to be filled out by the subject and/or guardian).

3.1.1 Trial Design Diagram



Subjects participating in PK subset will remain in the clinical research unit for needed blood draws at V2 and V3.

3.1.2 Trial Schedule

First patient first visit is estimated for October 2013 and last patient last visit is expected in May 2015. The expected overall duration of the trial will be approximately 20 months.

3.2 Planned Number of Trial Sites and Subjects

Approximately 6-8 sites in the US are planned. A sufficient number of subjects will be screened to ensure up to approximately 75 (~15 subjects per treatment arm).

3.3 Interim Analysis

No interim analysis is planned.

3.4 Data Monitoring Committee (DMC)

No DMC will be established for this study.

3.5 Discussion of Overall Trial Design and Choice of Control Groups

3.5.1 Trial Design

The study design is assessor-blinded and randomized. Blinding treatment to the endoscopist and his/her assistant(s) assessing the efficacy of the tested preparations removes possible bias. A placebo-controlled design would not be practical or ethical in this study as subjects would be required to have a second colonoscopy.

3.5.2 Selection of Endpoints

The primary endpoint, overall colon cleansing prior to colonoscopy, will be assessed by a blinded assessor endoscopist using the Aronchick scale. The Aronchick scale is a validated instrument that has been widely used and universally accepted, and has been previously used in pivotal trials that led to new drug application (NDA) approval, including the approval of HalfLytely.[28] However, this study will compare Prepopik to oral PEG local standard of care preparations. Essentially, each endoscopic center has its own preparation concoction based on some combination of diet PEG 3350 sports drinks, enemas and stimulant laxatives.

Each investigational site will be trained on the use of the Aronchick Scale both at the investigator meeting and at initial site visit; subjects will not be initiated until all assessing gastroenterologists involved in the study at the investigational site are confident in using this tool.

3.5.3 Blinding / Unblinding

Blinding

The study treatment(s) will be allocated according to computer-generated randomization codes prepared for all study sites. Treatment is blinded to the endoscopist and his/her assistant(s) performing the colonoscopy and assessing the efficacy of the tested preparations.

Prior to the start of the study, the investigator will assign a coordinator to act as the unblinded coordinator. This person will be responsible for distribution and accountability of the drug. The unblinded coordinator will instruct each subject as to the proper administration and the timing of the drug administration. This person will be available to answer the subject's and parent's/guardian's questions regarding the study drug and its administration.

The integrity of blinding will be further preserved by requiring each subject or parent/guardian and the unblinded coordinator to sign a nondisclosure affidavit form instructing subjects/parents/guardians and the unblinded coordinator not to disclose the treatment groups to the endoscopist performing the colonoscopy and his/her assistants.

Unblinding of Individual Subject Treatment

In case of an emergency, the emergency decoding envelope will be available to the investigator and the sponsor's medical officer. Breaking of the blind in individual subjects is only permitted in 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, only those individuals within Ferring Pharmaceuticals whose responsibility it is to report this information will know the identity of the IMP. Every attempt will be made to ensure that all other study and site personnel will continue to remain blinded throughout the course of the study.

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 event must also be recorded in the subject's medical record.

It may be necessary to unblind an individual subject's treatment for the purposes of expedited reporting to the authorities and/or IRBs. 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 suspected unexpected serious adverse reactions, 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.

3.5.4 Selection of Doses in the Trial

Doses of Prepopik are age-adjusted and follow the pediatric dosing instructions in the prescribing information of the product marketed for many years in other countries. That is, a dose of Prepopik is defined as either ½ or 1 sachet (x2) for subjects aged 9 years to 12 years and 1 sachet (x2) for subjects aged 13 to 16 years. This dosage is based on the EU dose and Canadian data. Both areas have extensive hands-on experience with the preparation[7].

The oral PEG based preparation/local standard of care will be administered per appropriate label and/or institutional instructions (with complete documentation as it will vary from site to site).

3.5.5 Selection and Timing of Dose for Each Subject

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

- "Split Dose" Prepopik: 2 doses with the first dose the night before and the second dose given approximately >6 hours after but at least 5 hours prior to the procedure.

- Oral PEG based preparation/local standard of care per appropriate label and/or institutional instructions.

Complete dosing (including "Day Before" option), as well as, timing instructions for the study drugs are found in Section 5.

3.5.6 Withdrawal Criteria

Every subject has the right to refuse further participation in the study at any time and without providing reasons. A subject's participation is to terminate immediately upon his/her request. The investigator should seek to obtain the reason and record this in the case report form (CRF).

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

The subject may be withdrawn from the study at any time at the discretion of the investigator; the reason should be discussed with the sponsor prior to discontinuing the subject and the reason fully documented in the CRF. Should the subject, during the course of the study, develop conditions, which would have prevented him/her entry into the study according to the exclusion criteria, he/she must be withdrawn immediately.

The withdrawal of subjects from the study will be agreed by the investigator and the sponsor.

3.5.7 Follow-up

During Visit 4 (5 [± 2] days after colonoscopy) the subject will return to the site for a laboratory sample (chemistry and hematology), urinalysis, orthostatic vital signs and an assessment of any AEs and concomitant medications.

At Visit 5 (28 [±5] days after colonoscopy), the investigator or coordinator will interview the subject or parent/guardian via phone 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.

4 SELECTION OF TRIAL POPULATION

4.1 Trial Population

4.1.1 Inclusion Criteria

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

1. Male or female, aged 9 years to 16 years, inclusive, being scheduled to undergo an elective colonoscopy
2. Females of childbearing potential must undergo a pregnancy test at screening and again at randomization
3. Subjects must have had ≥3 spontaneous bowel movements (SBM) per week for 1 month prior to the colonoscopy
4. Subjects should be willing, able, and competent to complete the entire procedure and to comply with study instructions
5. Written informed consent and assent obtained at screening

4.1.2 Exclusion Criteria

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

1. Acute surgical abdominal conditions (e.g., acute obstruction or perforation)
2. Hospitalized for inflammatory bowel disease
3. Any prior colorectal surgery, excluding appendectomy, hemorrhoid surgery, or prior endoscopic surgical procedures (subjects with diagnostic colonoscopy are not excluded)
4. Colon disease (history of colonic cancer, toxic megacolon, toxic colitis, idiopathic pseudo-obstruction, hypomotility syndrome, colon resection)
5. Ascites
6. Gastrointestinal disorder (active ulcer, outlet obstruction, retention, gastroparesis, ileus)
7. Upper gastrointestinal surgery (gastric resection, gastric banding, gastric bypass)
8. Significant cardiovascular disease as determined by the investigator
9. If subject has a history of renal insufficiency, serum creatinine and potassium must be within normal limits
10. Participation in an investigational study within 30 days prior to receiving study medication (or within 60 days for investigational drugs with an elimination half-life >15 days)
11. Any clinically significant laboratory value at screening, including pre-existing electrolyte abnormality, based on clinical history that the Investigator feels may affect the study evaluation

12. Hypersensitivity to active ingredients

4.2 Method of Assigning Subjects to Treatment Groups

4.2.1 Recruitment

The site will recruit subjects based on the inclusion/exclusion criteria and local recruitment practices. Recruitment materials cannot be used prior to Institutional Review Board (IRB) approval.

Each trial site will require potential participants to undergo a Screening Visit prior to randomization to a treatment group. Each patient will receive a unique screening number which must be entered in a screening log that must be maintained at each trial site. The screening number will be allocated sequentially in the order in which the patients are screened. The results of each screening should be recorded in the screening log. Selected data for screened patients should also be entered in the CRF, along with the reason for screening failure if the patient is not randomized to treatment. Under no circumstances will patients screened in the trial be permitted to be re-screened for a second time in this trial.

4.2.2 Randomization

At a clinic visit preceding the colonoscopy (Visit 2), eligible pediatric subjects will be randomized to one of the treatment arms by the age group. Subjects aged 9 years to 12 years will be randomized to Prepopik ½ sachet x2, Prepopik 1 sachet x2, or standard of care in 1:1:1 ratio. Subjects aged 13 years to 16 years will be randomized to Prepopik 1 sachet x2 or oral PEG based preparation/standard of care in 1:1 ratio. Randomization numbers will be allocated sequentially to the subjects at each site. This will occur in the order in which the subjects are enrolled.

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 Prior and Concomitant Therapies

Details of all concomitant medications within 7 days of screening and throughout the study will be collected. The indication for their use and start and stop date and times must be recorded in the source data and CRF at all visits. Required information includes the drug name, strength, and formulation, route of administration, dosing frequency, and duration of treatment. Any changes (including new therapies) must be recorded at each subsequent study visit.

4.3.2 Prohibited Therapy

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

1. Lithium
2. Laxatives (suspend for 24 hours prior to procedure. Laxatives as part of the SOC colonoscopy prep are not prohibited.)
3. Constipating drugs (suspend for 2 days prior to procedure)
4. Antidiarrheals (suspend for 72 hours prior to procedure)
5. Oral iron preparations (suspend for 1 week prior to procedure)

4.3.3 Other Restrictions

On the day before the procedure, subjects are limited to a liquid diet only. The unblinded coordinator, who dispenses the study drug, will instruct the subject and parent/guardian about the exact requirements during Visit 2. Diet intake will be collected on the CRF.

5 TREATMENTS

5.1 Treatments Administered

Subjects will be randomized to one of the treatment arms by the age group. Subjects aged 9 years to 12 years will be randomized to Prepopik ½ sachet x2, Prepopik 1 sachet x2, or standard of care. Subjects aged 13 years to 16 years will be randomized to Prepopik 1 sachet x2 or standard of care.

Dose: Prepopik (sodium picosulfate, magnesium oxide and citric acid) powder for oral solution administered in a divided dose. There are two dosing regimens, each requires two separate dosing times:

- "Split Dose" method is the preferred method
- "Day Before" method is the alternative method if "Split Dose" is not appropriate

Preparation: Prepopik is reconstituted by mixing the contents of the sachet in a cup with 5 ounces of cold water.

"Split Dose"

Day before colonoscopy procedure:

- First dose between 5:00 PM and 9:00 PM

Day of colonoscopy procedure:

Second dose is given ≥ 6 hours after first dose and approximately 5 hours before but no more than 9 hours prior to the procedure

"Day Before"

Day before colonoscopy procedure:

- First dose: during afternoon or early evening before the colonoscopy
- Second dose: 6 hours later during evening before colonoscopy

Following the first administration of Prepopik, subjects will consume five 8-ounce glasses of clear liquids over the next few hours and following the second administration, subjects will consume at least three 8-ounce glasses of clear liquids (all of the clear liquids should not be water).

For those subjects needing to consume the ½ sachet, reconstitution should be completed as follows: mix the contents of the sachet in a cup with 5 ounces of cold water; stir thoroughly for three minutes; measure half of the total volume (2.5 ounces); discard the remaining fluid.

The oral PEG based preparation/local standard of care will be administered per appropriate label and/or institutional instructions.

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 Prepopik

Dose: Prepopik is a white crystalline powder for oral solution. Each sachet of Prepopik contains:

- sodium picosulfate 10.0 mg
- magnesium oxide, light 3.5 g
- citric acid, anhydrous 12.0 g

Magnesium oxide and citric acid react in water solution to form magnesium citrate, a safe and well-known colon cleanser.

Prepopik will be supplied in boxes containing 2 foil sachets each.

5.2.2 Oral PEG Based Preparation

Oral polyethylene glycol based (no enema or suppository) as per standard of care-exact solution administered will be documented by unblinded study coordinator at the site and recorded as to type and timing of diet and colon cleansing agent.

5.3 Packaging and Labeling

5.3.1 Prepopik

Packaging and labeling of the medicinal product will be performed under the responsibility of the IMP Department at Ferring Pharmaceuticals A/S in accordance with GMP and national regulatory requirements.

The label of the investigational product contains one self-adhesive tear-off portion to be affixed to the drug accountability binder. The drug accountability binder will be managed by the unblinded coordinator, and will not be available to the blinded staff conducting the assessments.

5.3.2 Oral PEG Based Preparation

See Section 5.2.2.

5.4 Conditions for Storage and Use

The investigator will ensure that the investigational products are stored in appropriate conditions in a secure location with controlled access. The temperature in the storage compartment shall be regularly monitored with a minimum/maximum thermometer and the values documented. Deviations in storage temperature must be reported to sponsor without delay, the IMP cannot be used until acceptance from the sponsor is received.

The unblinded coordinator will dispense the medication only to the identified subjects of this study, following the procedures described in this study protocol and documented in the subject dispensing log.

Drug inventory/dispensing will be documented in the source and the drug accountability binder for each subject. The investigator is responsible for all drug supplies. Written documentation is mandatory. After completion of the study, all unused investigational product will be returned to the sponsor.

5.4.1 Prepopik

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

5.4.2 Oral PEG Based Preparation

See Section 5.2.2.

5.5 Treatment Compliance

5.5.1 Dispensing and Accountability

The IMP will only be dispensed to subjects who meet all the selection criteria. A drug-dispensing log will be maintained detailing the dates and quantities of investigational products dispensed to each subject, as well as the batch numbers. The monitor will verify the drug accountability during the study. Any unused investigational product, either not dispensed or returned by a subject will be accounted for and returned to the sponsor.

5.5.2 Assessment of Compliance

Subjects will be considered compliant if dosing occurs within ±30 minutes of specified timings. The time of administration will be provided to the subject/parent/guardian by the coordinator who dispenses the drug and will be verbally confirmed with the coordinator. Subject's response to "Have you taken the medication within specified time periods?" will be documented in the CRF by the coordinator during the procedure visit (Visit 3).

5.6 Return and Destruction of Medicinal Products and Auxiliary Supplies

The trial medication delegate at the site should ensure that the destruction of used medicinal products is done in accordance with local legislation/national requirements, after the drug accountability has been finalized, verified by the monitor, and signed off by the Investigator.

After completion of the study, all unused investigational product will be returned to the sponsor as instructed by Ferring IMP Department and in accordance with local requirements, after the drug accountability has been finalized, verified by the monitor, and signed off by the Investigator.

6 TRIAL PROCEDURES

6.1 Screening Visit (Visit 1)

Prior to or at the Screening Visit, the subject and parent/guardian must receive a detailed explanation of the study and must sign the Informed Consent Form/assent as appropriate after having sufficient time to consider his/her participation in the study. After the subject/parent or guardian has signed the Informed Consent/Assent Form, the investigator will:

- Obtain a thorough medical history and record demographic data
- Review inclusion/exclusion criteria
- Document any concomitant medications up to 7 days prior
- Measure body weight and height
- Measure orthostatic vital signs (blood pressure and pulse)
- Perform a complete physical examination
- Obtain laboratory sample: chemistry, hematology and coagulation
- Urinalysis
- Urine pregnancy test (onsite) for adolescent female subjects of childbearing potential
- Schedule date of colonoscopy (≤42 days from Visit 1)
- Schedule Visit 2 (date of randomization) (Visit 2 ≤ 14 days from Visit 3)

6.2 Randomization Visit (Visit 2)

The Randomization Visit (Visit 2) takes place ≤ 14 days from the Procedure (Visit 3). This visit may be combined with Visit 1 if all laboratory results are obtained prior to randomization.

If the study screening requirements, including positive laboratory results, are met:

- Urine pregnancy test (onsite) for adolescent female subjects of childbearing potential
- Measure orthostatic vital signs (blood pressure and pulse)
- Perform a directed physical examination
- Document any concomitant medications
- AEs (recorded by study personnel)
- Assign subject randomization number
- Dispense study medication
- Instruct the subject (and parent/guardian) how to self-administer the study medication and provide them with detailed information, complete with assigned times of drug administration

If the subject is participating in the PK subset, an additional laboratory sample will be obtained for baseline Mg ++. The baseline Mg^{++} sample can be obtained at any time prior to IMP dosing.

6.3 Procedure/Colonoscopy Visit (Visit 3)

The Procedure Visit (Visit 3) takes place ≤ 42 days from Visit 1.

Before colonoscopy, the following will be performed/recorded/checked:

- Treatment completed
- Perform a directed physical examination
- Acceptability and tolerability questionnaire completed by subject or parent/guardian
- Obtain vital signs
- Obtain laboratory sample: chemistry, hematology, coagulation
- Urinalysis
- AEs (recorded by study personnel)
- Document any concomitant medications
- Perform study drug accountability
- If the subject is participating in the PK subset, laboratory samples will be obtained at Hours 6, 8, 10 and 12 after first dose

The subject or parent/guardian should be instructed to fill out the questionnaire during the visit in a private area prior to contact with the investigator and return the completed questionnaire to the study coordinator. If the coordinator is not available during the procedure, the subject/parent or guardian will place 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 or guardian) should interpret questions or response choices for the subject.

During the colonoscopy procedure, the blinded gastroenterologist will use the Aronchick Scale to score the quality of the bowel preparation of the study drug for overall colon cleansing and record the outcome of the colonoscopy.

Post-colonoscopy, the following will be performed/recorded/checked:

- AEs (additional to those recorded prior to colonoscopy)
- Measure orthostatic vital signs (blood pressure and pulse)

6.4 Follow-up Visits (Visits 4 and 5)

During Visit 4 (5 (±2) days after colonoscopy), the following will be obtained:

- AEs
- Document any concomitant medications
- Obtain laboratory sample: chemistry, hematology and coagulation
- Urinalysis
- Measure orthostatic vital signs (blood pressure and pulse)

During Visit 5 (28 [±5] days after colonoscopy), the investigator or coordinator will interview the subject or parent/guardian via phone 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.

6.5 Trial Flow Chart

Table 6-1 Schedule of Assessments

Visit	V1[a] Screening	V2[a] Randomization	V3 Procedure	V4 Follow-up	V5[b] Follow-up
Day	≤ - 42 Days	≤ - 14 Days	Colonoscopy T = 0	5 Days ±2 Days	28 Days ±5 Days
Informed consent	x				
Inclusion/exclusion criteria	x				
Demographic and medical history	x				
Body weight and height	x				
Urine pregnancy test	x	x			
Schedule colonoscopy	x				
Laboratory (chemistry, hematology, coagulation)	x		x	x	
PK assessment		x[c]	x[c]		
Baseline Mg^{++}	x[d]	x[d]	x[d]		
Urinalysis	x		x	x	
Physical examination[e]	x	x	x		
Orthostatic vital signs (blood pressure, pulse)	x	x	x	x	
Concomitant medications	x	x	x	x	x
Adverse events		x	x	x	x
Randomization		x			
Study medication dispensed		x[f,g]			
Subject questionnaire[h]			x		
Perform colonoscopy			x		
Score overall colon – Aronchick Scale			x		
Drug accountability			x		

PK=pharmacokinetic

a. Visits 1 and 2 can be combined if all laboratory results are obtained prior to randomization.
b. Via telephone.
c. If the subject is participating in the PK subset, laboratory samples will be obtained at baseline and hours 6, 8, 10 and 12 after first dose.
d. The baseline Mg^{++} sample can be obtained at any time prior to IMP dosing.
e. Complete physical examination at Visit 1 and directed physical examination at Visits 2 and 3.
f. "Split Dose" Prepopik first dose between 5:00 PM and 9:00 PM 1 day before colonoscopy and second dose is given approximately ≥6 hours after on the next day but at least 5 hours prior to but no more than 9 hours prior to colonoscopy. Subjects will consume five 8-ounce glasses of clear liquids following the first administration of Prepopik and at least three 8-ounce glasses of clear liquids following the second administration. "Day Before" Prepopik option see Section 5.
g. Polyethylene glycol based as per standard of care-exact solution administered will be documented by unblinded study coordinator at the site.
h. Subject or parent/guardian will be instructed to complete the questionnaire prior to contact with the Investigator (and prior to sedation for colonoscopy) and to return it to the study coordinator. If the coordinator is not available during the procedure, the subject is to place the completed questionnaire in a sealed envelope to be given to the coordinator.

7 TRIAL ASSESSMENTS

7.1 Assessments Related to Endpoints

The efficacy of the overall colon cleansing will be measured by a blinded gastroenterologist using the Aronchick Scale. The overall colon will be graded as "Excellent." "Good, "Fair," or "Inadequate" according to the definitions below:

Table 7-1 Aronchick Scale

Scale	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 = "excellent" or "good" on this 4-point scale.

The endoscopist will record in the CRF 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.

A secondary efficacy endpoint will be assessed by the Subject's Tolerability and Satisfaction Questionnaire, administered to the subject prior to the colonoscopy during Visit 2. The 7 questions are:

1. How easy was it to drink the bowel cleanout regimen (1=very easy, 2=easy, 3=okay, 4=difficult, 5=very difficult)?
2. How did the bowel cleanout regimen taste (1=very good, 2=good, 3=okay, 4=bad, 5=very bad)?
3. For each of the following questions, mark the box with your answer (1=never, 2=rarely, 3=sometimes, 4=often, 5=very often)
   How often did your tummy hurt since you started the cleanout?
   How often did you feel fullness in your tummy since you started the cleanout?
   How often did you wake up last night?
   How often did you feel sick to your stomach (nausea) since you started the cleanout?
   How much were you bothered by going to the bathroom since you started your cleanout?

The Subject's Tolerability and Satisfaction Questionnaire is attached as APPENDIX 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 Visits 2 and 3, a directed physical examination will be performed. Height and weight will be measured at Visit 1 only.

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

7.2.2 Vital Signs

Orthostatic vital signs (supine and standing blood pressure and pulse) will be measured at Visits 1 through 4.

7.2.3 Clinical Laboratory Variables

All laboratory measurements will be performed using appropriately validated methods by the study site's local laboratory. All sites should follow their local regulations for sample handling and storage.

Laboratory values will be reported to the investigator and sponsor (or the sponsor's representative) and will be entered into the eCRF database, which will be maintained by a clinical research organization selected by the Sponsor.

Out-of-range values will be described in the reference ranges to be provided by the local laboratory. Investigators will assess all out of range values as being either clinically significant or not clinically significant via the eCRF.

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 AEs post study drug administration.

Samples will be collected during Visits 1, 3 and 4 for determination of the following test values:

- Hematology panel:
  - Full complete blood count and differential
- Coagulation panel:
  - Prothrombin time, activated partial thromboplastin time
- Full chemistry panel:
  - Calculated creatinine clearance
  - Serum magnesium (Mg++)
  - Serum chemistry: glucose, blood urea nitrogen, potassium, sodium, chloride, calcium, total protein, albumin, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, bicarbonate and gamma glutamyl transferase
- Urinalysis panel

In addition, urine pregnancy tests will be performed at the local laboratory for female subjects of childbearing potential at Visits 1 and 2.

7.3 Drug Concentration Measurements

For subjects that are participating in the PK subset, blood samples for measurement of picosulfate and magnesium plasma concentrations will be collected from approximately 15 subjects in the 3 Prepopik groups. Magnesium will be collected pre-dose at Visits 1, 2 or 3.). Picosulfate will be collected at Visit 3 (colonoscopy) in the (6-12 hour) window after the first dose of Prepopik. Sampling times at Visit 3 are at Hours 6, 8, and 12 for picosulfate concentrations and at Hour 10 for magnesium concentrations.

Analysis of the samples for sodium picosulfate and magnesium oxide will be performed by [redacted]

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 local safety 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. The volume of blood withdrawn from subjects is restricted to a minimum to allow evaluation of PK.

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

8 ADVERSE EVENTS

8.1 Adverse Event Definition

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

- Any unfavorable and unintended sign, symptom or disease temporally associated with the use of the IMP, whether or not considered to be caused by the IMP
- AEs commonly observed and AEs anticipated based on the pharmacological effect of the IMP
- Any laboratory abnormality, vital sign or finding from physical or gynecological examination assessed as clinically significant by the investigator (note: findings from assessments and examinations done during screening are not AEs, 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 being probably or possibly causally related to treatment with the IMP.

A serious ADR is an SAE evaluated by the investigator and/or by Ferring as being probably or possibly causally related to treatment with the IMP (further described in Section 8.2.2).

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 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 AEs 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 AEs in the Adverse Event Log provided in each subject's CRF with information about the:

- AE
- Date and time of onset (time can be omitted, if applicable)
- Intensity
- Causal relationship to IMP
- Action taken to IMP
- Other action taken
- Date and time of outcome (time can be omitted, if applicable)
- 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 AE more than once and the subject recovers in between the events, the AEs should be recorded separately. If an AE 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 AE; the reason for conducting the procedure is. Hospitalization is not an AE; the reason for hospitalization is. Death is not an AE, but the cause of death is (an exception is sudden death of unknown cause, which is an AE).

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

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 AE 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 AE must be classified using the following 3-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 AE 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 AE. The AE may occur as part of the pharmacological action of the IMP or may be unpredictable in its occurrence.

Examples:

- AEs that are uncommon but are known to be strongly associated with IMP exposure
- AEs 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 AE.

Examples:

- known consequences of the underlying disease or condition under investigation
- AEs 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 AE must be classified as one of the following:

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

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 AE, this medication should be entered in the Concomitant Medication Log.

Date and Time of Outcome

The date and time (time can be deleted/omitted, if applicable) the subject recovered or died.

Outcome

The outcome of an AE 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
- Not yet recovered
- Fatal

8.3 Pregnancy and Pregnancy Outcome

If a pregnancy occurs, the IMP should be immediately stopped and Pharmacovigilance at Ferring Pharmaceuticals must be informed. The mother and the fetus must be followed-up at least until the birth of the infant and 1 month after the birth of the infant. In general, the follow-up will include the course; duration, and the outcome of the pregnancy, as well as neonatal health. If a pregnancy results in an abnormal outcome (birth defect/congenital anomaly), this must be reported as an SAE to Pharmacovigilance at Ferring Pharmaceuticals.

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 an SAE to Pharmacovigilance at Ferring Pharmaceuticals.

8.4 Serious Adverse Events

8.4.1 Serious Adverse Event Definition

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 of existing hospitalization	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 at least 24 hours. Over-night stay for observation, stay at emergency room or treatment on an out-patient basis do not constitute a hospitalization. However, medical judgment 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 AEs, 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 judgment 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 judgment 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 but not later than within 24 hours of his/her knowledge of the occurrence of an 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.

Pharmacovigilance, Ferring Pharmaceuticals Inc.
[redacted]

Copies from CRFs regarding demographics, AEs, medical history, and concomitant medication are **mandatory** for initial reports and for follow-up reports if any changes have been made since the initial report.

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 AEs that are **serious, unexpected, and with a reasonable possible causality to the IMP**, as judged by either the investigator or Ferring, to the relevant parties within the stipulated timelines.

Serious AEs 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 AE 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 AE 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 Trial Visit

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

Details of the statistical methodology will be provided in a separate Statistical Analysis Plan. All tabulations will be done by treatment arm. All individual patient data will be listed by domain.

9.1 Determination of Sample Size

A total of at least 45 subjects will be exposed to Prepopik. In the two Phase 3 studies for adults, 83% and 84.2% of subjects were classified as success after bowel preparation with Prepopik. With 45 subjects, if 80% of subjects are classified as success in this study, the exact 95% confidence interval of the success rate will be calculated as 65% - 90%.

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 and presentation by category will present the frequency and corresponding percentages. The number of subjects screened and not randomized will be presented with the main reason for their non-inclusion.

9.3 Protocol Deviations

Major or minor protocol deviations will be defined and documented prior to database lock.

9.4 Analysis Sets

All randomized subjects who received any study drug will be included in one or more of the following analysis datasets.

9.4.1 Intention-to-Treat (ITT) Dataset

The ITT Dataset will include all subjects who are randomized independent of whether or not the subject receives study treatment dose. Subjects who do not have an efficacy assessment for the data (Aronchick Scale) will be scored as a non-responder. Analyses for the ITT will be conducted according to the randomized treatment.

9.4.2 Per Protocol (PP) Dataset

Subjects with major protocol deviations will be excluded from the PP (per-protocol) Analysis Set. 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.

9.4.3 Safety Dataset

All subjects consuming at least one dose of study medication will be included in the Safety Analysis Set. Analyses for the Safety Dataset will be conducted according to the treatment actually received.

9.5 Trial Population

9.5.1 Demographics and other Baseline Characteristics

Descriptive statistics of demographics, and other baseline characteristics will be presented by treatment group for the ITT, PP and safety populations. For quantitative variables, all summaries will include the sample size, mean, median, standard deviation, minimum, and maximum. For the qualitative variables, the summaries will include the number and percentage of subjects for each outcome.

9.5.2 Medical History, Concomitant Medication and Other Safety Evaluations

Medical history, concomitant medications and the physical examination results will be summarized and listed by subject and any abnormalities noted on the listings.

9.6 Endpoint Assessments

9.6.1 General Considerations

Nominal p-values and confidence intervals will be presented to aid in interpretation of the summary of data.

Qualitative data will be summarized by presenting the total number of subjects, frequency and percentages within categories by treatment group. The quantitative data will be summarized by presenting the number of subjects, the mean and standard deviation, median, minimum and maximum by treatment group.

9.6.2 Primary Efficacy Endpoint

The primary efficacy endpoint will be the proportion of subjects classified as success defined by excellent or good in the Aronchick scale. The primary efficacy analysis will be based on the ITT dataset.

The proportion will be presented by treatment group within each age group, for all Prepopik 1 sachet groups combined, for all Prepopik groups combined, and all standard of care groups combined with the 95% confidence interval.

The treatment group difference will be assessed by constructing the 95% confidence interval of the difference in proportion between each Prepopik group and standard of care within each age group, all Prepopik 1 sachet groups combined and all standard of care groups combined, and all Prepopik groups combined and all standard of care groups combined.

The analyses will be conducted for the PP populations as well.

9.6.3 Secondary Endpoint(s)

The following secondary endpoints will be summarized in the same manner as the primary endpoint: proportion of subjects who completed colon cleansing, proportion of subject who record treatment as tolerable or better and proportion who rate treatment as satisfactory as provided on the Tolerability and Satisfaction Questionnaire, and proportion of subjects who completed colonoscopy procedure.

9.7 Extent of Exposure and Treatment Compliance

The total study treatment exposure 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 age and 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

The safety analysis will include all randomized and dosed subjects, i.e., the Safety Analysis Set. Complete listings and summary tables for all safety information, including AEs, clinical laboratory vital signs, and physical examination, data will be included in the final report.

9.8.2 Adverse Events

All AEs will be coded by the most current version of MedRA (Medical Dictionary for Regulatory Activities) for system organ class and preferred term.

All AEs will be listed by subject, and the incidence of treatment-emergent AEs will be presented by treatment group, causality (relationship to the study medication), and intensity (severity). Deaths, SAEs, and AEs leading to discontinuation will be listed.

9.8.3 Safety Laboratory Variables

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

Continuous clinical laboratory safety data will be summarized by treatment group and nominal time point (V1 and V3 pre and post colonoscopy) using descriptive statistics: sample size, mean, median, standard deviation, minimum, and maximum values. Changes from pre-treatment will be summarized in the same way.

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

9.8.4 Other Safety Variables

9.8.5 Vital Signs

Each vital sign will be summarized by treatment group and nominal 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.

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

9.8.6 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.

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). The investigator will permit study-related monitoring, audit(s), IRB review(s) and regulatory inspection(s), with a direct access to all the required source records.

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

An investigator shall retain the source records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified. 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 e-CRF

In the trial an e-CRF 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 e-CRF 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 as write-protected Portable Document Format (PDF) files produced by the third party. The Investigator will approve/authorise the e-CRF entries for each patient with an electronic signature which equals a handwritten signature.

Trial data has to be entered into the system within a maximum of three working days after the patient 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 Data Management

A data management plan will be created under the responsibility of Ferring's Biometrics Department. 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.

The data management plan will describe captured methods, who is authorized to enter the data, decisions 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.

10.4 Provision of Additional Information

On request, the investigator will provide the sponsor with additional data relating to the study, or copies of relevant source records, duly anonymized. This is important when errors in data transcription are encountered. In case of particular issues or governmental queries, it may be necessary to have access to the complete study documents, provided that the subjects' confidentiality is maintained 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, International Conference on Harmonization (ICH)-GCP, standard operating procedures, applicable regulatory requirements, maintenance of study-related source records, and completeness, accuracy and verifiability of all CRF entries compared to source data. The investigator will cooperate with the monitor to ensure that any discrepancies that may be identified are resolved. When the first few subjects are enrolled at the center, a monitoring visit will take place shortly afterwards.

11.2 Audit and Inspection

The investigator will make all the study-related source data and records, both paper and electronic, available to a quality assurance auditor mandated by the sponsor, or to domestic or foreign regulatory inspectors, after reasonable notice. The main purposes of an audit or inspection are to confirm that the rights and well-being of the subjects have been adequately protected, compliance with the protocol and standard operating procedures has been adhered to, and that all data relevant for the evaluation of the investigational product have been processed and reported in compliance with ICH-GCP and applicable regulatory requirements.

The subject/parent or guardian 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. In the CRF or any other documents submitted to the sponsor, the subjects will not be identified by their names, but by an identification system consisting of their initials and assigned number in the study. Documents not intended for submission to the sponsor, e.g., the confidential subject identification code and the signed informed consent forms, will be maintained by the investigator in strict confidence.

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 the sponsor, and agreed upon by the investigator and the sponsor prior to its implementation.

Significant amendments will be submitted for consideration to the approving IRB(s) and regulatory authorities, in accordance with local regulations.

An approval is required for a significant amendment, e.g. one which could affect the safety of the subjects, or which entails a significant change of the scope/design of the study.

12.2 Deviations from the Protocol

Deviations from the protocol are discouraged. If deviations do occur, the investigator must inform the monitor, and the implications of the deviation must be reviewed and discussed. Any deviation must be documented on the protocol violation page in the source document and CRF with the visit number and type of violation. Any significant violations as determined by the sponsor and/or IRB must be reported to the IRB. Any paper documentation must be kept in the Investigator's File and in the Trial Master File.

12.3 Premature Trial Termination

Both the investigator (with regard to his participation) and the sponsor reserve the right to terminate the study at any time. Should this become necessary, the procedures will be agreed upon after consultation between the 2 parties. In terminating the study, the sponsor and the investigator will ensure that adequate consideration is given to the protection of the best interests of the subjects. Regulatory authorities and IRB(s) 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 study will be reported in a study report prepared by the sponsor. The final report may be used for the further development of the investigational product as considered necessary by the sponsor.

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

13.3.1 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 entirety in a responsible and coherent manner and results from subsets should not be published in advance or without clear reference to the primary publication of the entire trial.

Authorship is granted based on the International Committee of Medical Journal Editors (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 contract research organization 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 comment prior to submission. Comments will be given within 4 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.

13.3.2 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 registry, i.e., www.ClinicalTrials.gov, which is sponsored by the National Institutes of Health.

14 ETHICAL AND REGULATORY ASPECTS

14.1 Independent Ethics Committee or Institutional Review Board (IRB)

An IRB will review the study protocol and any amendments and advertisements used for recruitment. The IRB will review the subject information sheet and the informed consent form, their updates (if any), and any written materials given to the subjects. A list of all IRBs consulted and the name of the committee chair/s will be included in the study 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

At the end of the study, the IRB will be notified in writing.

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/parent or guardian after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards, and any other aspects of the trial which are relevant to the subject's/parent's or guardian's decision to participate. The trial subject/parent or guardian must be given ample time to consider participation in the trial, before the consent is obtained. The Informed Consent Documents and Assent (as per state regulations) must be signed and dated by the subject/parent or guardian and the investigator who has provided information to the subject/parent or guardian regarding the trial before any information regarding the subject is obtained.

The investigator (or the person delegated by the investigator) will explain that the subject/parent or guardian is completely free to refuse to have his or her information included in the trial or to withdraw consent at any time, without any consequences for his/her further care and without the need to justify his/her decision.

The subject/parent or guardian will receive a copy of the Subject Information and his/her signed Informed Consent and Assent form.

If new information becomes available that may be relevant to the trial subject's/parent's or guardian's willingness to have his or her data be included in the trial, a new Subject Information and Informed Consent Form (Assent) will be forwarded to the IRB(s) (and regulatory authorities, if required). The trial subjects/parent or guardian will be informed about this new information and re-consent will be obtained.

Each subject/parent or guardian who provided informed consent for this retrospective study 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 the guardian 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 Helsinki Declaration and the consolidated ICH-GCP shall constitute as 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 will be as 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

In case of any damage or injury occurring to a subject in association with the IMP or the participation in the trial, Ferring has contracted an insurance which covers the liability of Ferring, the investigator and other persons involved in the trial in compliance with the laws in the countries involved.

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 the completion or discontinuation of the trial, 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 named subject source records and anonymous CRF data 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 the completion or discontinuation of the trial.

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. Documents may be transferred to Ferring Global Quality Assurance, for example if the investigator retires and the documents no longer can be archived by the site.

16.2 Trial Master File

Ferring will archive the trial master file in accordance with ICH-GCP and applicable regulatory requirements.

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APPENDICES

APPENDIX 1: 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, pharmacokinetic blood draws (if applicable) 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 2: 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 the directions of the doctor for taking your insulin or pills.
- Your blood sugars should be monitored regularly. Please discuss this with your doctor, nurse or dietitian.
- 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 jello. Do not drink anything red. 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 white grape juice • one half cup regular soda pop • one third cup regular Kool-Aid • one quarter cup sherbet	• one third cup apple juice • one quarter cup regular jello • one half popsicle • two hard candies

Call the doctor……

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

APPENDIX 3: Subject's Tolerability and Satisfaction Questionnaire

1. How easy was it to drink the bowel cleanout medicine?

☐	☐	☐	☐	☐
1. Very easy	2. Easy	3. Okay	4. Difficult	5. Very difficult

2. How did the bowel cleanout medicine taste?

☐	☐	☐	☐	☐
1. Very well	2. Well	3. Okay	4. Bad	5. Very bad

3. For each of the following questions, tick the box with your answer.

1 = Never; 2 = Rarely; 3 = Sometimes; 4 = Often; 5 = Very Often

	1	2	3	4	5
How often did your tummy hurt since you started the cleanout?					
How often did you feel fullness in your tummy, since you started the cleanout?					
How often did you wake up last night?					
How often did you feel sick to your stomach (nausea) since you started the cleanout?					
How much were you bothered by going to the washroom since you started the cleanout?					